CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

HALOBETASOL PROPIONATE AND TAZAROTENE (DUOBRII — BAUSCH HEALTH, CANADA INC.)
Indication: Psoriasis, moderate to severe plaque.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that halobetasol propionate and tazarotene (HP/TAZ) be reimbursed for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria

1. Patients must have a clinical diagnosis of plaque psoriasis with all of the following characteristics:
   1.1. an Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe)
   1.2. an area of plaque psoriasis appropriate for topical treatment covering a body surface area (BSA) of 3% to 12%.
2. For use in patients whom have not adequately responded to a topical high-potency corticosteroid and for whom the addition of a second topical medication would be appropriate. Patients meeting the first initiation criterion would be considered to have had an inadequate response to a topical high-potency corticosteroid**.**

Discontinuation Criteria

1. Treatment should be discontinued if a response to HP/TAZ has not been demonstrated by eight weeks. A response to treatment is defined as at least a two-grade improvement from baseline in IGA score and an IGA score of "clear" or "almost clear" (0 or 1).

Pricing Conditions

1. The drug plan cost for HP/TAZ should not exceed the drug plan cost of treatment with the least costly topical combination reimbursed for the treatment of psoriasis.

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Reasons for the Recommendation

1. In two phase III randomized controlled trials (studies 301 and 302) of patients with plaque psoriasis who had an IGA score of 3 (moderate) or 4 (severe), a statistically significantly greater proportion of patients treated with HP/TAZ achieved treatment success at week 8 compared with vehicle (i.e., placebo treatment; treatment success was defined by at least a two-grade improvement from baseline in IGA score and an IGA score of 0 [clear] or 1 [almost clear]). Treatment success was experienced by 35.8% and 7.0% of patients treated with HP/TAZ and vehicle, respectively, in Study 301, and 45.3% and 12.5% of patients treated with HP/TAZ and vehicle, respectively, in Study 302.
2. There is no high-quality direct evidence comparing HP/TAZ to other topical treatments for plaque psoriasis. The indirect treatment comparisons (ITCs) submitted by the sponsor examined the relative treatment effect between active topical therapies compared to vehicle rather than between active therapies. Therefore, there is considerable uncertainty regarding the potential benefit of HP/TAZ compared to other topical treatments. Given the lack of comparative evidence for HP/TAZ to other topical therapies, the initiation criteria for HP/TAZ were informed based on consultation with clinical experts.
3. The cost-effectiveness of HP/TAZ for the recommended population in the Canadian setting is uncertain. At the submitted price, the drug acquisition cost of HP/TAZ is $200.00 per 100 g tube, which is more expensive than other relevant comparators, such as 50 mcg/g calcipotriol and 0.5 mg/g betamethasone dipropionate (BD/CAL).

Discussion Points

- As there is no available evidence demonstrating HP/TAZ has any therapeutic advantage over other treatments currently reimbursed for the treatment of moderate-to-severe plaque psoriasis, HP/TAZ does not address any need that is not currently met by other available treatments.
- Health-related quality of life (HRQoL) was identified as an important outcome by patients and was an exploratory outcome measured using the Dermatology Life Quality Index (DLQI) in studies 301 and 302. However, due to the lack of statistical assessment of the DLQI in both studies, no conclusions can be drawn in regard to the impact of HP/TAZ on HRQoL.

- Studies 301 and 302 assessed treatment response after eight weeks, which is insufficient to determine the long-term effectiveness and safety of treatment for a chronic condition that requires lifelong treatment such as plaque psoriasis. Therefore, there is uncertainty regarding the long-term effectiveness and safety of HP/TAZ.
- CDEC acknowledged the uncertainty associated with the external validity of studies 301 and 302, most notably with respect to patient demographics, disease severity, and place in therapy of HP/TAZ. It is unlikely that these study results are generalizable to all patients with plaque psoriasis routinely seen in Canadian clinical practice.
- HP/TAZ was administered as a monotherapy in studies 301 and 302; however, in clinical practice, HP/TAZ is anticipated to be used as an add-on to systemic treatment in patients with moderate-to-severe plaque psoriasis. There is a lack of evidence to support the use of HP/TAZ as an adjunctive treatment.
- The committee acknowledged the potential for use of HP/TAZ in patients with mild-to-moderate psoriasis; however, HP/TAZ is only approved for the treatment of patients with moderate-to-severe psoriasis, some of whom may be successfully treated with monotherapy of a high-potency topical steroid.

Background

HP/TAZ has a Health Canada indication for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis. HP/TAZ is a combination product composed of a super-potent corticosteroid (0.01% w/w [weight for weight] HP) and a retinoid prodrug (0.045% w/w TAZ). The mechanism of action of topical corticosteroids is unclear, but they are thought to induce proteins that inhibit phospholipase A2, which is postulated to control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. TAZ is a retinoid prodrug and, while the exact mechanism of action in psoriasis is not completely defined, TAZ appears to have a role in reducing cell proliferation and hyperplasia, suppressing inflammatory markers, and inhibiting elements of psoriatic scale. HP/TAZ is available as a topical lotion and the Health Canada–recommended dose is to be applied in a thin layer to the affected area once a day.

