Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	omalizumab (Xolair) (150 mg or 300 mg subcutaneous injection)
Indication	Treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment
Listing request	Treatment of adults and adolescents (12 years of age and above) with persistent (disease duration ≥ 6 months) moderate to severe (UAS7 score ≥ 16 OR DLQI ≥ 10) CIU who remain symptomatic (presence of hives or/and associated itching) despite H_1 antihistamine treatment.
Manufacturer	Novartis Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and immunology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

You are permitted to make copies of this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any material from this document in any form or by any means without the prior written permission to CADTH.

Please contact CADTH's Vice-President of Corporate Services at corporateservices@cadth.ca with any inquiries about this notice or other legal matters relating to CADTH's services.

TABLE OF CONTENTS

ABBREVIATIONS

CDR	CADTH Common Drug Review
CIU	chronic idiopathic urticaria
ICUR	incremental cost-utility ratio
LTRA	leukotriene receptor antagonist
QALY	quality-adjusted life-year
SOC	standard of care
UAS7	Urticaria Activity Score over seven days

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Omalizumab (Xolair)
Study Question	"From the Canadian health care system perspective, what is the cost-effectiveness of Xolair (omalizumab) + standard of care (SOC) compared to SOC alone for the treatment of chronic idiopathic urticaria (CIU)?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults and adolescents 12 years of age and over with moderate to severe CIU (UAS7 ≥ 16), still symptomatic despite SOC
Treatment	• **Scenario 1:** Omalizumab 300 mg SC (as third- or fourth-line drug) every four weeks added on to SOC (H_1 antihistamines up to four times the recommended dose combined with H_2 antagonists, LTRAs, or both) • **Scenario 2:** Omalizumab 150 mg SC (as second-line drug) every four weeks added on to SOC (H_1 antihistamine at recommended dose) • **Scenario 3:** Omalizumab 300 mg SC (as second-line drug) every four weeks added on to SOC (H_1 antihistamine at recommended doses)
Outcomes	QALYs, life-years
Comparators	SOC, defined as: • H_1 antihistamine up to four times the recommended dosing combined with H_2 antagonists or LTRAs, or both (scenario 1) • recommended H_1 antihistamine dosing (scenarios 2 and 3)
Perspective	Publicly funded health care system
Time Horizon	20 years
Results for Base Case	ICUR for omalizumab + SOC versus SOC alone: • $52,513 per QALY (scenario 1) • $57,193 per QALY (scenario 2) • $81,210 per QALY (scenario 3)
Key Limitations	CDR noted a number of key limitations with the submitted model: • The long-term clinical efficacy of omalizumab is uncertain; there are no data on the efficacy of omalizumab upon re-treatment. • Natural remission rates were sourced from van der Valk et al. 2002.[1] However, several other sources reported higher remission rates. • The assumption that patients in the mild CIU state after initial treatment (UAS7 7 to 15) are not re-treated upon relapse (UAS7 ≥ 16), may not reflect clinical practice

CDR Estimate(s)	CDR conducted a number of reanalyses to assess the impact of the key limitations identified, but was not able to account for all limitations due to the structure of the economic model. The following were considered: • reduced the time horizon to 10 years (to account for potential treatment waning, and other sources suggesting most patients have a complete resolution of symptoms by 10 years) • assumed initial response probabilities upon relapse (instead of assuming response to subsequent treatments would be the same as response observed for initial treatment) • higher spontaneous remission rates as reported in the literature • re-treatment of patients with mild CIU who relapse after the first course of treatment with omalizumab • cost of LTRAs equated to $0, as not covered by drug plans for this indication (for scenario 1 only) • higher proportion of females to males for the all-cause mortality values, to reflect ratio seen in trial data. When including these considerations, in scenario 1 (third- or fourth-line drug) the ICUR for omalizumab 300 mg + SOC versus SOC alone was $120,009 per QALY. In scenario 3 (second-line drug in patients refractory to H_1 antihistamines), the ICUR for omalizumab 300 mg + SOC versus SOC alone was $137,192 per QALY.

CDR = CADTH Common Drug Review; CIU = chronic idiopathic urticaria; ICUR = incremental cost-utility ratio; LTRAs = leukotriene receptor antagonists; QALY = quality-adjusted life-year; SC = subcutaneous; SOC = standard of care; UAS7 = Urticaria Activity Score over seven days.

EXECUTIVE SUMMARY

Background

Omalizumab is being reviewed for the treatment of chronic idiopathic urticaria (CIU) in patients 12 years of age and older who remain symptomatic despite H_1 antihistamine treatment.[2] The recommended dose is 150 mg or 300 mg administered once every four weeks by subcutaneous injection. Prescribers are advised to periodically reassess the need for continued therapy.[2]

The price of omalizumab is $612 per 150 mg single-use vial,[3] which corresponds to an annual cost of $7,956 (150 mg dose) and $15,912 (300 mg dose). The manufacturer is seeking reimbursement in line with the Health Canada indication and added the following criteria: disease duration greater than or equal to six months, moderate to severe CIU (Urticaria Activity Score over seven days [UAS7] ≥ 16 or Dermatology Life Quality Index ≥ 10), and CIU patients who remain symptomatic (presence of hives or associated itching) despite H_1 antihistamine treatment. Further, the manufacturer noted that response to treatment should be assessed 12 weeks following omalizumab initiation. For patients initiated on 150 mg every four weeks and who do not adequately respond by week 12, consideration should be given to increase the dose to 300 mg every four weeks. Response to treatment should be reassessed 12 weeks thereafter.

Omalizumab 150 mg was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC, now the Canadian Drug Expert Committee [CDEC]) for the treatment of moderate to severe persistent asthma in adults and adolescents whose symptoms are inadequately controlled with inhaled corticosteroids and received a "do not list" recommendation.[4]

A cost-utility analysis was submitted comparing omalizumab plus standard of care (SOC) to SOC alone, over a 20-year time horizon and under the perspective of a publicly funded health care system, in adults and adolescents 12 years of age and older with moderate to severe CIU who remain symptomatic despite standard of care treatment. Three base-case scenarios were presented:

- 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 [LTRAs], or both) with SOC alone. Efficacy and safety data were sourced from the GLACIAL[5] trial.
- 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. Efficacy and safety data were sourced from ASTERIA I[6] and ASTERIA II.[7]
- 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. Efficacy and safety data were sourced from ASTERIA I[6] and ASTERIA II.[7]

The economic submission was based on a Markov model with five key health states based on UAS7. Patients began in either the moderate or severe urticaria health states and moved through the model every four weeks for 24 weeks. Patients who responded to treatment at 24 weeks (UAS7 ≤ 6) were eligible for re-treatment upon relapse (UAS7 ≥ 16). Progression through the model was also driven by whether patients experienced a spontaneous remission of symptoms or dropped out. Utilities were obtained from pooled data from GLACIAL, ASTERIA I, and ASTERIA II.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations with the submitted model, the most important ones being the uncertain long-term clinical efficacy of omalizumab upon relapse, the lack of consideration of a treatment waning effect, and uncertainty with the natural remission rate. There is no evidence to suggest that the efficacy of omalizumab over repeated treatments is maintained. Further, CIU is a naturally remitting disease, and some sources reported natural remission rates of more than 80% within 10 years.[8] CDR was able to undertake reanalyses varying the following parameters: reducing the time horizon to 10 years (to account for potential treatment waning and the fact that a majority of patients might have complete resolution of symptoms by 10 years); assuming initial response probabilities upon relapse (instead of assuming response would be similar to that of initial treatment); applying higher spontaneous remission rates; assuming re-treatment of mild patients who relapsed after the first course of treatment; equating the costs associated with LTRAs to $0; and altering the proportion of males to females to determine all-cause mortality rates. When omalizumab is used as a third- or fourth-line drug (Scenario 1), a combined reanalysis of these limitations resulted in an incremental cost-utility ratio (ICUR) for omalizumab 300 mg plus SOC versus SOC alone of $120,009 per quality-adjusted life-year (QALY). Further, upon stratifying by severity of CIU (severe or moderate), the ICUR ranged from $88,480 per QALY when 100% of patients initiated treatment in the severe health state (UAS7 28 to 42) to $419,033 per QALY when 100% of patients initiated treatment in the moderate health state (UAS7 16 to 27). If omalizumab is used as a second-line drug (as an add-on to H_1 antihistamines), the ICUR was $137,192 per QALY. Upon stratifying by severity, the ICUR was $79,192 per QALY for the severe health state; for the moderate health state, omalizumab 300 mg plus SOC was dominated by SOC (less effective, more costly).

