CDEC FINAL RECOMMENDATION

ADALIMUMAB
(Humira — AbbVie Corporation)
New Indication: Polyarticular Juvenile Idiopathic Arthritis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that adalimumab be listed for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) if the following clinical criterion and condition are met:

Clinical Criterion:
- Inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).

Condition:
- Treatment should be initiated by a rheumatologist who is familiar with the use of DMARDs and/or biologic DMARDs in children.

Reason for the Recommendation:
One double-blind randomized controlled trial (RCT) (DE038; N = 133) demonstrated that adalimumab was superior to placebo for reducing the proportion of patients experiencing a disease flare, with or without methotrexate (MTX). In combination with MTX, adalimumab was superior to placebo in combination with MTX for achieving an American College of Rheumatology (ACR) pediatric (Pedi) 30 and ACR Pedi 70 response.

Of Note:
1. CDEC noted that there are no data to support preferential use of adalimumab compared with other less expensive biologic drugs for the treatment of pJIA.
2. Clinical criteria for the discontinuation of adalimumab treatment in patients who fail to demonstrate a meaningful response may vary among jurisdictions; however, a meaningful response for a biologic used in the treatment of pJIA should be considered to be greater than an ACR Pedi 30 response.

Background:
This submission for adalimumab is for the new Health Canada indication for use in combination with MTX for reducing the signs and symptoms of moderately to severely active pJIA in patients four to 17 years of age who have had an inadequate response to one or more DMARDs.

Adalimumab may also be used as monotherapy when continued treatment with MTX is not appropriate. The recommended dose of adalimumab for patients with pJIA, aged 4 to17 years old, is 24 mg/m^2 body surface area up to a maximum single dose of 40 mg administered every other week via subcutaneous (SC) injection. The volume for injection is selected based on the patients' height and weight. A 40 mg vial (for pediatric use) is available for patients who need less than the full 40 mg dose.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of adalimumab, a critique of the manufacturer's pharmacoeconomic evaluation, and a patient group submission regarding important outcomes and issues for patients.

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

- The most common symptoms that impact day-to-day life for people living with pJIA are pain, swelling of joints, fatigue, severe mobility impairments, stiffness, and the inability to use fine motor skills.
- Currently available therapies are limited by important adverse effects including food sensitivities, chronic infections, nausea, fatigue, headaches, rash, or anti–inflammatory-induced stomach problems, some of which may lead to hospitalization.
- Patients and caregivers hope for improved outcomes, including the following: improved ability to attend school, work, and physical activities; to return to some semblance of a normal life; and to suffer fewer hospital visits, less stomach bleeding, and less joint pain; and a reduced need for other medications for JIA, and thus reduce the adverse effects associated with them.

Clinical Trials
The systematic review included one double-blind, manufacturer-sponsored, placebo-controlled RCT. Study DE038 (N = 133) was a superiority trial comparing adalimumab 24 mg/m^2 SC every other week, as monotherapy or in combination with MTX, with placebo to reduce disease flares in patients with active pJIA who had previously responded to adalimumab treatment based on ACR Pedi 30 responses in a 16-week open-label run-in period. Upon enrolment, patients were divided into two strata based on prior use of MTX: patients with active disease despite receiving a stable dose of MTX (inadequate response) were assigned to the MTX stratum and were to continue the drug at the same dosage throughout the study; patients never treated with MTX or who discontinued treatment due to inadequate response or intolerance were assigned to the stratum without MTX. In the MTX stratum, patients were treated for a mean of 155 days with adalimumab and 132 days with placebo; in the stratum not receiving MTX, patients were treated for a mean of 158 days with adalimumab and 123 days with placebo.

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

- Disease flare — defined as a worsening of ≥ 30% in at least three of the six core criteria for JIA and a minimum of two active joints, as well as an improvement of ≥ 30% in no more than one of the core criteria.

- ACR Pedi responses — ACR Pedi responses are defined as an improvement of ≥ 30%, ≥ 50%, ≥ 70%, and ≥ 90% (ACR Pedi 30, 50, 70, and 90 respectively), in at least three of the six core criteria for JIA, and a worsening of ≥ 30% in no more than one of the criteria.

The primary efficacy outcome was the proportion of patients treated with adalimumab in the stratum without MTX who experienced a disease flare during the double-blind withdrawal phase. The proportion of patients experiencing a disease flare was also evaluated in the MTX stratum.

The core criteria were the following:

- Physician's global assessment of disease activity — measured using a 0 to 100 visual analogue scale.
- Patient or parent's global assessment of overall well-being — measured using a 0 to 100 visual analogue scale.
- Number of joints with active arthritis — defined as swelling not caused by deformity or, in the absence of swelling, limitation of passive motion accompanied by pain and/or tenderness.
- Number of joints with limitation of passive motion.
- Physical function — measured using the Childhood Health Assessment Questionnaire Disability Index (CHAQ–DI).
- Laboratory assessment of inflammation (C-reactive protein concentrations).

