CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

APREMILAST
(Otezla — Celgene)
Indication: Psoriatic Arthritis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that apremilast be listed for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response, intolerance, or contraindication to a previous disease-modifying anti-rheumatic drug (DMARD), if the following conditions are met:

Conditions:
- Under the care of a physician with experience in the diagnosis and treatment of PsA
- Reduced price.

Reasons for the Recommendation:
1. Three randomized controlled trials (RCTs) (PALACE-1, PALACE-2, and PALACE-3) demonstrated that apremilast was superior to placebo for reducing symptoms and improving the quality of life of patients with PsA.
2. Reanalyses of the manufacturer's pharmacoeconomic model conducted by the CADTH Common Drug Review (CDR) demonstrated that apremilast was associated with an incremental cost-utility ratio (ICUR) of $81,572 per quality-adjusted life-year (QALY) compared with best supportive care (BSC); therefore, at the submitted price of [redacted], apremilast is not considered to be a cost-effective treatment option for PsA.

Of Note:
- The manufacturer's network meta-analysis (NMA) suggested that [redacted].
- CDEC noted that there is a potential role for apremilast in the treatment of PsA for patients who have experienced inadequate control with a DMARD, but are unable to receive a biologic DMARD.

Background:
Apremilast is indicated for the treatment of the following: alone or in combination with methotrexate for adult patients with active PsA who have had an inadequate response, intolerance, or contraindication to a prior DMARD; and adult patients with moderate to severe

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plaque psoriasis who are candidates for phototherapy or systemic therapy. Apremilast is available as 10 mg, 20 mg, and 30 mg tablets, and the recommended dose is 30 mg twice daily.

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

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

- Individuals living with PsA experience joint pain, stiffness, fatigue and loss of function. Some patients have difficulty sitting, using the stairs, bending to pick up objects, and getting in and out of the bathtub. Daily activities become challenging for some patients, causing them to require help from caregivers. Patients also experience skin sensitivity, redness, flaking, and pain from the plaque psoriasis.
- The impact of the disease goes beyond affecting patients' physical well-being, with some patients likely to stop engaging in social and creative activities because they have limited time and energy and increased pain. Furthermore, the acute awareness of skin lesions sometimes has a substantial psychological impact.
- Current therapy includes biologic response modifiers, DMARDs, and nonsteroidal anti-inflammatory drugs. Patients are challenged by the heterogeneity of response to treatments and the waning effectiveness of therapies experienced by some individuals. Some have a strong preference for oral therapies. Patients indicated that a large array of treatment options is needed to ensure that they always have access to effective therapies.

Clinical Trials
The CDR systematic review included three pivotal, phase 3, double-blind, placebo-controlled RCTs (PALACE-1 [N = 504], PALACE-2 [N = 484], and PALACE-3 [N = 505]). All three studies were three-arm superiority studies that evaluated the efficacy and safety of apremilast 20 mg orally twice daily, or apremilast 30 mg orally twice daily compared with placebo over a double-blinded duration of 24 weeks. All three studies included adults with active PsA who previously had treatment with DMARDs or tumour necrosis factor (TNF) alpha inhibitors (up to 10% of enrolled). PALACE-3 also included patients with at least one ≥ 2 cm plaque psoriasis lesion in addition to active PsA. At week 16, all patients whose tender joint count and swollen joint count had not improved by ≥ 20% were required to enter early escape to blinded active treatment. Patients in the placebo group who met early escape criteria were to be re-randomized in a 1:1 ratio to receive either apremilast 20 mg twice daily or apremilast 30 mg twice daily. Patients on active treatment who met early escape criteria were to continue to receive the same dosage of apremilast to which they were originally assigned. At week 24, patients originally randomized to placebo and not re-randomized to escape treatment on week 16 were re-randomized in a 1:1 ratio to receive either apremilast 20 mg twice daily or apremilast 30 mg twice daily. In accordance with dosing recommendations in the product monograph, CDEC deliberations focused on the 30 mg twice-daily dosage regimen.