Conclusions

There is significant clinical uncertainty with omalizumab efficacy upon re-treatment. CDR reanalyses showed that at a dose of 300 mg by subcutaneous injection every four weeks, when omalizumab is used as either a second-line drug or a third- or fourth-line drug added on to SOC in patients refractory to H_1 antihistamines, the ICURs for omalizumab plus SOC compared with SOC alone were above $120,000 per QALY. A price reduction of 50% to 60% would be needed for the ICUR of omalizumab 300 mg plus SOC to be reduced to commonly accepted thresholds. Further, results of the stratified analysis suggest that the ICURs are substantially higher in moderate versus severe patients.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis using a decision analytic Markov model comparing omalizumab (Xolair) to standard of care (SOC) (defined as either the recommended dose of H_1 antihistamines or up to four times the recommended dosing combined with H_2 antagonists or leukotriene receptor antagonists [LTRAs], or both) in adolescent and adults patients with chronic idiopathic urticaria (CIU) who remain symptomatic despite H_1 antihistamine treatment. The manufacturer considered three different scenarios in its analysis, where it varied the dosage of omalizumab (150 mg or 300 mg) and where a different definition of SOC was used.

The model included five health states based on the Urticaria Activity Score over seven days (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, which is indicative of no symptoms of CIU and considered a full treatment response). The model followed a cohort of 100 patients (mean age 42 years) who entered the model in the severe (30%) or moderate (70%) health states based on observations from the GLACIAL, ASTERIA I, and ASTERIA II studies.[5-7] The model tracked this cohort for 20 years with a cycle length of four weeks. Response to treatment was assessed at 24 weeks and was defined as UAS7 score of ≤ 6 (well controlled or urticaria-free). All patients stopped treatment at week 24 regardless of response status. Responders either remained in the same health state (well controlled or urticaria-free), relapsed, or experienced spontaneous remission of symptoms. Prior responders who relapsed were re-treated with omalizumab plus SOC for another 24 weeks throughout the model; re-treated patients were assumed to have the same response profile as when they were initially treated. Alternatively, patients who did not respond to treatment at 24 weeks (i.e., who stayed in the mild, moderate, or severe health states) were only able to experience a spontaneous remission of symptoms; these patients remained on SOC for the remainder of their time in the model. The probability of transitioning between health states was based primarily on a change in UAS7 score (from data collected from GLACIAL, ASTERIA I, and ASTERIA II),[5-7] but was also driven by whether patients experienced a relapse (return to moderate or severe health state) or experienced a spontaneous resolution of symptoms (remission; rates obtained from a study conducted in CIU patients by van der Valk et al. [2002]).[1] The model also applied a dropout rate every four weeks to patients in the omalizumab treatment group for the first 24 weeks of treatment, based on data from the GLACIAL and ASTERIA I clinical trials.

Utility weights were associated with the health states based on pooled EuroQol 5-Dimensions Questionnaire (EQ-5D) data from the three key clinical trials (GLACIAL, ASTERIA I, and ASTERIA II) using a mixed-effects model. Resource utilization was based on clinical trial observations, clinical expert assumptions, and the literature. Costs were taken from Ontario health care cost sources. Administration costs associated with omalizumab were assumed to be [redacted].

2. MANUFACTURER'S BASE CASE

In scenario 1, for the cohort of 100 patients, the manufacturer reported that the total cost associated with treatment with omalizumab plus SOC was $3,068,469, an incremental cost of $1,920,489 compared with SOC alone. Further, omalizumab treatment resulted in 1099.6 quality-adjusted life-years (QALYs), an incremental QALY gain of 36.60 compared with SOC alone. Thus, the incremental cost-utility ratio (ICUR) was $52,513 per QALY. In scenarios 2 and 3, the ICUR was $57,193 and $81,210 per QALY, respectively (see Table 12, Appendix V).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty regarding the parameters chosen for the base-case analysis was addressed by the manufacturer using a one-way deterministic sensitivity analysis and a probabilistic sensitivity analysis. For the three scenarios, the following parameters had the greatest impact on the ICUR (± 25%): time horizon, perspective, natural remission rate, and utility weights.

The probabilistic sensitivity analysis showed that in scenario 1, in approximately 31% of iterations, the ICUR was below a willingness-to-pay threshold of $50,000 per QALY.

In scenario 3, the probabilistic sensitivity analysis showed that at a willingness-to-pay threshold of $50,000, omalizumab 300 mg added on as a second-line drug to H_1 antihistamines had a 1.6% probability of being cost-effective compared with H_1 antihistamines alone.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

4.1 Uncertain Long-Term Clinical Efficacy of Omalizumab

The paucity of long-term data (beyond six months) with omalizumab introduces substantial uncertainty in its comparative cost-effectiveness versus SOC. The manufacturer assumed that the response to re-treatment would be similar to that of the initial treatment. There is no evidence to suggest that the efficacy of omalizumab over repeated treatments is maintained over time, and the manufacturer did not include a treatment waning effect in the model. A Canadian open-label study prospectively followed 68 patients (61 with severe chronic spontaneous urticaria) for up to 25 months. Patients received omalizumab 150 mg administered every four weeks initially and then based on patient's response. The authors reported that during the 25-month follow-up, 8% of patients became refractory to treatment.[9]

4.2 Higher Spontaneous Remission Rates Reported in Literature

The manufacturer used the remission rates from van der Valk et al. (2002) (9.5% in year 1; 49% in year 10).[1] However, higher rates have been reported in the literature (up to 38% in year 1[10] and 83% in year 10[8]). The CADTH Common Drug Review (CDR) considered the rates reported by Toubi et al. (2004).[8] Spontaneous remission is a key driver in the economic model; thus, an increase in the overall rates will vary the ICUR substantially. Considering that the majority of patients might have complete remission at 10 years, this also brings into question the choice of a 20-year time horizon for the base-case analysis.

4.3 Assumption That Patients in the Mild CIU Health State Following Initial Treatment Are Not Re-treated Upon Relapse

Patients who are in the mild response health state after the first course of treatment with omalizumab would likely be re-treated upon relapse, as identified by the CDR clinical expert. Re-treatment of patients with mild urticaria would increase the overall costs, and thus the ICUR, substantially.

4.4 Stratification Based on Urticaria Severity Resulting in Small Sample Sizes

The model is stratified based on severity of urticaria at baseline as taken directly from the clinical trials. Although this allows one to assess the cost-effectiveness in the specific subgroups of moderate and severe urticaria, it results in small sample sizes, which introduces uncertainty in the efficacy data presented.

4.5 LTRAs are not Reimbursed for CIU by Public Drug Plans in Canada

The manufacturer included the cost of the LTRA montelukast in its analysis for the primary scenario (i.e., scenario 1); however, it is not reimbursed for this indication by any public drug plan in Canada. Although this does not significantly impact the overall conclusions, it should be noted that these costs are paid by the patients, not by the public drug plans.

4.6 Proportion of Females to Males Used for All-Cause Mortality Values

In the manufacturer's analysis, it was assumed the proportion of females to males was equal (50% each). However, in all three key clinical trials, the proportion of females was substantially higher (closer to 75%). Although this may not impact the overall costs in the model, it was noted as a limitation.

5. CADTH COMMON DRUG REVIEW ANALYSES

As stated in the CDR Clinical Review Report, the 150 mg dose of omalizumab failed to provide a clinically significant response in terms of UAS7 score at weeks 12 and 24. Therefore, CDR reanalysis did not consider scenario 2 and focused on the 300 mg dose of omalizumab from scenarios 1 and 3. Scenario 1 was identified to be the most representative of current Canadian clinical practice, where omalizumab will be used as a third- or fourth-line drug in the treatment of CIU, as mentioned in the Clinical Review Report. Scenario 3 is in line with requested listing criteria, where omalizumab would be used as a second-line drug.

1. Shortening of the time horizon to 10 years:
   a) In scenario 1, the ICUR increased to $65,495 per QALY.
   b) In scenario 3, the ICUR increased to $100,639 per QALY.

2. Treatment response (UAS7 ≥ 6) upon relapse (UAS7 ≤ 16) based on initial response probabilities:
   a) In scenario 1, the ICUR increased to $78,854 per QALY.
   b) In scenario 3, the ICUR increased to $95,434 per QALY.

3. Higher spontaneous remission rates (Toubi et al. [2004][8]):
   a) In scenario 1, the ICUR increased to $67,083 per QALY.
   b) In scenario 3, the ICUR increased to $102,737 per QALY.

