CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Brodalumab (Siliq — Valeant Canada LP)
Indication: Psoriasis, moderate to severe plaque

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that brodalumab 210 mg be reimbursed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy, if the following criteria and conditions are met:

Criteria

- Reimburse in a manner similar to other biologics reimbursed for the treatment of moderate to severe plaque psoriasis.
- Treatment should be discontinued if a response to treatment with brodalumab has not been demonstrated after 12 to 16 weeks

Condition

- Drug plan cost of treatment with brodalumab should not exceed the cost of the least expensive biologic therapy reimbursed for plaque psoriasis.

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- Discontinue treatment if a response has not been demonstrated after 12 weeks to 16 weeks.

Condition

- Drug plan cost of treatment with BDL should not exceed the cost of the least expensive biologic therapy reimbursed for plaque psoriasis.

Reasons for the Recommendation

1. The results of three phase III randomized controlled trials (RCTs) (AMAGINE-1, AMAGINE-2, and AMAGINE-3) in adults with moderate to severe plaque psoriasis demonstrated the efficacy of BDL 210 mg in providing statistically significant and clinically important improvements in skin clearance and dermatological symptoms (measured by the Psoriasis Area and Severity Index [PASI] and static Physician Global Assessment [sPGA]) over the short-term induction phase (12 weeks) compared with placebo. Results of AMAGINE-2 and AMAGINE-3 demonstrated that, at 12 weeks, BDL was statistically superior to ustekinumab (USK) in achieving a PASI 100 response in both trials and a PASI 75 response in AMAGINE-3.
2. The Health Canada–approved product monograph states that discontinuation of therapy with BDL should be considered if an adequate response has not been achieved after 12 weeks to 16 weeks of treatment because continuing treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.
3. Limitations in trial design in the AMAGINE clinical trial program, as well as the short duration of the trials in the context of proposed lifelong treatment, lead to uncertainty regarding the long-term clinical safety and effectiveness of BDL compared with USK. There is no direct evidence related to the comparative efficacy and safety of BDL versus other biologic therapies, and the available indirect treatment comparisons (ITCs) are associated with substantial uncertainty due to heterogeneity of the included trials, particularly due to large differences in the placebo response. Therefore, no evidence is available to clearly support a higher cost for BDL compared with other biologic therapies.
4. According to the CADTH Common Drug Review (CDR) probabilistic reanalysis of the manufacturer's cost-effectiveness model, at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) gained, BDL had a 70.5% probability of being cost-effective. However, because of the lack of comparative effectiveness data versus all relevant biologic treatments and the inability of CDR to consider the confidential negotiated prices of other treatments, the true cost-effectiveness of BDL is uncertain and likely less favourable than the values estimated using publicly available prices.

Of Note:

- A response to treatment is defined as an achievement of at least a 75% reduction in the PASI 75 score.
- Related to the risks of suicidal ideation and behaviour that have occurred in patients treated with BDL, the Health Canada–approved product monograph specifies that prescribers are required to register in the Siliq Patient Support Program before prescribing BDL. Prescribers are educated regarding the appropriate use of BDL and are expected to educate patients on the

benefits and risks of treatment, especially on the risks of suicidal ideation and behaviour. Patients who are prescribed Siliq are required to enrol in the Siliq Patient Support Program and provide consent that they understand the risks of treatment.

- Reimbursement strategies for biologic therapy for psoriasis vary among jurisdictions; confidential pricing agreements may result in differences in relative cost-effectiveness. There are currently two other biologics with a mechanism of action similar to that of BDL (i.e., inhibition of human interleukin 17 receptor A [IL-17A]) that are reimbursed for the treatment of moderate to severe plaque psoriasis. There is no clear evidence to suggest that a jurisdiction should list BDL preferentially, or at a price premium, compared with other IL-17A inhibitors (secukinumab and ixekizumab) or other biologics reimbursed for the treatment of psoriasis.

Discussion Points:

- The Committee discussed that, in clinical practice, one strategy for patients with insufficient response to a biologic is to increase the dose. The Committee determined that this would not be an appropriate strategy for patients treated with BDL, as 210 mg biweekly is the only Health Canada–recommended dosage regimen for BDL for the treatment of psoriasis.
- While the drug cost for BDL appears to be lower compared with publicly available list prices of comparators, the additional costs of monitoring patients, given Health Canada's black-box warning about suicidal ideation and behaviour in the BDL product monograph, could offset any cost savings.
- The Committee discussed the potential for BDL to be associated with an increased risk of suicide relative to the need for patients to have access to another treatment, and concluded that the potential benefits to patients outweighed the potential risk of harm in this context.

