Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**omalizumab**
Brand Name	Xolair®
Dosage Form	Sterile powder for reconstitution 150 mg vial
Manufacturer	Novartis Pharmaceuticals Canada Inc.
Submission Type	**Resubmission**
Use Reviewed	For the treatment of adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.
Common Drug Review (CDR)	Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details: www.cadth.ca/sites/default/files/cdr/complete/SR0457_complete_Xolair_Resub-May_19_16.pdf
Drug Benefit Council (DBC)	The DBC met on June 16, 2016 and considered various inputs including: the final reviews completed by the CDR, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC); Patient Input Questionnaire responses from three patients and one Patient Group; CDR Patient Group input; Clinical Practice Reviews from one specialist; and a Budget Impact Assessment.
Drug Coverage Decision	**Non-Benefit**
Date	April 28, 2020
Reasons	**Drug coverage decision is consistent with the DBC recommendation.** • The clinical evidence for the drug was inconsistent with respect to efficacy and quality of life. • Based on economic considerations and the submitted product price, the drug was not cost-effective and did not offer optimal value for money. • The BC Ministry of Health did not participate in the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations with Novartis Pharmaceuticals Canada Inc. for the drug; however, negotiations between the pCPA and Novartis Pharmaceuticals Canada Inc. concluded without reaching an agreement.
Other Information	None

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Common Drug Review (CDR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

OMALIZUMAB — RESUBMISSION
(Xolair — Novartis Pharmaceuticals Canada Inc.)
Indication: Asthma

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that omalizumab be reimbursed for adults and adolescents (12 years of age and older) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen, if the following clinical criterion and conditions are met:

Criterion:
Inability to use, intolerance to, or inadequate response to an inhaled corticosteroid (ICS) long-acting beta-agonist (LABA) combination, and at least one other reimbursed alternative asthma treatment.

Conditions:
1. Patients should be managed by a physician with experience in treating asthma.
2. At a reduced price.

Reasons for the Recommendation:
1. Evidence from six clinical trials that comprise new evidence available since the previous review of omalizumab for the same indication suggested that omalizumab reduces the rates of hospitalization, emergency room [ER] visits, and medical doctor (MD) visits in patients who were inadequately controlled by ICS or an ICS plus a LABA with or without other asthma medications, although the evidence was inconsistent across studies and the magnitude of the effect was uncertain. In addition, the same studies provided evidence that omalizumab might have some benefit on important clinical outcomes such as reducing asthma exacerbations and some important asthma-related outcomes.
2. The cost of omalizumab is considerably higher than all other drugs reimbursed for the treatment of asthma. The available economic evidence was severely limited by the absence of an updated cost-effectiveness analysis. Therefore, the international cost-utility ratio for omalizumab is highly uncertain; however, it could be substantially higher than what would normally be considered acceptable.

Of Note:

1. Inability to use, intolerance to, or inadequate response to an ICS plus LABA and at least one alternative reimbursed treatment should be aligned with existing drug plan reimbursement criteria.
2. Other reimbursed alternative asthma treatments that could be considered include leukotriene receptor antagonists (LTRA) and tiotropium.
3. There is considerable uncertainty regarding the cost-effectiveness of omalizumab for the treatment of moderate-to-severe persistent asthma in Canada. A reduced price from the one submitted by the manufacturer will improve the cost-effectiveness of omalizumab, but in the absence of an updated economic analysis, no guidance can be provided regarding the magnitude of price reduction required.

Background:

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody to immunoglobulin E (IgE). Omalizumab has a Health Canada indication for adults and adolescents (≥ 12 years of age) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs. It is administered by subcutaneous injection, given once every 2 or 4 weeks, depending on the dose. The dose is based both on body weight and IgE levels (IU/mL), targeting 0.016 mg/kg IgE IU/mL.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials and pivotal studies of omalizumab in the treatment of allergic asthma and information submitted by patient groups about outcomes and issues that are important to individuals living with asthma. As the manufacturer declined to provide updated pharmacoeconomic information for this review, CDEC considered a review of the pharmacoeconomic report from the April 2005 submission as well as a review of published economic studies of omalizumab for the treatment of patients with moderate-to-severe persistent asthma in Canada.

Patient Input Information

Three patient groups (the Asthma Society of Canada/National Asthma Patient Alliance (ASC), the British Columbia Lung Association, and the Ontario Lung Association) responded to the CDR call for patient input. Information in their submissions was obtained through research review, best practice guidelines, direct patient involvement, certified respiratory educators, and from five online surveys. The following key issues were raised by the patient groups.