4. Re-treatment of patients in the mild urticaria health state:
   a) In scenario 1, the ICUR increased to $94,686 per QALY.
   b) In scenario 3, the ICUR increased to $127,576 per QALY.

5. Equating the costs of LTRAs to $0.00 (scenario 1 only):
   a) The ICUR increased to $52,986 per QALY.

6. Higher proportion of females to males for the all-cause mortality values:
   a) In scenario 1, the ICUR increased to $52,474 per QALY.
   b) In scenario 3, the ICUR increased to $81,130 per QALY.

For more detailed CDR reanalyses, see Table 13 in Appendix 5.

5.1 CADTH Common Drug Review Multi-Way Analysis

Upon conducting a multi-way analysis considering the limitations identified above, and assuming the manufacturer's proposed 70% and30% patient split between severe and moderate patients respectively, in scenario 1, the ICUR for omalizumab 300 mg plus SOC versus SOC alone was $120,009 per QALY. Upon stratifying by severity (assuming 100% of patients are severe and 100% are moderate) considering these limitations, the ICUR ranges from $88,480 per QALY for the severe health state to $419,033 per QALY for the moderate health state.

In scenario 3, the ICUR for omalizumab 300 mg plus SOC versus SOC alone was $137,192 per QALY. Upon stratifying by severity, the ICUR was $79,192 per QALY for the severe health state; for the moderate health state, omalizumab 300 mg plus SOC was dominated by SOC.

5.1.1 Price reduction analysis

A price reduction of approximately 50% to 60% would be needed such that the ICUR for omalizumab 300 mg plus SOC compared with SOC alone would be at commonly accepted thresholds (Table 2).

TABLE 2: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Omalizumab Versus Best Supportive Care		
Scenario (Price)	**Reanalysis by CDR[a] (Scenario 1: Used as Third- or Fourth-Line Drug)**	**Reanalysis by CDR[a] (Scenario 3: Used as Second-Line Drug)[b]**
Submitted ($1,224.00)	$120,009	$137,192
10% reduction ($1,101.60)	$107,275	$122,787
20% reduction ($979.20)	$94,541	$108,383
30% reduction ($856.50)	$81,807	$93,978
40% reduction ($734.40)	$69,073	$79,573
50% reduction ($612.00)	$56,339	$65,169
60% reduction ($489.60)	$43,606	$50,764
70% reduction ($367.20)	$30,872	$36,359
80% reduction ($244.80)	$18,138	$21,955
90% reduction ($122.40)	$5,404	$7,550

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

[a] CDR reanalysis considered the key limitations identified in the text (see CDR Analysis), using a 10-year time horizon.

[b] Scenario 3 is in line with requested listing criteria, where omalizumab would be used as a second-line drug.

6. ISSUES FOR CONSIDERATION

- There is no evidence to inform the optimal interval between courses of treatment or to compare the efficacy (and thus the cost-effectiveness) of a dose titration from 150 mg to 300 mg.
- Many of the CDR participating drug plans do not reimburse standard doses of several H_1 antihistamines. Although the overall costs associated with H_1 antihistamines are minimal and thus have little impact on the ICUR, they are typically an out-of-pocket expense for patients.
- Costs of omalizumab (sourced from the Ontario Drug Benefit by the manufacturer) may be different if there are alternate pricing arrangements in place between the manufacturer and public drug plans. The price of omalizumab on the Alberta Drug Benefit formulary ($600 for 150 mg dose) is lower than on the Ontario Drug Benefit formulary.
- In the manufacturer's analysis, the costs associated with the administration of omalizumab (e.g., injection, nurse time, and physician time) are [redacted]. It should be noted that [redacted].

6.1 Patient Input

Input was received from one patient group, the Canadian Skin Patient Alliance. In this input, patients reported that the occurrence of itchy hives cause a significant amount of anxiety, affect sleep, impact the foods they can consume, and influence the jobs they can obtain. The majority of patients also reported a decrease in self-confidence. Patients reported currently using over-the-counter antihistamines (doxepin, hydroxychloroquine, and prednisone) and that concerns with current treatment include treatment effectiveness and intolerable side effects. Patients expressed that omalizumab managed their symptoms better than previous treatments, effectively treating the skin eruptions and swelling. They also noted that the side effects with omalizumab were minimal.

7. CONCLUSIONS

There is significant clinical uncertainty around omalizumab efficacy upon re-treatment. CDR reanalyses showed that at a dose of 300 mg by subcutaneous injection every four weeks, when omalizumab is used as either a second-line drug or a third- or fourth-line drug added on to SOC in patients refractory to H_1 antihistamines, the ICURs for omalizumab plus SOC compared with SOC alone were above $120,000 per QALY. A price reduction of 50% to 60% would be needed for the ICUR of omalizumab 300 mg plus SOC to be reduced to commonly accepted thresholds. Further, results of the stratified analysis suggest that the ICURs are substantially higher in patients with moderate CIU compared with patients with severe CIU.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in the table; as such the table may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE FOR CHRONIC IDIOPATHIC URTICARIA

Drug or Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Omalizumab (Xolair)	**150 mg**	**Single-use vial**	**612.0000[a]**	**150 mg or 300 mg SC every 4 weeks**	**21.80[b] (150 mg) 43.59[b] (300 mg)**	**7,956.00[b] (150 mg) 15,912.00[b] (300 mg)**
Histamine H_1 Receptor Antagonists (Second and Third Generation)						
Cetirizine hydrochloride (*generics*)	5 mg 10 mg 20 mg	Tablet	0.5400[c] 0.4083[c] 0.9326[d]	5 to 10 mg daily (can be increased up to 40 mg daily)	0.41 to 0.54 1.63 (4 × recommended dose[e])	149.03 to 197.10 596.12 (4 × recommended dose[e])
Desloratadine (Aerius)	5 mg	Tablet	0.7000[f]	5 mg daily (can be increased up to 20 mg daily)	0.70 2.80 (4 × recommended dose[e])	255.50 1022.00 (4 × recommended dose[e])
Fexofenadine hydrochloride (Allegra)	60 mg 120 mg	Tablet	0.3250[d] 0.5850[d]	60 mg twice daily (can be increased up to 240 mg twice daily)	0.65 2.34 (4 × recommended dose[e])	237.25 854.10 (4 × recommended dose[e])
Loratadine (Claritin)	10 mg	Tablet	0.5170[f]	10 mg daily (can be increased up to 40 mg daily)	0.52 2.07 (4 × recommended dose[e])	188.71 754.82 (4 × recommended dose[e])
Other Treatments Used That Are Not Currently Indicated[g]						
Histamine H_2 Receptor Antagonists						
Cimetidine (*generics*)	200 mg 300 mg 400 mg 600 mg 800 mg	Tablet	0.3284 0.0860 0.1350 0.1702 0.2530	800 mg twice daily 400 mg four times daily	0.51 to 0.54	184.69 to 197.10
Ranitidine hydrochloride (*generics*)	150 mg 300 mg 15 mg/mL 50 mg/2mL	Tablet, Solution	0.1800 0.3600 0.1480 2.8410	150 mg twice daily	0.36	131.40

Drug or Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Famotidine (*generics*)	20 mg 40 mg	Tablet	0.2658 0.4834	20 mg once daily 20 mg twice daily (or 40 mg daily)	0.27 to 0.53	97.02 to 194.03
Nizatidine (*generics*)	150 mg 300 mg	Capsule	0.2098 0.3802	150 mg daily	0.21	76.58
Leukotriene Receptor Antagonists						
Montelukast (*generics*)	4 mg 5 mg 10 mg	Tablet	0.3646 0.5565[h] 0.8195[h]	10 mg daily	0.82	299.12
Immunosuppressants						
Cyclosporine (*generics*)	10 mg 25 mg 50 mg 100 mg 100 mg/mL	Capsule, Solution	0.6238 0.9952 1.9400 3.8815 3.7707	3 mg to 5 mg/kg daily	10.33 to 16.52[i,j]	3,769.28 to 6,030.24[i,j]
Corticosteroids						
Prednisone (*generics*)	5 mg 50 mg	Tablet	0.0220 0.1735	20 to 50 mg daily[k]	0.09 to 0.17	32.12 to 63.33
Antidepressants						
Doxepin hydrochloride (*generics*)	10 mg 25 mg 50 mg 75 mg 100 mg 150 mg	Capsule	0.1889 0.2140 0.3971 0.3916 0.5160 0.7820	10 mg three times daily (higher doses may be used)	0.57	206.85
Antimalarials						
Hydroxychloroquine sulphate (*generics*)	200 mg	Tablet	0.2620	400 mg daily	0.52	191.26

All prices are from the Ontario Drug Benefit Formulary (accessed January 2015) unless otherwise indicated and do not include dispensing fees.

