CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

APREMILAST RESUBMISSION
(Otezla — Celgene Inc.)
Indication: Moderate-to-Severe Plaque Psoriasis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that apremilast be reimbursed for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy, if the following clinical criteria and conditions are met:

Clinical Criteria
- Patients with documented inadequate response, contraindication, or intolerance to conventional systemic therapies, such as methotrexate and cyclosporine.
- Patients otherwise eligible to receive but who have a contraindication (specifically: severe or repeated infections attributable to biologics, chronic hepatitis B infection, or active malignancy) that would preclude treatment with a biologic.
- Treatment discontinued if a Psoriasis Area and Severity Index (PASI) 75 response has not been demonstrated after 16 weeks of treatment with apremilast.

Conditions
- Patients should be managed in consultation with a dermatologist
- Reduced price.

Reasons for the Recommendation:
1. One randomized controlled trial (LIBERATE [N = 250]) demonstrated that apremilast 30 mg twice daily was statistically significantly superior to placebo in achieving a PASI 75 response (difference in percentages: 27.5% (95% confidence interval [CI], 14.9% to 40.1%; *P* < 0.0001) and improved Dermatology Life Quality Index (DLQI) score from baseline after 16 weeks of treatment among patients with a history of an inadequate response, intolerance, or contraindication to at least one conventional systemic drug for the treatment of moderate-to-severe plaque psoriasis.
2. No studies directly comparing apremilast with conventional systemic therapies or biologics were available. LIBERATE included a comparison that demonstrated etanercept 50 mg subcutaneously once weekly was statistically significantly superior to placebo for a PASI 75 response after 16 weeks (difference in percentages: [redacted]% (95% CI, [redacted] to [redacted]; *P* < [redacted]). However, the study was not designed to directly compare apremilast with

etanercept. In a manufacturer-submitted network meta-analysis (NMA), [redacted].

3. 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 $105,935 per quality-adjusted life-year (QALY) compared with standard of care (SoC); therefore, at the submitted price of $[redacted] per 10 mg, 20 mg, or 30 mg tablet, apremilast is not considered to be a cost-effective treatment option for plaque psoriasis.

Background:
Apremilast is a phosphodiesterase-4 (PDE4) inhibitor and has a Health Canada indication for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Apremilast is also indicated for adult patients with active psoriatic arthritis who have had an inadequate response, intolerance, or contraindication to a prior disease modifying anti-rheumatic drug. Apremilast is available as 10 mg, 20 mg, and 30 mg tablets, and the recommended dose is 30 mg twice daily.

Submission History:
Apremilast was previously reviewed by CDEC for moderate-to-severe plaque psoriasis and received a "do not list" recommendation (see CDEC Final Recommendation, July 22, 2015). The reasons for the recommendation were as follows:

1. Although two randomized controlled trials (RCTs) (ESTEEM-1 [N = 844] and ESTEEM-2 [N = 413]) demonstrated that apremilast was superior to placebo for improving plaque psoriasis symptoms and quality of life, there is insufficient evidence to evaluate the comparative clinical benefit of apremilast relative to other available therapies, including oral therapies with demonstrated effectiveness in moderate-to-severe plaque psoriasis, due to the absence of direct comparisons.
2. The NMA submitted by the manufacturer had important limitations; however, the findings suggested that [redacted] for plaque psoriasis.
3. There was insufficient evidence to evaluate the use of apremilast for the treatment of adult patients with moderate-to-severe plaque psoriasis who have had an inadequate response to, or are intolerant or contraindicated to, a conventional systemic therapy.

CDEC noted that there was a lack of clinical and pharmacoeconomic evidence to suggest sequencing apremilast between conventional systemic treatments and biologic therapies.

The original CDR systematic review of apremilast included two pivotal, phase 3, double-blind, placebo-controlled RCTs. Both ESTEEM-1 and ESTEEM-2 enrolled patients with moderate-to-severe plaque psoriasis for at least 12 months prior to randomization. Participants were randomized (2:1) to either apremilast or placebo. Both studies included an initial 16-week double-blind phase, which was the focus of the review.

The manufacturer has resubmitted based on new clinical information provided in Study PSOR-010 (LIBERATE). LIBERATE was ongoing at the time of the initial apremilast submission and therefore was not included in the initial CDR review.