Asthma can negatively affect many aspects of patients' lives. Common symptoms and challenges include wheezing, shortness of breath and chest tightness and/or coughs, limitation of routine activities, fatigue, difficulty fighting infections, difficulty managing weight loss, and impact on family life. About 35% patients with severe asthma feel their symptoms are not well controlled, with particular concern regarding the effects of exacerbations. Patients would like more asthma treatment options along with more affordable and timely treatment. In addition, since many patients are high frequency users of medications, they felt that the frequency of medication, better and more options, the convenience, and the affordability were all important aspects associated with treatment. Patients expressed a desire for more asthma treatments,

including Xolair, to be reimbursed by public drug plans to allow for increased access, especially for low income families.

Clinical Trials

The CDR systematic review included six new randomized, placebo controlled trials (RCTs), specifically four double-blind (DB) RCTs [EXTRA (N = 850; 48 weeks), CIGE025AUS23, referred to hereafter as AUS23 (N = 271, 24 weeks), ICAC-08 (N = 419, 60 weeks), and PROSE (N = 513, four months)] and two open-label studies [CIGE025A2425, referred to as A2425 hereafter (N = 404, 32 weeks) and the Rubin study (N = 116, 20 weeks)]. Two of the four DB RCTs (ICAC-08 and PROSE) were conducted mainly in children (age 6 to 20). All patients had a diagnosis of persistent moderate-to-severe allergic asthma inadequately controlled at least by the treatment of a high dose or maximal tolerable dose of ICS or an ICS plus a LABA with or without other medications such as LTRAs.

Outcomes

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

- hospitalizations, ER visits, MD visits due to asthma exacerbation
- acute asthma exacerbations
- use of oral corticosteroids (OCSs)
- quality of life
- days of missed school or work
- change in pulmonary function (FEV_1)
- symptom reduction
- change in the number of asthma symptom-free days or nights
- incidence of nocturnal awakenings
- reduction of the use of ICS
- reduction of the use of rescue medications
- mortality.

Efficacy

New clinical evidence available since the previous CDR review of Xolair for asthma comprised six new RCTs. All patients had a diagnosis of persistent moderate-to-severe allergic asthma inadequately controlled by a high dose or a maximal tolerable dose of ICS, ICS plus a LABA, or ICS plus a LABA with or without other medications such as LTRAs. Patients 12 to 75 years of age were included in four RCTs, while the other two studies included patients from 6 to 20 years old. "Inadequately controlled asthma" was not defined consistently across studies, but in general, to be classified as having inadequately controlled asthma, patients were required to have one or more night-time awakenings per week; daytime asthma symptoms requiring the use of rescue medication for two or more days per week; or at least one asthma exacerbation in the last year.

Patients were randomized to receive either add-on omalizumab (OMA), SC, 75 mg to 300 mg every 4 weeks or 225 mg to 375 mg every 2 weeks, or a placebo matched to the background asthma treatment in the double-blind trials or to the control group without additional add-on treatment in the open-label trials. The primary outcomes in the included studies were asthma exacerbations (in two studies), symptom control (in three studies), or quality of life (Asthma Quality of Life Questionnaire [AQLQ] in one study), all of which were outcomes of interest for

this review. Sample sizes ranged from 116 to 850 patients. Trial duration ranged from 20 weeks to 60 weeks. Limitations of the included studies were the inclusion of patients < 12 year old in two studies, which could limit generalizability of findings to older patients; the potential for bias in favour of OMA for patient-reported outcomes in the two open-label studies; lack of adjustment for multiplicity when assessing secondary outcomes; and no statistical comparisons between OMA and control/placebo in many cases.

Hospitalizations

Hospitalizations due to exacerbation was reported for three studies. In the EXTRA study, a smaller proportion of patients experienced hospitalization due to exacerbation in placebo-treated patients than those who received OMA (4.0% in OMA versus 3.6% in placebo; *P* value, not reported). In study A2425, 6% fewer patients in the OMA group experienced hospitalization compared with the placebo group. Although there was no statistical test of significance available for this metric, the clinical expert consulted for this review believed this difference between treatment groups to be clinically relevant. In study ICAC-08, statistically significantly fewer patient in the OMA group experienced hospitalization due to exacerbation compared with the patients in placebo group (mean difference: –4.7%, 95% CI, –8.6 to –0.9, *P* = 0.02). The event rate for hospitalization per patient was low and similar in both OMA and placebo groups in the EXTRA study. In study A2425, the hospitalization rate in patients receiving OMA was reduced by 67% over 32 weeks compared with patients receiving placebo (rate ratio [RR], 0.33, 95% CI, 0.118 to 0.937, *P* =0.037).