[a] Manufacturer-submitted price, obtained from the Ontario Drug Benefit Formulary.

[b] Assumes 13 doses per year.

[c] Nova Scotia Drug Benefit Formulary (accessed January 2015).[11]

[d] McKesson Canada wholesale price, includes markup (accessed January 2015).[12]

[e] Recommended as a second-line treatment in the international guidelines for the management of urticaria (2014)[13] and by the CADTH Common Drug Review clinical expert.

[f] Alberta Drug Benefit Formulary (accessed January 2015).[14]

[g] Recommended dose based on the international guidelines for the management of urticaria (2014)[13] and CADTH Common Drug Review clinical expert feedback.

[h] Saskatchewan Drug Benefit Formulary (accessed January 2015).[15]

[i] Average weight (84 kg) obtained from baseline characteristics of patients in the manufacturer-submitted RCT Q4883g Clinical Study Report.[7]

[j] For 3 mg/kg dose: use of 2 × 100 mg capsules + 1 × 50 mg capsule + 1 × 10 mg capsule; for 5 mg/kg dose: 4 × 100 mg capsule + 1 × 25 mg capsule; assumes wastage.

[k] As identified by the clinical expert, treatment with corticosteroids is recommended for only a short duration.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS OMALIZUMAB RELATIVE TO STANDARD OF CARE?

Omalizumab Versus Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$52,513 per QALY (manufacturer's scenario 1) $57,193 per QALY (manufacturer's scenario 2) $81,210 per QALY (manufacturer's scenario 3) $120,009 per QALY (CDR best estimate; based on scenario 1 and 10-year time horizon)					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments *Reviewer to provide comments if checking "no"*	The methods detailed in the PE report were not adequately described for CDR to validate (e.g., around the calculation of the utility weights, response and dropout data) — additional information was needed from the manufacturer.[16] It should also be noted that there was a lack of transparency regarding some of the values used in the model given hard-coding of the data. This included being unable to change the risk of relapse and treatment waning, spontaneous remission rates, etc.		
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		

CDR = CADTH Common Drug Review; PE = pharmacoeconomic.

TABLE 6: AUTHOR INFORMATION

Authors	Affiliations
Amy Lee	Optum
Debbie Becker	Optum

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Summaries of the National Institute for Health and Care Excellence (NICE) draft recommendations and the Scottish Medicines Consortium (SMC) recommendations are provided in Table 4.

TABLE 7: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE[a]	SMC
Drug	Omalizumab 150 mg solution for subcutaneous injection in a prefilled syringe	Omalizumab 150 mg solution for injection (Xolair)
Price	£3,074 per 24 weeks (£256.15 per syringe, thus £512.30 per dose) excluding tax	£3,074 per 24 weeks (£512 per 4 weeks)
Treatment	300 mg by subcutaneous injection once every four weeks, for up to 24 weeks	
Comparator	No further pharmacological treatment (i.e., H_1 antihistamines (up to four times the licensed dose), with either H_2 antihistamines or LTRAs, or all three drugs together	Background medication (up to four times licensed dose H_1 antihistamines ± LTRA ± H_2 antihistamines)
Population Modelled	Add-on therapy for treating chronic spontaneous urticaria in adults and young people aged 12 years and over	Add-on therapy for chronic spontaneous urticaria in adult and adolescent (≥ 12 years) patients with inadequate response to H_1 antihistamine
Time Horizon	10 years	10 years
Cycle Length	4 weeks	4 weeks
Discount Rate	3.5% per annum on both costs and outcomes	Not specified
Type of Model	Cost-utility analysis (Markov model with five health states: urticaria-free and well-controlled, mild, moderate, and severe urticaria; patients can also relapse or die). Patients enter model in severe or moderate health state.	Cost-utility analysis (Markov model with five health states: urticaria-free and well-controlled, mild, moderate and severe urticaria; patients can also spontaneously remit, relapse, die, or drop out). Patients enter model in severe or moderate health state.
Key Outcomes	UAS7 score at defined time points based on clinical trials. Relapse and dropout rates based on clinical trials. Spontaneous remission based on published literature. Primary analysis based on GLACIAL. Utility values based on pooled EQ-5D from GLACIAL, ASTERIA I, and ASTERIA II. Disutility for AEs from published literature.	Model health states are based on UAS7 scores. No other clinical outcomes reported by SMC.
Results	*Base case:* £19,632 per QALY gained (including Patient Access Scheme). SAs that were presented indicated that ICER most sensitive to omalizumab acquisition cost, cumulative relapse risk for urticaria-free patients, utilities, and discount rate.	*Base case:* £19,632 per QALY (including Patient Access Scheme, which offers a confidential discount). *PSA:* 52% ICER < £20,000 and 100% ICUR < £30,000 (including Patient Access Scheme).

	NICE[a]	SMC
	PSA: 49.6% ICER < £20,000 and 100% ICER < £30,000. Various scenario analyses where omalizumab dominated comparator when indirect costs were taken into account. ICERs for rest of scenario analyses ranged from £15,665 to £24,301.	Results sensitive to omalizumab acquisition cost, cumulative relapse for patients who are urticaria-free after initial treatment, utility values, response to re-treatment, background medication costs, and adopting treatment period of 12 weeks.
Sources of Uncertainty	*Model structure:* This did not permit comparison with other potential comparators (e.g., cyclosporine). *Missing data:* Using LOCF method in the model may have overestimated the proportion of patients who responded to omalizumab. *Response:* The definition for response (patients having UAS7 of 6 or lower) has no empirical basis and could miss clinically significant responses. *Patient-level data:* No details provided on quality assurance; minor differences seen between data used in the model and the published data. *Stopping rule:* Including a stopping rule for "non-responders" at week 16 was not clinically realistic. *Remission rates:* Although data were correctly extracted from the text of Nebiolo et al. 2009 study for estimating remission rates, the paper reported discrepant values between the text and the published KM curves, which meant the approach to extrapolating the log-logistic function resulted in an extremely poor fit to the KM curves in the Nebiolo paper, thus overestimating remission up to around 24 months and underestimating remission over longer time periods. The extrapolated remission rates did not represent (were much lower than) the natural history of disease. *Relapse:* Revising the curve fitting to estimate the probability of relapse in patients who initially responded resulted in a slight increase in the ICER.	Omalizumab is likely to replace other non-comparator treatments used in clinical practice. Assuming 10 years of maintenance medication with no clinical benefit is not consistent with guidelines and clinical practice. Clinical study data reported at week 40 indicate UAS7 scores for the omalizumab group converged to the absolute levels observed for those on background treatment. Stopping medication may be difficult to achieve in practice, especially in responders at 24 weeks. There is limited evidence on the effectiveness of re-treatment with omalizumab, and the results are sensitive to the values assumed for this parameter. No rationale to support choice of sensitivity analyses is provided. Given the medicine does not modify disease and so the disease returns, some clinicians may prescribe for more than 24 weeks.

	NICE[a]	SMC
	Dropout and stopping rates: These could not be independently verified given the limited information provided. *All-cause mortality:* This was modelled assuming an equal proportion of men and women, which differs from the split in GLACIAL. *Utility estimates:* The utility estimates for health states were sourced from a directly relevant population, but noted utility decrements used for AEs were sourced from populations not relevant for this appraisal. Utility estimates were seen as not likely to reflect health states, especially for subsequent treatments. *DSA:* Approach to changes in DSAs not justified and did not cover all important parameters. *PSA:* It was unclear whether all important uncertainties were correctly captured in the PSA.	
Recommendation	Committee is minded not to recommend omalizumab within its marketing authorization. Further clarification and analyses are required.	Accepted for restricted use.
CDR Assessment	The economic evaluation submitted to CDR appears to be similar to the economic evaluations submitted to NICE and SMC. There appear to be some differences regarding the information included within the model (e.g., NICE and SMC include safety information whereas the submission to CDR does not; shorter time horizon was used [10 years versus 20 years]) although the base-case (first listed) analysis in all submissions appears to be based on the GLACIAL clinical trial. NICE and SMC have found a substantial number of limitations with the submitted models, several of which have been identified within the CDR review of the submitted model.	