Background:

BDL has a Health Canada indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. BDL is a monoclonal antibody directed against IL-17 RA. It is available as a subcutaneous injection. The Health Canada–approved dose is 210 mg administered at weeks 0, 1, and 2, followed by 210 mg every two weeks.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of double-blind RCTs of BDL, a critique of two ITCs, and the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience in treating patients with psoriasis and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

Two patient groups, the Canadian Skin Patient Alliance and the Arthritis Consumer Experts, provided input for this submission. Patient perspectives were obtained from online surveys, one-to-one interviews, and past submissions. The following is a summary of key input from the perspective of the patient groups:

- The most prominent physical symptoms of psoriasis include plaques, scales, flaking, and itching of the skin and scalp. These affect patients physically (pain and discomfort) and psychologically (anxiety, depression, social isolation, and lack of self-confidence). Caregivers' personal and social lives are also negatively affected. Reductions in itching, scaling, pain, and flaking were the top improvements patients and caregivers would like in new treatments.
- Most patients receive topical treatments; a relatively small proportion receives systemic therapy. Patients frequently noted the following issues with topical treatments: need for frequent and time-consuming application, lack of effectiveness and side effects (such as loss of hair, loss of libido, and mood swings). Some patients voiced concern about the immune-modifying effects of systemic drugs in addition to issues related to the health care system, such as long wait times to see dermatologists, costs of treatments, and barriers to accessing specific treatments.

- Patients indicated a lack of complete clearance as an unmet need in current treatments. They expected that a treatment with improved effectiveness and minimal side effects would also benefit their psychosocial lives and overall quality of life.

Clinical Trials

The systematic review included three double-blind, parallel-group RCTs of patients with stable moderate to severe plaque psoriasis. One of them was a placebo-controlled trial (AMAGINE-1, N = 661); the remaining two were double-dummy, active-controlled trials (AMAGINE-2 and AMAGINE-3, N = 1,831 and 1,881, respectively). AMAGINE-1 consisted of a 12-week double-blind induction phase where patients were randomized to receive one of two doses of BDL (210 mg or 140 mg) or placebo every two weeks. A 40-week double-blind withdrawal and retreatment phase followed in which responders to BDL were re-randomized to continue their original dose of BDL or switch to placebo; non-responders and patients in the original placebo group were not re-randomized and received BDL 210 mg every two weeks instead.

AMAGINE-2 and -3 were identically designed, composed of a 12-week double-blind induction phase followed by a 40-week double-blind maintenance phase. During the induction phase, patients received one of two doses of BDL (210 mg or 140 mg every two weeks), USK (45 mg if ≤ 100 kg or 90 mg if > 100 kg, at day 1 and week 4), or placebo. During the maintenance phase, patients who were originally randomized to either dose of BDL were combined and re-randomized to one of four doses of BDL (210 mg every

2 weeks, 140 mg every 2 weeks, 140 mg every four weeks, or 140 mg every 8 weeks); whereas patients on ustekinumab and placebo were not re-randomized and continued to receive ustekinumab (at week 16, thereafter every 12 weeks) and switched to brodalumab 210 mg every two weeks, respectively. Following the 52-week double-blind phase, patients in all three trials could enter the long-term open-label extension phase, lasting up to week 266. Of the different brodalumab dosages, this CDR review only focused on the 210 mg every two weeks approved by Health Canada. The proportion of patients who discontinued treatment during the induction phase was low across all trials (approximately 5% or lower in all relevant treatment arms).

The main limitations of the trials included the use of an enriched population after week 12 (AMAGINE-1), the lack of any statistical comparisons between the relevant treatment arms (BDL 210 mg and USK) after week 12 (AMAGINE-2 and 3), and the availability of rescue therapy at any point beginning at week 16 (all trials). Therefore, the most robust findings and useful information are limited to the 12-week induction phase.