ER visits

In the EXTRA study, the incidence of patients with ER visits due to asthma exacerbation was 3.4% fewer in OMA-treated patients compared with the placebo group (3.7% and 7.1% in OMA and placebo groups respectively) over 48 weeks. The ER visit rate per patient was reduced by 48% in OMA-treated patients compared with those who received placebo (RR: 0.52, 95% CI, 0.27 to 0.98, *P* value not reported). In study A2425, the ER visit rate was 60% lower in OMA-treated patients compared with patients who received placebo (RR, 0.40, 95% CI, 0.24 to 0.65, *P* <0.001).

MD visits

In the 48-week EXTRA study 15% of patients receiving OMA and 19% in placebo reported MD visits due to asthma exacerbation, a 4% reduction in OMA-treated patients (95% CI, not reported; *P* value, not reported). The MD visit rates per patient were 0.25 in OMA and 0.31 in placebo respectively, with the rate ratio of 0.77 (95% CI, 0.54 to 1.08). Although none of the included studies was powered to assess the statistical significance of differences between groups for the rates of hospitalization, ER visits, and MD visits due to exacerbation, these results suggest that adding OMA to ICS +LABA, with or without other asthma controllers, in patients inadequately controlled with these combination therapies is associated with a reduction in the rates of hospitalizations, ER visits, and MD visits due to exacerbation; although the precise magnitude of the effect of OMA on these outcomes in uncertain. Nevertheless, this evidence would appear to address one of the inadequacies identified in the previous CDR review of this drug.

Asthma exacerbation

Asthma exacerbations were reported for all included studies except study AUS23. However, none of the studies was powered to evaluate the differences in the proportion of patients with asthma exacerbation between treatment groups. The exacerbation rate (the number of events

per patient) was reported as the primary outcome in the EXTRA study and the PROSE study. Overall, the results showed that adding OMA to existing therapy (ICS, ICS + LABA, with or without other asthma controllers) reduced the proportion of patients with exacerbations by 5.4% to 18.5% compared with placebo, and this reduction was statistically significant in study ICAC-08 ($P < 0.001$) and the PROSE study, (relative risk: 0.45: 95% CI, 0.25 to 0.92). Similarly, the exacerbation rate was statistically lower in OMA-treated patients in the EXTRA study, (25% reduction; $P = 0.006$) and in study A2425 (43% reduction; $P <0.001$). This new evidence suggests that OMA reduces asthma exacerbations when added to the existing asthma therapy in patients with moderate-to-severe allergic asthma, which is consistent with the clinical findings reported in previous CDR review of this agent.

The mean difference between OMA and placebo for OCS use was a reduction of 6.7%, 7.5%, and 3.6% in OMA-treated patients in the EXTRA study, study AUS23, and study A2425, respectively. The statistical significance of differences between treatments for the reduction in the use of OCS was not reported.

Quality of life

Quality of life, assessed using the AQLQ, was reported for three studies. A statistically and clinically significant improvement was observed in OMA-treated patients compared with the placebo group in both open-label studies. However, this finding must be interpreted with caution because the potential for bias in favour of OMA due to the open-label design of this study. There was no clinical meaningful difference between OMA and placebo in the DB RCT of OMA, although none of the studies was powered to detect significant differences in AQLQ scores. The absence of a consistent and significant improvement in quality of life compared with placebo is consistent with the clinical findings reported in the previous CDR review of OMA in 2006.

Days of missed school or work

A small treatment effect of OMA on reduction of missed work or school time was observed in all four studies that reported this outcome. However, statistically significantly less time missed from work in OMA-treated patients was reported only in study ICAC-08 (mean difference: –0.09 days (95% CI, –0.18 to –0.01, $P = 0.038$).

Other outcomes

A larger improvement in forced expiratory volume in one second (FEV_1) was reported for OMA-treated patients versus placebo or controls in five RCTs. However, only one study reported a statistically and clinically significant improvement in FEV_1 (mean difference compared with the control group = 0.13 L; $P = 0.049$). These findings regarding the effect of OMA on FEV_1 are consistent with the evidence reported in the previous CDR review of this drug in 2006.

Harms

Overall, the safety profile of OMA in terms of adverse events (AEs), serious AEs, and withdrawal due to AEs was similar to placebo, although the incidence of AEs and the events of AEs were variable across the included studies. AEs of special interest, such as anaphylaxis, were rare, and no patients experienced Churg–Strauss syndrome or thromboembolic events in any of the six studies. The incidence of injection site reactions was similar in both treatment groups across studies. Therefore, the new clinical evidence did not reveal any new or notable safety concerns compared with those reported in the previous CDR review of this drug in 2006.