AE = adverse event; CDR = CADTH Common Drug Review; DSA = deterministic sensitivity analysis; EQ-5D = EuroQol 5-Dimensions Questionnaire; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; KM = Kaplan-Meier; LOCF = last observation carried forward; LTRA = leukotriene receptor antagonist; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; SA = sensitivity analysis; SMC = Scottish Medicines Consortium; UAS7 = Urticaria Activity Score over 7 days.

[a] Appraisal consultation document; final consultation to be released April 2015.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis based on a decision analytic Markov model, where patients with chronic idiopathic urticaria (CIU) transition between five health states based on urticaria severity (defined by Urticaria Activity Score over seven days [UAS7] range) over a 20-year time horizon. The baseline distribution of patients, in addition to the mean age of patients (42 years), was based on that observed in three placebo-controlled phase 3 studies (GLACIAL, ASTERIA I, and ASTERIA II) at baseline.[5-7] The health states were defined as follows:

- severe urticaria: UAS7 score of 28 to 42 (70% of the cohort at baseline, applied to cycle 1)
- moderate urticaria: UAS7 score of 16 to 27 (30% of the cohort at baseline, applied to cycle 1)
- mild urticaria: UAS7 score of 7 to 15
- well-controlled urticaria: UAS7 score of 1 to 6
- urticaria-free: UAS7 score of 0, which is indicative of no symptoms of CIU and considered a full treatment response.

In the model, patients began in either the moderate or the severe health state. Patients were treated with omalizumab plus standard of care (SOC) or SOC alone every four weeks for 24 weeks. Following this, treatment with omalizumab was terminated (for all patients), but SOC was continued indefinitely. Patients considered "responders" at 24 weeks (defined by a UAS7 score ≤ 6, i.e., well-controlled urticaria or urticaria-free) remained in this same health state for the duration of the time horizon, unless they experienced either a spontaneous remission of symptoms (UAS7 score = 0) or a relapse (defined by a UAS7 score ≥ 16). It was assumed that patients who experienced a spontaneous remission of symptoms remained in the urticaria-free state until death. Patients who relapsed were eligible for re-treatment with omalizumab for another 24 weeks. It was assumed that patients who relapsed would have the same response profile as in the first course of treatment. That is, if patients finished in the "well-controlled" or "urticaria-free" health state after the first course of treatment, they would finish in this same health state after subsequent treatments.

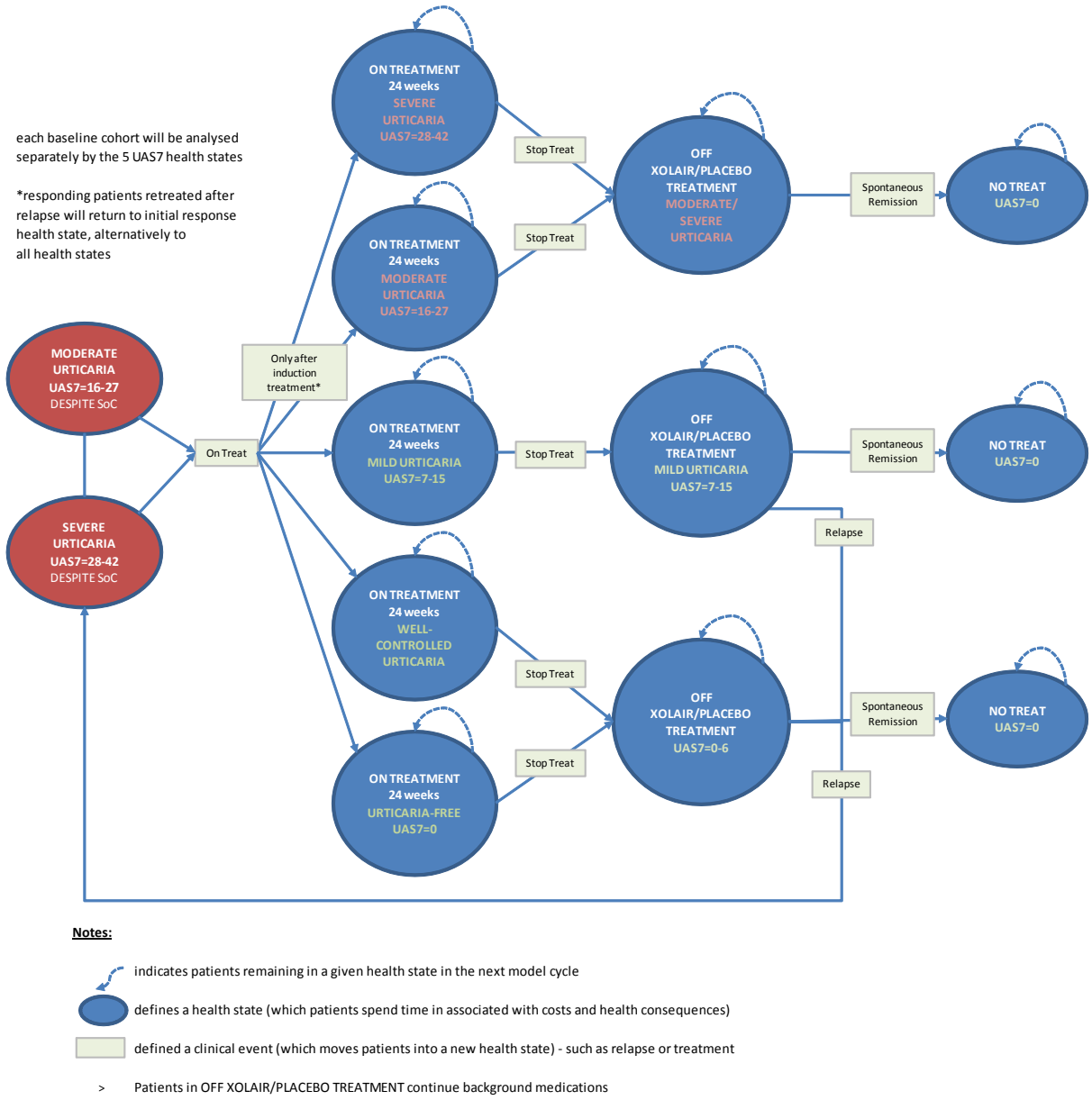
Alternatively, patients who did not respond to the first course of treatment with omalizumab (i.e., remained in the mild, moderate, or severe health state) were able to spontaneously remit only, and thus were not eligible for re-treatment.

The model also incorporated a dropout rate from treatment; this was applied at each four-week cycle. Upon dropping out, a patient moved from treatment with omalizumab plus SOC to SOC alone. All-cause mortality was also included in the model using annual rates based on life tables in Canada; no additional risk of mortality was assumed in patients with CIU.

The manufacturer considered three different treatment scenarios:

- Scenario 1 compared omalizumab 300 mg as an add-on therapy to SOC (defined as up to four times the standard H_1 antihistamine dose in combination with H_2 antagonists or leukotriene receptor antagonists [LTRAs], or both) with SOC alone. The manufacturer considered this scenario as the base case, as it was assumed to be the most representative of the Canadian setting.
- Scenarios 2 and 3 compared omalizumab 150 mg and 300 mg, respectively, as an add-on therapy to SOC (defined as standard dose of H_1 antihistamines) with SOC alone.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



SOC = standard of care; UAS7 = Urticaria Activity Score over 7 days.
Source: Manufacturer's pharmacoeconomic submission.[17]

The manufacturer stated that the model was validated; this included checking the model inputs and whether a given change in input parameters resulted in the expected change in the output, programming of formulas and macros, and screening of cell references.