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Outcomes

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

- American College of Rheumatology (ACR) responses — provides a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including Patient/Physician Global Assessment of disease activity (10 cm visual analogue scale [VAS]), Health Assessment Questionnaire–Disability Index (HAQ-DI), patient assessment of pain intensity, level of C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR). The ACR20 is generally accepted as the minimal clinically important difference (MCID) indicating a response to treatment, while the ACR50 and ACR70 more likely reflect important changes for the long-term management of arthropathy.
- Psoriatic Arthritis Response Criteria (PsARC) — measures signs and symptoms of PsA assessed by tender and/or swollen joint count, Physician Global Assessment (0 to 5 Likert scale), and Patient Global Assessment (0 to 5 Likert scale). The PsARC was modified in all three studies by the use of tender and swollen joint counts, rather than joint scores, and the assessment of improvement or worsening in patient self-assessment and physician assessment using a 20 mm change on a 100 mm VAS, rather than a one-category change on a Likert scale. A modified PsARC treatment response was defined as improvement in at least two of the four measures, one of which must be tender joint count or swollen joint count, and no worsening in any of the four measures.
- Psoriasis Area and Severity Index (PASI) — an instrument used to assess and grade the severity of psoriatic lesions and the patient's response to treatment (scores range from 0 to 72).
- HAQ-DI — a self-assessment questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities); patients' difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The MCID for the HAQ-DI ranges from 0.3 to 0.35.
- Short Form (36) Health Survey (SF-36) — a 36-item, general health status instrument consisting of eight health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical challenges, and role limitations due to emotional challenges. The physical component summary (PCS) and the mental component summary (MCS) range from 0 to 100, with higher scores indicating better health status. The MCID for either the PCS or MCS of the SF-36 for the change from baseline is typically between 2.5 and 5 points.
- Patient's assessment of pain — scored on a 0 mm to 100 mm horizontal line on which 0 represents "no pain," and the 100 mm mark represents "pain as severe as can be imagined." The MCID of patient's assessment of pain was defined as an improvement (reduction) in pain of 10 mm or more from baseline.
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) — a validated enthesis index for ankylosing spondylitis developed by assessing measures of disease activity, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Mander enthesis index (MEI). The score for MASES index ranges from 0 to 13, correlating with the number of painful entheses out of the total of 13 assessed. MASES has not been assessed specifically for PsA.

The primary outcome in all three included studies was the proportion of patients achieving an ACR20 response at 16 weeks.

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Efficacy

- In all three trials, apremilast 30 mg twice daily was associated with a statistically significantly greater proportion of patients achieving an ACR20 response compared with placebo at week 16. A greater proportion of apremilast patients achieved an ACR50 response at week 16 compared with placebo; however, ACR70 responses were rare in the PALACE trials. Statistical testing was not conducted for the ACR50 and ACR70 end points, as the pre-specified hierarchical testing failed at a higher order comparison. The differences in proportions for ACR20, ACR50, and ACR70 responses were modest:
  - ACR20: 19.0% (95% confidence interval [CI], 9.7 to 28.3) in PALACE-1; 13.4% (95% CI, 4.0 to 22.7) in PALACE-2; and 22.3% (95% CI, 13.0 to 31.6) in PALACE-3
  - ACR50: 10.3% (95% CI, 3.7 to 16.8) in PALACE-1; 5.6% (95% CI, −0.2 to 11.3) in PALACE-2; and 6.8% (95% CI, 0.0 to 13.5) in PALACE-3
  - ACR70: 3.1% (95% CI, −0.4 to 6.5) in PALACE-1; 0.6% (95% CI, −1.5 to 2.7) in PALACE-2; and 1.2% (95% CI, −2.4 to 4.8) in PALACE-3.
- A greater proportion of apremilast-treated patients demonstrated PsARC and PASI responses at week 16. The differences in proportions for PsARC and PASI 75 were:
  - PsARC: 16.7 (95% CI, 6.6 to 26.8) in PALACE-1; 14.9 (95% CI, 4.3 to 25.5) in PALACE-2; and 25.4 (95% CI, 15.5 to 35.3) in PALACE-3
  - PASI 75: [redacted] (95% CI, [redacted] to [redacted]) in PALACE-1; [redacted] (95% CI, [redacted] to [redacted]) in PALACE-2; and 14.6 (95% CI, 4.5 to 24.8) in PALACE-3.
- There were no statistically significant differences in the change from baseline in Dactylitis Severity Score or MASES scores at 16 weeks. Mean differences in Dactylitis Severity Scores and MASES were:
  - MASES: −0.4 (95% CI, −1.2 to 0.4) in PALACE-1; −0.4 (95% CI, −1.2 to 0.4) in PALACE-2; and −0.2 (95% CI, −1.0 to 0.5) in PALACE-3
  - Dactylitis Severity Score: −0.3 (95% CI, −1.1 to 0.4) in PALACE-1; −0.2 (95% CI, −1.0 to 0.5) in PALACE-2; and −0.8 (95% CI, −1.7 to 0.1) in PALACE-3.
- There were statistically significant improvements in physical functioning, as measured by the change from baseline in HAQ-DI. The least squares mean differences in HAQ-DI were −0.159 (95% CI, −0.258 to −0.060) in PALACE-1; −0.140 (95% CI, −0.236 to −0.045) in PALACE-2; and −0.127 (95% CI, −0.220 to −0.034) in PALACE-3.
- There were statistically significant improvements in the SF-36 physical functioning domain score with apremilast 30 mg compared with placebo at week 16.
- Apremilast was associated with statistically significant improvements in the patient's assessment of pain compared with placebo at 16 weeks in PALACE-1 and PALACE-3, but not in PALACE-2. The mean differences between groups were −7.9 (95% CI, −12.9 to −2.8) in PALACE-1; −4.9 (95% CI, −10.0 to 0.3) in PALACE-2; and −7.8 (95% CI, −12.8 to −2.9) in PALACE-3.