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

Patient Input Information
The following is a summary of key information provided by the Canadian Skin Patient Alliance, which responded to the CDR call for patient input:

- Persons with psoriasis experience painful, itchy, bleeding, cracking, crusting, and flaking lesions and plaques. These symptoms can negatively affect the ability of patients to sleep, participate in sports, and perform day-to-day tasks, and can result in missed days of work or lost employment. Patients report lesions in facial and other visible areas that impact perception of attractiveness and in genital areas that impact intimacy. Psychosocially, patients experience stigma, depression, shame, feelings of helplessness, frustration, and isolation.
- Patients noted that current treatment options include topical ointments, creams and gels, methotrexate, cyclosporine, etanercept, adalimumab, infliximab, ustekinumab, and phototherapy. Adverse effects of these treatments can include toxicities such as liver and kidney damage, as well as nausea, headaches, and feelings of malaise.
- Patients emphasized the importance of having multiple treatment options available, noting that treatments are not effective for all patients, and some that are initially effective may eventually lose effectiveness.
- Patients also expressed a preference for oral therapies over those that require infusion or injection.

Clinical Trials
The systematic review included one study, LIBERATE, a double-blind randomized controlled trial that included both a placebo and etanercept group in addition to apremilast, specifically in patients with moderate-to-severe psoriasis who had had an inadequate response, intolerance, or contraindication to previous conventional systemic therapies. Patients were randomized 1:1:1 to oral apremilast 30 mg twice daily, subcutaneous etanercept 50 mg once weekly, or matching placebo over a 16-week double-blind treatment period. LIBERATE was designed to compare apremilast to placebo and etanercept to placebo, but not to compare apremilast to etanercept; therefore, this lack of direct comparison of the two active drugs remains a key limitation of this review.

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

- Proportion of patients with a PASI 75 response
- Proportion of patients with a Static Physician's Global Assessment (sPGA) response
- Percentage change from baseline in affected body surface area (BSA)
- Proportion of patients achieving a PASI 50 response
- Health-related quality of life measured as change from baseline in DLQI and the mental component summary (MCS) of the Short Form (36) Health Survey (SF-36)

- Proportion of patients with a Lattice System Physician's Global Assessment (LS-PGA) score of clear or almost clear.

All outcomes were assessed at week 16 of LIBERATE. The primary outcome in LIBERATE was the proportion of patients achieving a PASI 75 after 16 weeks' treatment.

Data were available for outcomes reported as being important to patients, including quality of life and various assessments of disease involvement and/or symptoms (e.g., PASI, PGA, BSA).

Efficacy

- There was a higher proportion of patients treated with apremilast who achieved a PASI 75 versus placebo (difference in proportions between groups of 27.5% [95% CI,14.9 to 40.1], *P* < 0.0001). There was also a higher proportion of patients treated with etanercept who achieved a PASI 75 compared with placebo (difference in proportions between groups of [redacted]% [95% CI, [redacted] to [redacted]] *P* < [redacted]).
- There were more apremilast-treated patients who achieved a PASI 50 after 16 weeks when compared with placebo, and this difference between groups was statistically significant. A higher proportion of etanercept-treated patients achieved PASI 50 after 16 weeks versus placebo; however, claims with respect to statistical significance could not be made because [redacted].
- There were more apremilast-treated and etanercept-treated versus placebo-treated patients who achieved a PASI 90 after 16 weeks and these differences were statistically significant, [redacted]. The clinical expert consulted by CDR for this review indicated that while the PASI 75 remains a reasonable choice for primary outcome, expectations of treatment success have increased over time and PASI 90 has become a more relevant outcome than the PASI 50.
- Although there was a statistically and clinically significant improvement from baseline in DLQI total scores for apremilast versus placebo, this was not the case when apremilast was compared with placebo using the [redacted]. Etanercept also appeared to improve [redacted] and [redacted] from baseline versus placebo; however, statistical significance could not be ascertained because the [redacted]. While the efficacy of apremilast with respect to health-related quality of life was mixed, with a statistically and clinically significant response versus placebo in a disease-specific instrument but with a failure to achieve statistical significance on the generic [redacted], the clinical expert stated that the DLQI is likely the more clinically meaningful measure.

