CDEC FINAL RECOMMENDATION

APREMILAST
(Otezla — Celgene)
Indication: Moderate to Severe Plaque Psoriasis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that apremilast not be listed for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Reasons for the Recommendation:

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 network meta-analysis (NMA) submitted by the manufacturer had important limitations; [redacted].
3. There was insufficient evidence to evaluate the use of apremilast for the treatment of adult patients with moderate to severe plaque psoriasis who [redacted]

Of Note:
CDEC noted that the manufacturer requested that apremilast be listed for use in patients [redacted]; however, there is insufficient clinical and pharmacoeconomic evidence to support [redacted]. In addition, the listing request [redacted], but there are no data to suggest that the use of apremilast [redacted].

© 2015 CADTH

Background:
Apremilast is an orally administered phosphodiesterase-4 (PDE-4) inhibitor indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The product monograph states that apremilast has not been studied and is therefore not indicated in combination with other systemic (conventional or biologic) therapies or phototherapy for psoriasis. Apremilast is available for sale as 30 mg tablets; the recommended dose is 30 mg twice daily.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals living with plaque psoriasis.

Patient Input Information
The following is a summary of key information provided by two patient groups that jointly 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. Patients report lesions in sensitive areas that impact perception of attractiveness and sexuality. Psychosocially, patients experience stigma, depression, suicidal ideations, shame, feelings of helplessness, frustration, and isolation.
- Current treatment options include 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 expressed the importance of having multiple treatment options available, noting that treatments 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 CDR systematic review included two pivotal, phase 3, double-blind, placebo-controlled RCTs. Both ESTEEM-1 (N = 844) and ESTEEM-2 (N = 413) 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 followed by a 16-week maintenance phase where patients originally assigned to apremilast remained on the drug, while patients originally assigned to placebo were switched to apremilast. Finally, weeks 32 to 52, referred to as the randomized treatment withdrawal phase, tested the durability of response to apremilast. At week 32, responders (those achieving a PASI score of at least 75 in ESTEEM-1 and 50 in ESTEEM-2) were re-randomized to either continue on apremilast or switch to placebo.

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

- PASI — a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area

© 2015 CADTH

involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores indicating greater disease severity. PASI 75 represents a 75% reduction in PASI scores and PASI 50 is a 50% reduction.

- Static Physician Global Assessment (sPGA) — a five-point scale used by the investigator to provide an assessment of the overall disease severity at the time of evaluation. Scores range from 0 (clear) to 4 (severe); the total score represents a summary assessment of the severity of the three primary signs of the disease: erythema, scaling, and plaque elevation. An sPGA response was defined as an sPGA score of clear (0) or almost clear (1) with at least 2-point reduction from baseline at week 16. The minimal clinically important difference (MCID) is unknown.
- Nail Psoriasis Severity Index — used to evaluate one target thumbnail or fingernail representing the worst nail psoriasis involvement at baseline for nail matrix psoriasis and nail bed psoriasis. Scores range from 0 to 8, with higher scores indicating greater nail psoriasis severity. The MCID is unknown.
- Scalp Physician Global Assessment (ScPGA) — a six-point scale used to assess scalp involvement if present at baseline. Scores ranges from 0 (clear) to 5 (very severe). An ScPGA response was defined as patients who achieve score of 0, 1 or 2.The MCID is unknown.
- Palmoplantar Physician Global Assessment (PPPGA) — a five-point scale used to assess palms of hands and soles of feet for psoriasis involvement if present at baseline. Scores range from 0 (clear) to 4 (severe). The MCID is unknown.
- The Dermatology Life Quality Index (DLQI) — a 10-item questionnaire completed by the participant. The DLQI total score has a possible range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best score. Higher scores indicate poorer quality of life. The MCID is considered to be 3.2 for the DLQI total score.
- For pruritus, each patient was asked to assess itch in the previous week by placing a vertical stroke on a 100 mm visual analogue scale (VAS), on which the left-hand boundary represented no itch at all and the right-hand boundary represented itch as worst itch imaginable. The distance from the mark to the left-hand boundary was to be recorded. The MCID is unknown.

The primary outcome of both studies was the proportion of patients achieving a PASI 75 response.

Efficacy

- Compared with placebo, there was a statistically significant reduction from baseline to 16 weeks in the least squares (LS) mean PASI scores in both ESTEEM-1 [redacted] and ESTEEM-2 [redacted].
- A statistically significantly greater proportion of apremilast-treated patients achieved PASI 75 and PASI 50 responses compared with placebo in both ESTEEM-1 and ESTEEM-2. The differences in proportion were (ESTEEM-1 and ESTEEM-2, respectively):
  - PASI 75: 27.8% (95% CI, 23.1 to 32.5) and 23.0% (95% CI, 16.3 to 29.6)
  - PASI 50: 41.7% (95% CI, 35.7 to 47.7) and 35.8% (95% CI, 26.9 to 44.7).
- For health-related quality of life measures, there were statistically significant improvements for apremilast versus placebo in DLQI total scores (both trials), EuroQol 5-Dimensions Questionnaire (EQ-5D) index scores (both trials), and EQ-5D VAS (ESTEEM-2 only). The LS mean differences at 16 weeks were (ESTEEM-1 and ESTEEM-2, respectively):

© 2015 CADTH

  - DLQI: [redacted]
  - EQ-5D index: [redacted]
  - EQ-5D VAS: [redacted]
- A statistically significantly greater proportion of apremilast-treated patients achieved sPGA responses and ScPGA responses compared with placebo in both studies. The differences in proportion at 16 weeks were (ESTEEM-1 and ESTEEM-2, respectively):
  - sPGA response: [redacted]
  - ScPGA response: [redacted]
- There was a statistically significant reduction in affected body surface area (BSA), based on differences in proportions at 16 weeks, in apremilast-treated patients compared with placebo in both ESTEEM-1 (−40.78%; 95% CI, −46.34 to −35.21) and ESTEEM-2 (−42.15%; 95% CI, −51.11 to −33.20).