Outcomes

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

- sPGA
- PASI response
- Psoriasis Symptoms Inventory (PSI)
- Adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and suicidal ideation and behaviour

Health-related quality of life (HRQoL) was assessed using three patient-reported instruments: the Dermatology Life Quality Index (DLQI), the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire, and the Short Form (36) Health Survey (SF-36), version 2. Only DLQI was the common HRQoL measure in all three trials.

Across all studies, the primary end points to evaluate the superiority of BDL to placebo included the proportion of patients with PASI 75 and sPGA success (score of 0 or 1). In AMAGINE-2 and -3, the primary outcome evaluating the superiority of BDL to USK included the proportion of patients with PASI 100 at week 12.

Efficacy

All three trials met their primary and secondary end points at week 12 for the comparison of BDL with placebo.

- Across all trials, a statistically significantly greater proportion of patients in the BDL-treated group achieved PASI 75 compared with placebo: 83.3% versus 2.7%, 86.3% versus 8.1%, and 85.1% versus 6.0% (adjusted *P* value < 0.001, all trials).
- The percentage of patients achieving sPGA success was statistically significantly greater in the BDL-treated group compared with placebo: 75.7% versus 1.4%, 78.6% versus 3.9%, and 79.6% versus 4.1% (adjusted *P* value < 0.001, all trials).
- Compared with placebo, the percentage of patients achieving PASI 100 was statistically significantly greater in the BDL group in all trials: 41.9% versus 0.5%, 44.4% versus 0.6%, and 36.7% versus 0.3% (adjusted *P* value < 0.001 in all trials).
- The proportion of patients in the BDL group who achieved an sPGA score of 0 was statistically significantly greater than placebo in all three trials: 41.9% versus 0.5%, 44.8% versus 0.6%, and 36.7% versus 0.3% (adjusted *P* value < 0.001 in all trials).

In AMAGINE-2 and -3, the primary end point for the comparison of BDL with USK was met, but not the secondary end point.

- The percentage of patients achieving PASI 100 at week 12 was statistically significantly greater for BDL compared with USK: 44.4% versus 21.7% and 36.7% versus 18.5%, respectively (adjusted *P* value < 0.001 in both trials).

Results for the DLQI in all trials showed evidence of an improvement with BDL versus placebo; however, the analyses were not adjusted for multiple comparisons. In AMAGINE-1, results for the EQ-5D-3L and both the Physical Component Score and Mental Component Score of the SF-36 (version 2) favoured BDL in terms of improvement in HRQoL; however, analyses were not controlled for multiplicity. No statistical comparisons were made between BDL and USK for the DLQI at week 12 in AMAGINE-2 and AMAGINE-3.

Harms (Safety and Tolerability)

- AE profiles were similar between the treatment groups overall. The most common AEs throughout the trials included nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. The overall incidences of SAEs and WDAEs were low across all trials, and did not vary substantially between the treatment groups. However, the long-term safety profile is currently limited to approximately one year.
- Among the notable harms, the incidence of inflammatory bowel disease among BDL-treated patients was low (< 1 event per 100 subject-years through week 52); however, all trials excluded patients with a history of Crohn disease. In AMAGINE-2 and -3, a total of 13 and two cases of suicide-related events (suicidal ideation, behaviour, and attempt) were registered among patients treated with BDL, respectively. The Health Canada–approved product monograph contains a boxed warning regarding suicidal ideation and behaviour, but notes that a causal association between treatment with BDL and suicidality has not been established. However, the manufacturer has developed a risk management plan as requested by Health Canada to minimize the risk of suicidal ideation and behaviour. Prescribers are directed to register in the Siliq Patient Support Program before prescribing, and to educate patients on the benefits and risks of treatment, especially the risk of suicidal ideation and behaviour; patients who are prescribed Siliq are to enrol in the Patient Support Program.

Indirect Treatment Comparisons

Two ITCs were included in this review, one submitted by the manufacturer and the other identified through a systematic review of published ITCs on this topic. Both ITCs evaluated the clinical efficacy (PASI response) of a number of relevant biologics on patients with moderate to severe plaque psoriasis. A total of 43 and 54 RCTs were included in the manufacturer-submitted and the published ITCs, respectively. Both ITCs exhibited heterogeneity in terms of placebo response, likely due to differences in patient characteristics across trials, which may bias the results of the ITCs. The conclusions of the two ITCs were largely similar; the relative risk of achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses was statistically greater for BDL than for adalimumab, apremilast, etanercept, USK, infliximab, and secukinumab over short-term induction periods (ranging from 10 weeks to 16 weeks). BDL and ixekizumab appeared to result in similar PASI responses after short-term induction treatment, based on the results of both ITCs,

while the comparative efficacy of BDL versus guselkumab was less certain given that it was included only in one of the ITCs. In addition, the relative efficacy of BDL compared with that of other biologics beyond the short-term induction periods remains unknown. Safety outcomes and HRQoL data were not evaluated in the ITCs.