Harms (Safety and Tolerability)

- In LIBERATE, there were numerically more serious adverse events (4% versus 1%) with apremilast compared with etanercept. No patients in the placebo group had a serious adverse event.
- There were numerically more adverse events (70% versus 53%) for apremilast versus etanercept.
- Withdrawals due to adverse event (WDAEs) (4% versus 2%) were more common for apremilast than etanercept.
- The most notable harm for apremilast is weight loss, and the manufacturer reported changes in weight under safety in LIBERATE. A weight loss of > 5% to 10% of body weight

occurred in numerically more apremilast patients than placebo ([redacted] versus [redacted] of patients, respectively), while weight decrease reported as an adverse event occurred in [redacted] of patients in each of the apremilast and placebo groups.
- The extension study to LIBERATE did not identify any unexpected safety signals; however, few conclusions can be drawn from the extension study data because it followed patients only 52 weeks, there was no comparator arm, the population was likely highly selected, and the results appeared to be sensitive to missing data. Therefore, the long-term safety of apremilast is still not known.

Cost and Cost-Effectiveness

The confidential submitted price for apremilast is $[redacted] per 30 mg tablet. At the recommended dose of 30 mg twice daily, the daily cost of apremilast is $[redacted], or an annual cost of $[redacted] in the first year and $[redacted] in subsequent years.

The manufacturer submitted a cost-utility analysis comparing apremilast and biologics (adalimumab, etanercept, infliximab, subsequent entry biologic [SEB] infliximab, secukinumab, and ustekinumab) to SoC (defined as receiving topical agents, phototherapy, and physician visits) in patients with moderate-to-severe plaque psoriasis who have had an inadequate response to, or are intolerant or contraindicated to, previous conventional systemic therapies. The analysis was undertaken from the Canadian publicly funded health care system perspective over a 10-year horizon. The analysis was based on a Markov model, in which response (PASI 75) was assessed after a trial period and then every four weeks to determine whether patients continue treatment or move to SoC (having failed to respond to or having withdrawn from treatment upon loss of efficacy or onset of adverse events). Data on comparative efficacy for all comparators, in terms of PASI response, were obtained from a manufacturer-sponsored NMA, while annual withdrawal rates from treatment were based on values from the literature. The manufacturer reported that, compared with SoC, apremilast was the most cost-effective option, with an ICUR of $83,480 per QALY, followed by SEB infliximab (sequential ICUR of $99,747 per QALY compared with apremilast). All other options were either dominated or extendedly dominated (being less effective and more costly than another treatment option or a combination of compared treatment options).

CDR noted a number of limitations with the manufacturer's analysis:
- The manufacturer failed to include comparators relevant to the full Health Canada indication population. Available evidence suggests that apremilast may be no more effective than methotrexate or cyclosporine but is considerably more expensive. Consequently, apremilast is likely dominated by methotrexate.
- The new clinical information submitted by the manufacturer failed to address concerns previously raised by CDEC regarding a lack of direct comparative clinical effectiveness information compared with other treatments.
- Incorrect coding of QALY gain among SoC patients biased results in favour of apremilast.
- Assumptions regarding equal all-cause withdrawal rates for all comparators were questionable.
- Assumptions regarding schedule of monitoring and laboratory tests may not reflect clinical practice.
- The use of a 10-year model horizon is likely too long, given uncertainty in the long-term maintenance of PASI response and observed times to treatment discontinuation in practice.

Based on CDR reanalyses to account for some of the above limitations (i.e., correction of utility coding error, alternative monitoring costs, and use of a five-year horizon), apremilast was associated with an ICUR of $105,935 versus SoC and was extendedly dominated by SoC and SEB infliximab. A price reduction of more than 50% would be necessary for apremilast to achieve an ICUR of less than $50,000 per QALY versus SoC in the CDR base case. Based on available clinical evidence, apremilast is dominated (less effective and more costly) by methotrexate.

Other Discussion Points:
CDEC discussed the following:

- [redacted] based on the manufacturer-provided NMA. Therefore, treatment with the more efficacious (and potentially cost-effective) biologics — instead of apremilast — is likely a more desirable option for patients.
- The Committee noted that the numbers of patients who have had an inadequate response, or are intolerant or contraindicated to prior conventional systemic therapies, and cannot receive treatment with biologics is likely to be small.
- CDEC noted that cost-effectiveness information for apremilast was not available for patients with moderate-to-severe plaque psoriasis who have had an inadequate response, or are intolerant or contraindicated to, prior conventional systemic therapies, and cannot receive biologics.

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.

Regrets:

July 20, 2016: None

October 19, 2016: 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 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.

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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