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Natural History		
Commonly used H_1 antihistamines, H_2 antagonists and LTRAs (and approved daily doses)	H_1 antihistamines indicated for CIU. Other comparators were verified by two Canadian CIU experts.	The recommended dosages may be slightly higher for the H_2 antagonists cimetidine and famotidine upon verifying with the CDR clinical expert.
Definition of health states by UAS7 score	• Severe urticaria: UAS7 ≥ 28 is a criterion cited by clinicians as sometimes applied to select severe patients for current treatment with omalizumab. There was no identified data source for this range. • Moderate urticaria: UAS7 ≥ 16 is one of the inclusion criteria for the ASTERIA and GLACIAL trials.[5-7] • Mild urticaria: This range of UAS7 scores lies between a good response and moderate symptoms. There was no identified data source for this range. • Well-controlled urticaria: UAS7 ≤ 6 is the definition of a responder from the ASTERIA and GLACIAL trials.[5-7] • Urticaria-free: UAS7 score of 0 (full treatment response). There was no identified data source for this value.	Although the definition of "responder to treatment" (absolute UAS7 ≤ 6) was the response definition from the ASTERIA and GLACIAL trials, the MCID for the change in UAS7 is between 9.5 and 10.5.
Baseline characteristics (distribution of participants, mean age)	• Based on three phase 3 trials.[5-7] • All studies employed a multi-centre, double-blind, randomized, placebo-controlled, parallel-group design. ASTERIA I and ASTERIA II included 75 mg, 150 mg, and 300 mg doses of omalizumab administered every four weeks over 24 weeks and 12 weeks, respectively, versus placebo. Alternatively, the GLACIAL study included omalizumab at the 300 mg dose administered every four weeks over 24 weeks versus placebo. The ASTERIA I and GLACIAL studies both included a 16-week follow-up period after 24 weeks of treatment with omalizumab.	
Spontaneous remission (remain asymptomatic despite no treatment)	Taken from a study in CIU patients by van der Valk et al. 2002.[1] Regression analyses were conducted by the manufacturer to calculate remission rates for each four-week cycle in the model.	The rates reported in literature are generally higher. The CDR clinical expert also indicated that the rates would be higher in clinical practice, especially in year 1. It should be noted that the rates reported in the studies seemed to have been adapted by the manufacturer when conducting its regression analyses. Thus, it was not possible for CDR to validate model inputs.

Data Input	Description of Data Source	Comment
Proportion of patients using each of the SOC medication types and using each dose of the antihistamines (recommended dose up to four times the recommended dose)	Obtained from the ASTERIA I, ASTERIA II and GLACIAL patient-level baseline data[5-7]	
Efficacy		
Proportion of responders	• Defined by the proportion of patients achieving a response (UAS7 ≤ 6) at each assessment time point (every four weeks) in the clinical trial. • For scenario 1, patient-level data from the GLACIAL trial were used.[7] Data were stratified by the moderate and severe health states.[7] • For scenarios 2 and 3, patient-level data from ASTERIA I and ASTERIA II were pooled for weeks 4, 8, and 12 and ASTERIA I data were used for weeks 16, 20, and 24.[5,6]	The patient response data are derived from relatively small sample sizes.
Relapse rates	Relapse rates were obtained from the 16-week follow-up (week 24 to week 40) patient-level data in ASTERIA I and GLACIAL.[5,7] Rates were calculated by the proportion of patients who were responders at week 24 and met the relapse threshold (UAS7 score ≥ 16) at 40 weeks.	Lack of long-term data introduces substantial uncertainty (e.g., risk of relapse the same over the entire time horizon, no treatment waning considered).
Dropout rate	A dropout rate was applied to the omalizumab + SOC treatment group based on patient-level data (GLACIAL for scenario 1 and ASTERIA I for scenarios 2 and 3).[5-7] It was calculated based on baseline severity and the treatment group by subtracting the number of patients at 24 weeks from the number of patients at baseline. This was applied to each four-week cycle for a total of six model cycles.	The proportion of patients who dropped out was limited to those for whom UAS7 data at week 24 were available (i.e., not all patients).

Data Input	Description of Data Source	Comment
Utilities	**Base case:** Utility weights were determined by pooling patient-level data from all three key studies: ASTERIA I, ASTERIA II, and GLACIAL.[5-7] This included combining all treatment arms (placebo, 75 mg, 150 mg, and 300 mg) and all time points (baseline, 12 weeks, 28 weeks [ASTERIA II], and 40 weeks [ASTERIA I and GLACIAL]). Patient-level data were collected using the three-level EQ-5D questionnaire. **Sensitivity analysis:** Alternative utility values were tested using only Canadian patient data (n = 88, stratified by health states). These were obtained from the manufacturer's ASessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic URticaria PatiEnts (ASSURE) trial,[17] which is an ongoing multi-country retrospective chart review and patient survey of CIU patients.	There is no evidence to suggest utility weights for Canadian patients would differ from those determined from the international sample of patients in the three clinical trials. Further, the sample size used to determine the utility weights from the ASSURE trial are very small. Therefore, the utilities used in the base case are considered to be the most appropriate.
Resource use	The manufacturer stated that patients with moderate or severe urticaria are typically required to undergo routine physician visits (with a clinical immunologist or dermatologist), hospitalization or emergency room visits, and laboratory tests. These were identified by a retrospective chart review study of 50 patients by Delong et al. 2008.[18] For patients with mild or well-controlled urticaria, 1.5 physician visits per year were estimated. Patients in these states would not require hospitalization, emergency room visits, or laboratory testing. This was based on the clinical expert opinion of two Canadian CIU specialists. Note: Physician visits were not related to administration of omalizumab.	The costs associated with laboratory testing were significantly higher in patients with moderate urticaria versus those with severe urticaria. There was no appropriate explanation for this.
Mortality	All-cause mortality was included in the manufacturer's submitted model, based on the life tables for Canada.[19] The manufacturer stated that there was no additional risk of mortality due to CIU.	The proportion of males and females as seen in the clinical trials was not accurately captured in the model (in terms of mortality values).

Data Input	Description of Data Source	Comment
Costs		
Drugs (omalizumab and comparators)	• The cost of omalizumab in the 150 mg and 300 mg dose ($612 and $1,224, respectively) was obtained from the Ontario Drug Benefit Exceptional Access Program formulary (listed under another indication).[3] • The price for each of the H_1 antihistamines was obtained by the manufacturer from a local Ontario pharmacy.[17] If there was generic product available, this price was used instead of the price for the brand name. An average daily cost for antihistamines was calculated for use in the economic model. • The price for each of the H_2 antagonists was obtained from the Ontario Drug Benefit Formulary/Comparative Drug Index.[17] An average daily a cost for H_2 antagonists was also calculated for use in the economic model. • The price of LTRAs was obtained by the manufacturer from a local Ontario pharmacy.[17]	The drug costs used in the model may be different if there are alternate pricing arrangements in place, which may affect the overall costs used in the model. Standard doses of H_1 antihistamines are typically not reimbursed by public drug plans in Canada (with the exception of a few). Further, the costs of LTRAs should not have been included as they are not reimbursed by public drug plans in Canada (only a restricted benefit, for another indication) and are paid for by patients.
Administration	The manufacturer indicated that the costs associated with administration of omalizumab will be [redacted]. This includes any costs associated with omalizumab injection, including nurse and physician time.[17]	In the case where this is not feasible, the overall costs used in the model would increase substantially. This parameter should have been tested in the manufacturer's sensitivity analysis.
Health state	Costs associated with both the moderate and severe urticaria health states were obtained from the study by Delong et al. 2008,[18] as there were no Canadian data available. Direct annual costs reported in this study were converted to Canadian dollars and inflated to 2014 using the Consumer Price Index for health and personal care.[20] For patients in the mild or well-controlled urticaria states, the cost per physician visit (e.g., partial assessment for a clinical immunologist and a dermatologist) was obtained from the Ontario Schedule of Benefits.[21]	
Indirect costs	The manufacturer included any productivity losses due to CIU as part of its sensitivity analysis. Data from the ASSURE study and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI-SHP) was employed to determine the overall productivity and work loss associated with severe, moderate, mild, or well controlled urticaria.[17]	

ASSURE = ASessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic URticaria PatiEnts; CDR = CADTH Common Drug Review; CIU = chronic idiopathic urticaria; EQ-5D = EuroQol 5-Dimensions Questionnaire; LTRA = leukotriene receptor antagonist; MCID = minimal clinically important difference; UAS7 = Urticaria Activity Score over 7 days.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Mild patients would not be re-treated upon relapse after the first course of treatment with omalizumab.	As identified by the CDR clinical expert, patients who are in the mild health state after the first course of treatment would likely be re-treated with omalizumab upon relapse. This should have been included in the manufacturer's base-case scenario.
The risk for relapse starts immediately after the first course of treatment, and the same risk is maintained the entire time horizon.	Lack of long-term data makes this very difficult to predict and introduces much uncertainty into the model.
Patients who are re-treated would have the same response as the first time they were treated, and efficacy will be maintained over 20 years.	There are no long-term data to suggest that the magnitude of the effectiveness of treatment would be the same every time a patient experiences a relapse and is re-treated with omalizumab. The manufacturer would have ideally considered treatment waning, where a patient would not respond in the same manner as the first course of treatment and could end up in a worse health state (moderate or severe).
Proportion of females to males used for all-cause mortality values is equal.	The manufacturer assumed that the proportion of females to males is equal. However, in all three key clinical trials, the proportion of females is substantially higher (75%). Although all-cause mortality is not a key driver in the economic model, it was noted as an incorrect assumption.
The sample size from the ASTERIA I and ASTERIA II and GLACIAL clinical trials for each treatment group is large enough to inform the economic model.	Although the trials may have been powered to detect any differences, the sample size decreased further after the manufacturer stratified the patients by moderate and severe urticaria. Even a minor movement of patients in the model may have had a substantial impact on the overall results.
Patients who spontaneously remit remain in this state until death.	Valid assumption.