Cost and Cost-Effectiveness

The published price of omalizumab is a $612.00 per vial; the annual cost varies substantially based on the Health Canada approved treatment regimen, ranging from $7,956 for a patient receiving one vial per month to $47,736 for a patient receiving three vials every two weeks.

The manufacturer of omalizumab was invited to submit pharmacoeconomic information for this submission. In response, the pharmacoeconomic report from the April 2005 submission to CDR was provided (but not the underlying economic model). In the absence of an economic model, CDR considered the pharmacoeconomic report provided by the manufacturer, and also performed a literature review to identify published economic studies of omalizumab for the treatment of patients with moderate-to-severe persistent asthma in Canada. One study was identified that assessed the cost-effectiveness of omalizumab in addition to standard therapy (defined as high-dose ICS plus a LABA, plus additional controller medication if required) compared with standard therapy alone over a lifetime time horizon in patients with severe persistent asthma despite treatment with high-dose ICS plus LABA. While Canada was reported to be the reference country for this study and Canadian costing information was reportedly used, the clinical data were obtained from a subpopulation of a European study and a Swedish model was adapted for the analysis. The authors reported a 69.7% probability that omalizumab was cost-effective at a willingness-to-pay threshold of C$50,000 per quality-adjusted life-year (QALY). Due to the limitations of this analysis, and because it did not consider any of the clinical studies reviewed by CDR as part of the current submission, it was deemed to be of limited value in informing the cost-effectiveness of omalizumab.

The pharmacoeconomic report from 2005 submitted to CDR by the manufacturer reported an incremental cost per clinically significant exacerbation avoided of $53,000 from a 28-week trial-based evaluation, and $13,000 from a 1-year modelled evaluation. CDR considered this report to be of limited value since it is dated and could not be validated in the absence of the underlying model. CDR noted that the 2006 Canadian Expert Drug Advisory Committee (CEDAC) recommendation for omalizumab referred to a different manufacturer-submitted pharmacoeconomic analysis from the 2005 report provided by the manufacturer for the current submission; the reported international cost-effectiveness ratio in the recommendation was $63,000 per QALY (range: $35,000 to $219,000 per QALY). At the time, CEDAC noted that the rates of asthma exacerbation in the analysis potentially overstated the benefits of omalizumab, and that the true cost-effectiveness of omalizumab was “likely to be much less favourable.”

The CDR Clinical Review identified several new studies since the previous review that showed omalizumab may have benefits on key outcomes of interest such as ER visits or hospitalizations due to asthma exacerbations, although the consistency and magnitude of the observed effects was uncertain. In the absence of an economic model, CDR was unable to assess the cost-effectiveness of omalizumab in light of the new clinical information.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

April 20, 2016 Meeting:

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary reimbursement 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 drug reimbursement recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has/has not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC drug reimbursement recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

Drug Coverage Decision for B.C. PharmaCare

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Drug	**omalizumab**
Brand Name	Xolair®
Dosage Form(s)	150 mg vial
Manufacturer	Novartis Pharmaceuticals Canada Inc.
Submission Type	**New Indication**
Use Reviewed	Chronic idiopathic urticarial (CIU)
Common Drug Review (CDR)	Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details: www.cadth.ca/about-cadth/what-we-do/products-services/cdr/reports
Drug Benefit Council (DBC)	DBC met on June 1, 2015. DBC considered various inputs including: final review completed by the CDR, which included clinical and pharmacoeconomic evidence review material and the recommendation from the Canadian Drug Expert Committee (CDEC). The DBC also considered Clinical Practice Reviews from two specialists, as well as a Budget Impact Assessment (BIA) and Patient Input Questionnaire responses from three patients.
Drug Coverage Decision	**Non-Benefit**
Date	November 29, 2016
Reason(s)	**Drug coverage decision is consistent with the DBC recommendation.** • Omalizumab was similar to or demonstrated some advantage over placebo with respect to efficacy, safety and/or quality of life. However, there are no studies directly comparing omalizumab against less costly oral drugs (e.g., montelukast or cyclosporine). • Based on economic considerations and the submitted product price, the drug was not cost-effective and/or did not offer optimal value for money. • The Ministry initially participated in negotiations with the manufacturer through the pan-Canadian Pharmaceutical Alliance (pCPA), but subsequently withdrew as the terms of the agreement did not meet the needs of the Ministry.
Other Information	None

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