Harms (Safety and Tolerability)

- In ESTEEM-1, 69% of apremilast patients and 56% of placebo patients reported an adverse event after 16 weeks of therapy, while in ESTEEM-2, [redacted] of apremilast patients and [redacted] of placebo patients experienced an adverse event. The most commonly reported adverse events were diarrhea (18% of apremilast patients versus 7% of placebo patients across studies) and nausea (17% of apremilast patients and 7% of placebo patients).
- Serious adverse events were reported in 2% of patients in the apremilast group and 3% of patients in the placebo group after 16 weeks in ESTEEM-1, and in [redacted] of the apremilast and placebo groups in ESTEEM-2.
- Withdrawals due to adverse events occurred in 5% and [redacted] of apremilast-treated patients and 3% and [redacted] of placebo-treated patients in ESTEEM-1 and ESTEEM-2, respectively. Nausea was the most commonly cited adverse event leading to withdrawal.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing apremilast with “palliative care” (physician visits without active treatment — supportive care), methotrexate, cyclosporine, and biologics (adalimumab, etanercept, ustekinumab, and infliximab) in patients with moderate to severe plaque psoriasis (PASI ≥ 12, BSA ≥ 10%, and sPGA scores ≥ 3) who are candidates for phototherapy or systemic therapy. The analysis was undertaken from the public payer perspective over a 10-year time 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 if patients continued treatment or moved to supportive care (having failed to respond or withdrew from treatment). Data on the 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. Incremental cost-utility ratios (ICURs) for all comparators were calculated compared with supportive care. The manufacturer reported that apremilast was associated with an ICUR of $97,607 per quality-adjusted life-year (QALY) when compared with supportive care, which is higher than methotrexate but less than cyclosporine and biologics.

CDR noted a number of limitations with the manufacturer’s analysis:

- The manufacturer presented ICURs for all comparators relative to supportive care; sequential analysis was not reported.
- No cost-effectiveness information was provided by the manufacturer at the time of the initial submission on the requested listing population of patients with [redacted]

© 2015 CADTH

[redacted]

- Assumptions for the use of methotrexate and cyclosporine biased results in favour of apremilast: higher withdrawal rates were assumed for methotrexate than apremilast; a disutility multiplier was applied to methotrexate and cyclosporine to account for adverse events, while adverse events were not considered for other comparators.
- Subsequent entry biologic (SEB) infliximab was not included as a comparator.
- There is uncertainty regarding reported QALYs based on indirect mapping from PASI to utilities.

Considering a sequential analysis using the manufacturer's base case results, regardless of a decision-maker's willingness to pay per QALY, apremilast would not be preferred compared with both methotrexate and adalimumab (extended dominance).

Based on analyses to account for the above limitations (e.g., use of alternate assumptions around methotrexate), apremilast was more costly and associated with [redacted] compared with methotrexate (i.e., methotrexate dominates apremilast). When including SEB infliximab and alternate assumptions for cyclosporine, regardless of a decision-maker's willingness to pay per QALY, apremilast would not be preferred compared with both cyclosporine and SEB infliximab (i.e., extended dominance).

At the recommended dose of 30 mg twice daily, the daily cost of apremilast is $[redacted], which translates to an annual cost of $[redacted] in the first year and $[redacted] in subsequent years. The annual cost of apremilast is higher than methotrexate ($132 to $464) and cyclosporine ($1,304 to $1,578) and less than the biologics (adalimumab 40 mg: $19,249 to $20,730; etanercept 50 mg: $20,313 to $25,000; ustekinumab 45 mg and 90 mg: $20,669 to $22,966; infliximab (Remicade) 5 mg/kg: $32,096 to $39,502; SEB infliximab (Inflectra) 5 mg/kg: $21,125 to $26,000), based on current list prices.

Other Discussion Points:

CDEC noted the following:

- While the patient groups emphasized patients' desire for another effective therapy and for a safer therapy than those available, the data from the trials provided no evidence of apremilast's comparative efficacy and safety against the efficacy and safety of other active therapies. Further, the data suggest that the proportion of patients who took apremilast in the trials and who experienced significant symptom improvement was considerably less than the proportion of patients who had taken apremilast and who reported such improvement when responding to the patient groups' survey.
- The product monograph, in the Warnings and Precautions sections, states 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 are no direct comparisons of apremilast against other treatments approved for use in the management of plaque psoriasis. The manufacturer is currently conducting an active controlled trial comparing apremilast with etanercept; however, the study is ongoing and the results were not available at the time of this review.

© 2015 CADTH

- The long-term efficacy and safety profile of apremilast for the treatment of plaque psoriasis require further evaluation.

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:

April 8, 2015: None
July 15, 2015: None

Conflicts of Interest:

April 8, 2015: None
July 15, 2015: 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 CDR reviews and used in 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.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

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.

© 2015 CADTH