Cost and Cost-Effectiveness

At the submitted price, BDL (210 mg at weeks 0, 1, and 2, and every two weeks thereafter; $18,060 in year 1, $16,770 subsequent years) is less costly than biologics for the treatment of plaque psoriasis based on publicly available list prices.

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing BDL with currently available treatments for adult patients with plaque psoriasis. Comparators included ixekizumab, secukinumab, etanercept (Enbrel), infliximab (Remicade and the subsequent biosimilars), adalimumab, USK, and best supportive care (BSC). In the scenario analysis, additional comparators were considered: guselkumab, etanercept (biosimilar), and adalimumab (biosimilar). At entry into the model, patients with moderate to severe plaque psoriasis were assigned to a health state based on the PASI response (< 50, 50 to 74, 75 to 89, 90 to 99, 100) based on their treatment. After the treatment induction, patients with a PASI score < 75 moved to BSC. The manufacturer then estimated the proportion of patients in each PASI response score at the end of year 1 and all subsequent years. Patients remaining on treatment maintained the same response (i.e., did not transition between response scores), but could withdraw from treatment, moving to BSC or died based on the background probability of death (which did not vary by health state). The manufacturer assumed full continuation of treatment effect beyond the induction period. Those moving to BSC were all assumed to obtain a PASI response of < 50: they also remained in this state each cycle or died, based on the background probability of death. Treatment effects were based on a manufacturer-commissioned, unpublished ITC. Discontinuation rates were assumed the same for all biologics. AEs were not included within the model. Utility values for baseline and PASI response score were derived from the AMAGINE-1 clinical trial. Costs included were drug costs, administration costs, physician visits, and laboratory tests.

In the base-case probabilistic analysis, the manufacturer reported that BDL was less costly and more effective (i.e., more QALYs) compared with infliximab (brand and subsequent-entry biologic), secukinumab, and USK. Etanercept and adalimumab were subject to extended dominance through BSC and BDL — that is, greater QALYs at a lower cost could be achieved through the use of BSC and BDL. BDL was more effective and costly compared with BSC, resulting in an incremental cost per QALY gained for BDL of $118,741 compared with BSC. Ixekizumab was more effective and costly compared with BDL, resulting in an incremental cost per QALY gained for ixekizumab of $6,948,457 (compared with BDL). BSC has a 100% probability of being optimal when a QALY is valued at $50,000.

CDR identified the following key limitations:

- There is uncertainty in the results of the ITC for short-term efficacy, arising from between-study heterogeneity that may not have been adequately controlled in the manufacturer-commissioned ITC. Further, longer-term comparative efficacy data from RCTs are lacking.
- No studies have been conducted in populations for which there may be a need for an additional biologic treatment (e.g., patients having failed or being intolerant to other biologic therapies or patients who are treatment-resistant).
- The assumption of maintained clinical efficacy for the 10-year time horizon without consideration of any waning of treatment effect is unsupported. This could not be explored through reanalysis of the model, given the model structure.
- The analyses are based on the list price of comparators. If product listing agreements are in place for any of the available biologic therapies, then the conclusions from the analysis would not hold.

CDR conducted further analysis that involved removing BSC from the analysis. Under this analysis, BDL was more effective and costly compared with adalimumab, resulting in an incremental cost per QALY gained for BDL of $42,981. There was a 70.5% probability that BDL was optimal given an incremental cost per QALY value of $50,000. It should be noted that the economic model did not allow CDR to assess the impact of assumptions relating to the waning of treatment effect. This, combined with the lack of comparative effectiveness data versus all biologics and the inability to consider negotiated prices, suggests that the interpretation of results may warrant care, as the true cost-effectiveness of BDL is uncertain.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

May 16, 2018 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None.