Harms (Safety and Tolerability)

- The most commonly reported adverse events associated with apremilast were diarrhea and nausea. The proportions of patients who experienced at least one adverse event were:
  - PALACE-1: 61.3% with apremilast and 48.2% with placebo
  - PALACE-2: 59.3% with apremilast and 45.3% with placebo
  - PALACE-3: 62.3% with apremilast and 49.4% with placebo.
- The proportions of patients who experienced at least one serious adverse event were:
  - PALACE-1: 5.4% with apremilast and 4.2% with placebo

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  - PALACE-2: 2.5% with apremilast and 1.9% with placebo
  - PALACE-3: 3.6% with apremilast and 5.4% with placebo.
- Withdrawals due to adverse event were more commonly reported in the apremilast groups compared with the placebo groups. The most common reason for withdrawal across groups was diarrhea in PALACE-1 and nausea in PALACE-2 and PALACE-3. The proportions of patients who withdrew as a result of adverse events were:
  - PALACE-1: 7.1% with apremilast and 4.8% with placebo
  - PALACE-2: [redacted]% with apremilast and [redacted]% with placebo
  - PALACE-3: [redacted]% with apremilast and [redacted]% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing apremilast to both BSC, defined by the manufacturer as the use of a conventional DMARD (methotrexate, sulfasalazine, or leflunomide), and to biologic DMARDs (certolizumab pegol, adalimumab, etanercept, infliximab, subsequent entry biologic [SEB] infliximab, golimumab, and ustekinumab) in patients with active PsA who have previously failed, are intolerant to, or have a contraindication to a conventional DMARD — both apremilast and biologics were administered with concomitant BSC as background therapy. The analysis was based on a Markov model and was undertaken from the public-payer perspective over a 40-year horizon. Efficacy inputs to the economic model were obtained from the manufacturer's NMA. Response to treatment (defined as achieving a PsARC response) was assessed after a treatment trial period ranging from 12 to 16 weeks (depending on the treatment option). In the model, responders to treatment entered and remained in the continued use state until withdrawal due to loss of treatment efficacy or onset of adverse events. Non-responders and patients withdrawing from the continued use state moved to the BSC state, where they could either achieve a PsARC response (based on rates observed in the placebo groups of the PALACE trials) or fail to respond (at which point they would experience disease progression). Utility values were based on changes in HAQ-DI and PASI scores, which were mapped to EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities. The manufacturer reported that, compared with BSC, apremilast was the most cost-effective option, with an ICUR of $40,572 per QALY, followed by golimumab and SEB-infliximab (sequential ICURs of $50,630 and $150,378 per QALY, respectively). All other agents were either dominated or extendedly dominated (i.e., less effective and more costly than another treatment option or a combination of treatment options).

CDR noted a number of limitations with the manufacturer's pharmacoeconomic evaluation:

- Disease progression and quality of life: the manufacturer's base case used the assumption that upon treatment discontinuation, patient quality of life equals the initial treatment response, as compared with a more conservative assumption in which quality of life rebounds to the natural disease progression. This assumption may have overestimated the cost-effectiveness benefit of apremilast.
- The costs associated with BSC may have been overestimated, and the total costs of apremilast treatment underestimated.
- The long-term maintenance of treatment effects with apremilast has not been demonstrated in clinical studies, but was assumed for apremilast responders in the model, which may have biased the cost-effectiveness results in favour of apremilast.
- Use of differential treatment trial periods across agents (ranging from 12 to 16 weeks) may overestimate the cost-effectiveness of apremilast.

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When CDR accounted for the above limitations in varying cost inputs and the quality of life assumption upon treatment discontinuation, and considering a 10-year time horizon to vary the assumption of long-term maintenance of effect, apremilast was associated with an ICUR of $81,572 compared with BSC, with apremilast being extendedly dominated by BSC and golimumab. Under this CDR reference case, a price reduction of 10% for apremilast would be required for it to be considered among the cost-effective options at an ICUR of $73,218 per QALY versus BSC.

At the recommended dose of 30 mg twice daily, the cost of apremilast ([redacted] per day or [redacted] per year) is more than DMARDs (range: $255 to $997 per year) and less than all biologics evaluated in the cost-utility analysis (range: $17,277 to $32,096 per year), based on current list prices.

Other Discussion Points:
CDEC noted the following:

- The manufacturer's NMA suggested that [redacted].
- The PALACE trials failed to demonstrate that apremilast was superior to placebo for improvements in enthesitis and dactylitis.
- The Consumer Information and Warnings and Precautions sections of the product monograph state that "Otezla can cause weight loss" and "in phase 3 studies, clinically significant weight loss was observed.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There is no evidence that apremilast is better tolerated than biologic therapies, and longer-term safety data for apremilast are required.
- No radiographic assessments were performed in the apremilast trials. This absence of any evidence that apremilast slows radiographic progression is important, given the evidence for anti-TNF alpha drugs, which do have evidence for reduced rates of radiographic progression of joint damage.
- No trials were identified that compared apremilast with DMARDs or with biologic DMARDs for the treatment of PsA.

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.

November 18, 2015 Meeting
Regrets:

None

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Conflicts of Interest:

None

About This Document:

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

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

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