Results

Efficacy

- Adalimumab was associated with a statistically significant reduction in the proportion of patients experiencing a disease flare compared with placebo, regardless of whether the study drug was administered concomitantly with MTX (37% versus 65%; relative risk [RR] 0.6; 95% confidence interval [CI], 0.4 to 0.9), or without MTX (43% versus 71%; RR 0.6; 95% CI, 0.4 to 0.97).
- Compared with placebo plus MTX, patients treated with adalimumab plus MTX were statistically significantly more likely to achieve an ACR Pedi 30 response (RR 1.7; 95% CI, 1.0 to 2.7) and an ACR Pedi 70 response (RR 2.3; 95% CI, 1.3 to 4.2).
- For patients in the stratum without MTX, a greater proportion of adalimumab-treated patients demonstrated an ACR Pedi 30 response (RR 1.8; 95% CI, 0.9 to 3.3) and an ACR Pedi 70 response (RR 1.6; 95% CI, 0.8 to 3.3) compared with placebo; however, the differences were not statistically significant.

Harms (Safety and Tolerability)

- A larger proportion of adalimumab-treated patients experienced at least one serious adverse event compared with placebo-treated patients in the MTX stratum (7.9% versus 5.4%) and in the stratum without MTX (3.3% versus 0%).
- The proportion of patients with at least one adverse event was *(confidential data was removed at the manufacturer's request)*.
- Compared with placebo, the proportion of patients reporting an infection was *(confidential data was removed at the manufacturer's request)*. Serious infections were rare and no opportunistic infections, including tuberculosis, were reported.
- No withdrawals due to adverse events were reported throughout the double-blind phase.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing adalimumab SC 40 mg/0.8 mL with or without MTX to placebo with or without MTX in children with pJIA. The economic evaluation was based on a Markov model, over a seven-year and lifetime time horizon (90 years). Data from study DE038 were used to inform health states, transition probabilities and utility values. The manufacturer reported that treatment with adalimumab with or without MTX was associated with an incremental cost of $60,296 per quality-adjusted life-year (QALY) gained compared to placebo, with or without MTX over a seven-year time horizon; and, $25,759 per QALY over a lifetime time horizon. Univariate and probabilistic sensitivity analyses reported that the model was stable.

A number of limitations were noted with the economic evaluation:

- The submission considered the comparison of adalimumab with or without MTX and placebo with or without MTX, even though most jurisdictions reimburse one or more biologic DMARDs for pJIA, including etanercept and abatacept. Consequently, a broader consideration for the comparator should have been given.
- The methods used to determine the health states, transition probabilities between health states, and mapping of quality of life data have not been validated for this population.

Evidence was presented that supported an assumption of comparative clinical effectiveness between adalimumab and other biologic DMARDs for pJIA. CDR considered the comparative drug costs for adalimumab with relevant biologic DMARDs reimbursed for pJIA in Canada, namely etanercept and abatacept. The annual cost of adalimumab SC 40 mg/0.8 mL ($19,249) is at the upper end of the range of costs for etanercept SC 25 mg/mL and 50 mg/mL ($9,850 to $19,705) and abatacept intravenous 250 mg/15 mL ($7,206 to $28,825). The lower costs for the comparator biologic DMARDs are associated with lower patient weights. The weight threshold at which the cost of abatacept and etanercept are equal to adalimumab ranges from 50 kg to 60 kg. The higher cost of adalimumab is primarily due to wastage because adalimumab is only available in 40 mg single-use vials; whereas, other biologic drugs are provided in various sizes and/or are available in multi-use vials.

Other Discussion Points:

CDEC noted the following:

- There were no direct comparisons between adalimumab and the other biologics indicated for use in the treatment of pJIA (etanercept and abatacept). An indirect comparison suggested that these agents may have similar efficacy for reducing the risk of disease flares; however, the analysis is limited by substantial heterogeneity between the included trials.
- Study DE038 did not include patients with uveitis; therefore, the efficacy of adalimumab for the treatment of JIA-associated uveitis has not been demonstrated in a controlled clinical trial.
- There were no data from the double-blind phase of study DE038 for pain reduction, joint damage/deformity, health care resource utilization, and patient's or parent's treatment satisfaction.
- ACR Pedi 30 was the primary efficacy outcome in DE038; however, ACR Pedi 70 is considered a more clinically relevant assessment of treatment effectiveness.

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

- There are no direct comparisons of adalimumab with other biologic agents for the treatment of pJIA.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 19, 2013 Meeting

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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

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