CDR = CADTH Common Drug Review.

Manufacturer's Results

The manufacturer reported total drug and non-drug related costs associated with each of the health states for both omalizumab and SOC in all three scenarios, as seen in Table 10. In the manufacturer's primary scenario (scenario 1), the total cost associated with omalizumab was $2,417,589, while the total cost associated with SOC was $472,550.

TABLE 10: SUMMARY OF COSTS BY HEALTH STATE (DRUG AND NON-DRUG RELATED)

	Scenario 1		Scenario 2		Scenario 3	
Cost Category	**Omalizumab 300 mg + SOC**	**SOC[a]**	**Omalizumab 150 mg + SOC**	**SOC[b]**	**Omalizumab 300 mg + SOC**	**SOC[b]**
Urticaria-free	$1,070,817	$0	$194,816	$0	$1,088,668	$0
Well-controlled urticaria	$619,466	$3,339	$225,380	$3,833	$572,472	$3,833
Mild urticaria	$384,146	$11,222	$204,587	$14,922	$530,713	$14,922
Moderate urticaria	$148,486	$100,129	$175,626	$117,709	$119,474	$117,709
Severe urticaria	$194,674	$357,860	$152,131	$195,616	$121,749	$195,616
Total	**$2,417,589**	**$472,550**	**$952,539**	**$332,081**	**$2,433,075**	**$332,081**

LTRA = leukotriene receptor antagonist; SOC = standard of care.
[a] SOC = H_1 antihistamine up to four times the recommended dosing combined with H_2 antagonists or LTRAs, or both.
[b] SOC = recommended H_1 antihistamine dosing.
Source: Adapted from manufacturer's pharmacoeconomic submission.[17]

Additionally, the manufacturer reported total drug and direct non-drug associated costs by scenario, as seen in Table 11. The drug costs included the costs associated with omalizumab and any of the background SOC regimens, which was dependent on the scenario. Direct non-drug related costs included drug administration, physician visits, emergency department visits or hospitalizations, and costs associated with laboratory tests. In scenario 1, the total cost associated with omalizumab was $3,068,469 while the total cost associated with SOC was $1,147,980.

TABLE 11: DISAGGREGATED DISCOUNTED COST OUTCOMES

	Scenario 1		Scenario 2		Scenario 3	
Cost Category	**Omalizumab 300 mg + SOC**	**SOC[a]**	**Omalizumab 150 mg + SOC**	**SOC[b]**	**Omalizumab 300 mg + SOC**	**SOC[b]**
Drug cost	$2,877,458	$675,011	$903,719	$182,388	$2,489,143	$182,388
Direct non-drug costs	$191,011	$472,969	$235,695	$333,494	$134,394	$333,494
Total	$3,068,469	$1,147,980	$1,139,414	$515,882	$2,623,537	$515,882

SOC = standard of care.
[a] SOC = H_1 antihistamine up to four times the recommended dosing combined with H_2 antagonists or LTRAs, or both.
[b] SOC = recommended H_1 antihistamine dosing.
Source: Adapted from manufacturer's pharmacoeconomic submission.[17] It should be noted that several costs in the pharmacoeconomic report were not in line with the costs in the model.

In summary, in scenario 1 the manufacturer reported the incremental cost and quality-adjusted life-years (QALYs) gained associated with treatment with omalizumab 300 mg plus SOC to be $1,920,489 and 36.60, respectively, compared with SOC alone. Treatment with omalizumab 300 mg plus SOC would also result in an incremental 0.10 life-years gained. Thus, the incremental cost-effectiveness ratio (ICUR) was calculated to be approximately $52,513 (Table 12).

Further, under scenarios 2 and 3, the manufacturer calculated the ICURs to be $57,193 and $81,210, respectively.

TABLE 12: SUMMARY OF THE MANUFACTURER'S BASE CASE

	Total			Incremental			ICUR	ICER
	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years		
Scenario 1								
Omalizumab 300 mg + SOC	$3,068,469	1,099.6	1,282.6	$1,920,489	36.60	0.10	$52,513	$19,204,890
SOC[a]	$1,147,980-	1063.0	1,282.5					
Scenario 2								
Omalizumab 150 mg + SOC	$1,139,414	1,089.1	1,282.6	$623,532	10.89	0.10	$57,193	$6,235,320
SOC[b]	$515,882	1,078.2	1,282.5					
Scenario 3								
Omalizumab 300 mg + SOC	$2,623,538	1,104.2	1,282.5	$2,107,656	26.00	0.00	$81,210	–
SOC[b]	$515,882	1,078.2	1,282.5					

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.
[a] SOC = H_1 antihistamine up to four times the recommended dosing combined with H_2 antagonists or LTRAs, or both.
[b] SOC = recommended H_1 antihistamine dosing.
Source: Adapted from manufacturers pharmacoeconomic submission.[17] It should be noted that several costs in the pharmacoeconomic report were not in line with the costs in the model.

Summary of Manufacturer's Sensitivity Analysis

Uncertainty around the parameters chosen for the base-case analysis was addressed by the manufacturer using a one-way deterministic sensitivity analysis and a Monte Carlo simulation probabilistic sensitivity analysis, with 1,000 iterations. The manufacturer illustrated the cost-effectiveness on a plane, in addition to providing cost-effectiveness acceptability curves at various willingness-to-pay thresholds. Sensitivity analyses were conducted separately for scenario 1 and for scenarios 2 and 3 (together).

Deterministic Sensitivity Analysis

The parameters varied individually in each of the scenarios by the manufacturer included:

- discount rates for costs and QALYS (0%, 3%)
- time horizon (10 years, lifetime)
- perspective (societal)
- natural remission rates (use of other data sources)
- re-treatment of mild patients
- relapse rates (± 20%)
- population (only angioedema population)
- utility weights (use of other data source)
- response profile (± 20%)
- dropout rates (± 20%)
- direct health care costs (± 20%).

In all scenarios, the following parameters had the greatest impact on the ICUR (± 25%): time horizon, perspective, natural remission rate, and utility weights. When these parameters were varied

individually, the ICUR ranged from $24,967 to $67,083 for scenario 1. For scenarios 2 and 3, the ICUR ranged from $29,535 to $80,625 and from $42,680 to $102,737, respectively.

Probabilistic Sensitivity Analysis

The variables considered in the probabilistic sensitivity analysis included efficacy data, transition probabilities, utility weights, costs, maximum price achievable for a given incremental cost-effectiveness ratio threshold or willingness to pay as an additional functionality to calculate maximum value-based prices, relapse rates, rate of spontaneous remission, resource utilization, and annual dropout rate. Following 1,000 iterations, the ICUR was calculated to be $57,672 for scenario 1. In scenarios 2 and 3, the ICUR was calculated to be $57,192 and $89,777, respectively.

At a willingness-to-pay threshold of $50,000, omalizumab 300 mg plus SOC had a 31.0% probability of being cost-effective when compared with SOC alone (scenario 1). In scenarios 2 and 3, at a willingness-to-pay threshold of $50,000, omalizumab plus SOC had 32.5% and 1.6% probability, respectively, of being cost-effective when compared with SOC alone.

CADTH Common Drug Review Reanalysis

A CADTH Common Drug Review (CDR) multi-way analysis was conducted considering the following:

- Shortening of the time horizon to 10 years and a more conservative approach of 40 weeks (duration of GLACIAL and ASTERIA I trials, including the follow-up time period)
- Treatment response (UAS7 ≤ 6) upon relapse (UAS7 ≥ 16) based on initial response probabilities from the trial data instead of assuming that patients would have the exact same response as initial treatment
- Higher spontaneous remission rates using the study by Toubi et al. (2004)[8] (the remission rates used could not be altered due to hard-coding of the data in the economic model; thus, CDR was able to use only the alternative values that the manufacturer had provided)
- Re-treatment of patients in the mild health state (UAS7 7 to 16) who relapsed after the first course of treatment with omalizumab
- Cost of LTRAs equated to $0.00 (applied only to multi-way analysis with scenario 1, as LTRAs were included as part of the SOC definition in only this scenario)
- Higher proportion of females (75%) to males (25%) for the all-cause mortality values.

CDR also calculated the ICUR considering these limitations and patient stratification by health state at baseline (e.g., moderate or severe).

Under scenario 1, using data from the GLACIAL clinical trial, a multi-way analysis considering these limitations resulted in an ICUR for omalizumab 300 mg plus SOC versus SOC alone ranging from $120,009 to $185,932 per QALY based on a 10-year or 40-week time horizon, respectively. Upon stratifying by health state considering these limitations (and a 10-year time horizon), the ICUR ranges from $88,480 per QALY for the severe health state to $419,033 per QALY for the moderate health state.

Under scenario 3, using ASTERIA I and ASTERIA II pooled data for weeks 4, 8, and 12 and ASTERIA I data for weeks 16, 20, and 24, a multi-way analysis considering these limitations resulted in an ICUR for omalizumab 300 mg plus SOC versus SOC alone ranging from $137,192 to $184,105 per QALY based on a 10-year or 40-week time horizon, respectively. Upon stratifying by health state considering these limitations (and a 10-year time horizon), the ICUR was $79,192 per QALY for the severe health state; for the moderate health state, omalizumab 300 mg plus SOC was dominated by SOC.

Results of each CDR reanalysis and multi-way analysis are reported in Table 13. These were conducted under scenario 1 (using GLACIAL data) and scenario 3 (using ASTERIA I and ASTERIA II pooled data).

TABLE 13: CADTH COMMON DRUG REVIEW REANALYSIS INCREMENTAL COST-UTILITY RATIOS FOR OMALIZUMAB VERSUS STANDARD OF CARE

		Scenario 1		Scenario 3	
		ICUR (GLACIAL[5] Data Only)	ICUR[a] From Multi-Way Analysis (10-Year Time Horizon)	ICUR (ASTERIA I and ASTERIA II[6,7] Data[b])	ICUR[a] From Multi-Way Analysis (10-Year Time Horizon)
Manufacturer's base-case ICUR		**$52,513**		**$81,210**	
Time horizon	10 years	$65,495	$120,009	$100,639	$137,192
	40 weeks	$173,992		$202,064	
Initial response probabilities applied to patients who experience a relapse		$78,854		$95,434	
Spontaneous remission rates[c]	Beltrani 2002[10]	$57,225		$88,789	
	Toubi et al. 2004[8]	$67,083		$102,737	
Re-treatment of mild patients (after first course of treatment) who experience a relapse		$94,686		$127,576	
Cost of LTRA set to $0		$52,986		N/A[d]	
Proportion of males to females for the all-cause mortality values (75% females, 25% males)		$52,474		$81,130	
Stratification by health state	100% severe	$40,088	$88,480	$60,588	$79,192
	100% moderate	$114,923	$419,033	$246,087	Dominated
Cost of H_1 antihistamine = $0		$52,840	Not included[e]	$81,170	Not included[e]

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LTRA = leukotriene receptor antagonist.
[a] Cumulative ICUR (multi-way analysis) calculated based on spontaneous remission rates from Toubi et. al 2004.[8]
[b] Data were pooled for weeks 4, 8, and 12. Only ASTERIA I data were used for the other weeks.
[c] Based on manufacturer's provided rates within the economic model, as CDR could not verify the regression performed by the manufacturer on original rates.
[d] LTRAs were not included in the definition of standard of care in the ASTERIA trials.
[e] Some public drugs plan in Canada do cover the cost of H_1 antihistamines; thus, these costs were not included in the multi-way analysis.

Based on the CDR multi-way analysis, for all scenarios the ICUR for omalizumab 300 mg plus SOC versus SOC alone is greater than $120,000 per QALY. The stratified analysis suggests that the ICUR is higher if 100% of patients are in the moderate health state as compared with the severe health state.

REFERENCES

1. van der Valk PG, Moret G, Kiemeney LA. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. Br J Dermatol. 2002 Jan;146(1):110-3.
2. [PR]Xolair® (omalizumab): sterile powder for reconstitution 150mg vial [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Aug 26.
3. Ontario Ministry of Health and Long-Term Care [Internet]. Toronto (ON): Queen's Printer for Ontario. Formulary: Exceptional Access Program (EAP); 2015 [cited 2015 Feb 4]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx
4. Common Drug Review. Omalizumab (Xolair® - Novartis Pharmaceuticals Canada Inc.). Indication: adults and adolescents (> 12 years of age) with moderate to severe persistent asthma. [Internet]. Ottawa (ON): Canadian Coordinating Office for Health Technology Assessment; 2006. (CEDAC final recommendation). [cited 2015 Feb 4]. Available from: www.cadth.ca/media/cdr/complete/cdr_complete_Xolair_March7-06.pdf
5. Final clinical study report: 1054397 (Protocol Q4881g). A phase III, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of Xolair® (omalizumab) in patients with chronic idiopathic urticaria (CIU) who remain symptomatic despite antihistamine treatment (H1) [**CONFIDENTIAL** internal manufacturer's report]. San Francisco (CA): Genentech Inc.; 2013.
6. Final clinical study report: 1053093 (Protocol Q4882g). A phase III, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy, response duration and safety of Xolair® (omalizumab) in patients with chronic idiopathic urticaria (CIU) who remain symptomatic despite antihistamine treatment (H1) [**CONFIDENTIAL** internal manufacturer's report]. San Francisco (CA): Genentech Inc.; 2013.
7. Final clinical study report: 1054065 (Protocol Q4883g). A phase III, multicenter, randomized, double-blind, placebo-controlled safety study of Xolair (omalizumab) in patients with chronic idiopathic urticaria (CIU) who remain symptomatic despite treatment with H1 antihistamines, H2 blockers, and/or leukotriene receptor antagonists [**CONFIDENTIAL** internal manufacturer's report]. San Francisco (CA): Genentech Inc.; 2013.
8. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. Allergy. 2004 Aug;59(8):869-73.
9. Sussman G, Hébert J, Barron C, Bian J, Caron-Guay RM, Laflamme S, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. Ann Allergy Asthma Immunol. 2014 Feb;112(2):170-4.
10. Beltrani VS. An overview of chronic urticaria. Clin Rev Allergy Immunol. 2002 Oct;23(2):147-69.
11. Nova Scotia Formulary [Internet]. Halifax (NS): Nova Scotia Department of Health; 2015 Jan. [cited 2015 Feb 4]. Available from: http://novascotia.ca/dhw/pharmacare/documents/formulary.pdf
12. McKesson Pharmaclick [Internet]. Saint-Laurent (QC): McKesson Canada. 2015 [cited 2015 Feb 4]. Available from: https://www.mckesson.ca/ Subscription required.
13. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014 Jul;69(7):868-87.

14. Interactive drug benefit list [Internet]. Edmonton (AB): Alberta Health; 2015 [cited 2015 Feb 4]. Available from: https://idbl.ab.bluecross.ca/idbl/load.do

15. Saskatchewan online formulary database [Internet]. Regina (SK): Government of Saskatchewan, Drug Plan and Extended Benefits Branch; 2015 [cited 2015 Feb 4]. Available from: http://formulary.drugplan.health.gov.sk.ca/

16. Novartis response to 2015 Jan 20th CDR request for additional information regarding the Xolair CDR review: technical report detailing the methods and results of the mixed-effect model used to calculate the EQ-5D based utility weights used in the model for the base case analysis [**CONFIDENTIAL** additional manufacturer's information]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2015 Jan 23.

17. Pharmacoeconomic evaluation. In: CDR submission: [PR]Xolair® (omalizumab), 150mg sterile powder for reconstitution. Company: Novartis Pharmaceuticals Canada Inc [**CONFIDENTIAL** manufacturer's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2014.

18. Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. Arch Dermatol. 2008 Jan;144(1):35-9.

19. Statistics Canada [Internet]. Ottawa (ON): Government of Canada; 2015. Table 2: Age-specific mortality rates per 1,000 population by age group and sex, Canada, provinces and territories, 2009; 2013 [cited 2015 Jan 29]. Available from: http://www.statcan.gc.ca/pub/91-209-x/2013001/article/11785/tbl/tbl02-eng.htm

20. Statistics Canada [Internet]. Ottawa (ON): Government of Canada; 2015. Consumer Price Index, health and personal care, by province (Canada); 2015 Jan 23 [cited 2015 Jan 29]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm

21. Ontario Ministry of Health and Long-Term Care [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015. Schedule of benefits for physician services under the Health Insurance Act; 2014 [cited 2015 Jan 29]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html