Submission History

HP/TAZ was previously submitted to CADTH and voluntarily withdrawn by the sponsor in February 2019.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of two double-blind randomized controlled trials of HP/TAZ, an indirect comparison submitted by the sponsor, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with plaque psoriasis, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Three patient groups, the Canadian Psoriasis Network (CPN), the Canadian Skin Patient Alliance (CSPA), and the Canadian Association of Psoriatic Patients (CAPP), provided input through a joint patient input submission. Patient perspectives were obtained from three surveys conducted for this submission. These surveys were distributed through membership lists, social media, CPN's website, and e-newsletters, as well as from a prior patient survey and related published report on the topic of psoriasis. The following is a summary of key input from the perspective of the patient groups:

- The impact of plaque psoriasis on patients varies by disease severity, course of disease progression, how a patient views their disease, and the efficacy of treatments. The patient groups stressed that having access to a variety of treatments that are safe, effective, and affordable is of fundamental importance. They also expressed that currently, the symptoms of psoriasis are not being properly treated in a large number of patients and there is a need for improved treatments for itchiness, redness, flakes, and other symptoms. However, ultimately, patients want a cure for plaque psoriasis.
- The patient groups described living with plaque psoriasis as having a significant impact on their quality of life. Patients also reported feelings of low self-esteem, depression, and avoidance of social activities.
- Patients reported that challenges with current topical treatments include side effects, inconvenience, high cost, and that they are ineffective after prolonged use.

- Patients expect a new treatment that is more efficacious in terms of resolution of plaques, itching, redness, burning sensation, bleeding, joint pain, general pain, and improvement in the emotional toll of the disease such as depression, anxiety, and stigma. Moreover, patients expect a treatment that addresses all of their symptoms, or a cure.

Clinical Trials

The systematic review included two identically designed, double-blind, randomized, parallel-group, vehicle-controlled trials of patients with moderate-to-severe plaque psoriasis. Study 301 (N = 203) and Study 302 (N = 215) enrolled adults with plaque psoriasis based on an IGA score of 3 or 4. Patients were required to have an area of plaque psoriasis appropriate for topical treatment that covered between 3% and 12% (inclusive) of the BSA and a target lesion that measured between 16 cm^2 and 100 cm^2, inclusive. Patients were excluded if they received prior treatment for plaque psoriasis and failed to respond, or if they received treatment for psoriasis within a specified amount of time. Prior use of phototherapy, photochemotherapy, or non-biologic systemic psoriasis therapy within the four weeks prior to baseline, and prior use of biologics known to affect psoriasis within three months of baseline were also exclusion criteria. Patients were randomized in a 2:1 ratio to receive HP/TAZ or vehicle lotion once daily for eight weeks as monotherapy. Overall, study discontinuation rates were similar between treatment groups and across trials (HP/TAZ versus vehicle = Study 301: 17.0% versus 16.2%; Study 302: 14.9% versus 17.6%).

Key limitations are the lack of comparative evidence, lack of long-term data, and generalizability of the patient population.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed HRQoL and skin clearance. The primary outcome in both trials was treatment success, defined as having at least a two-grade improvement from baseline in IGA score and an IGA score of "clear" or "almost clear" (0 or 1) at week 8. The secondary outcomes were treatment success by IGA score at weeks 12, 6, 4, and 2.

- HRQoL was assessed as an exploratory outcome using the DLQI in both studies. The DLQI is a 10-item self-reported questionnaire that covers six domains: symptoms and feeling, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment. A four-point Likert scale is used to measure how much the skin disease has affected a patient's life over the past week, where "not at all" or "not relevant" are scored as zero, "a little" is a score of one, "a lot" is a score of two, and "very much" is a score of three. The overall DLQI score is a numeric score derived from a sum of the 10 items, for a total score that ranges from zero to 30, with a lower score indicating greater HRQoL. There is evidence of validity, reliability, and responsiveness for the DLQI in patients with psoriasis. A within-groups minimal important difference (MID) for patients with psoriasis ranges from 2.2 to 6.9.
- The IGA is a subjective measurement of the clinical signs of psoriasis. A five-point static version of the IGA was used in the two trials. To generate the IGA score, psoriatic lesions are graded for erythema, thickness, and scaling based on an ordinal scale from 0 to 4. These scores are averaged across all lesions to obtain a single estimate of the patient's overall severity of disease at a given point in time. The three items are given equal weighting. The sum of the three scales are added and then divided by three $[(E + I + S)/3]$ for a final IGA score of zero (clear), one (almost clear), two (mild), three (moderate), or four (severe), which correspond to increasing disease severity. There are no studies that evaluate the validity, reliability, and responsiveness of the five-point scale used in the trials. However, the six-point IGA scale has been validated in terms of validity and reliability. No MID for the IGA scale in patients with psoriasis has been identified in the literature.
- BSA is used to determine the extent of psoriasis coverage within a patient. The one percent rule was used to calculate BSA in the HP/TAZ trials, where the subject's palm represents approximately 1% of the total BSA and is used to measure the affected area. The BSA calculation in the trials did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas. It is generally accepted that a patient presenting with an affected BSA of 0% to 3% or less is considered low BSA affected, that coverage of 3% to 10% or less is considered medium BSA affected, and that coverage of 10% or more is considered a high amount of BSA involvement. Evidence of an MID for reduction in BSA was not identified in the literature for patients with psoriasis. The clinical expert consulted by CADTH for this review indicated that a one-third reduction in BSA is a clinically important difference for patients.

Efficacy

HRQoL was identified as an outcome that is important to patients and was included as an exploratory outcome and measured using the DLQI. At week 8 (end of treatment), the DLQI score for patients in Study 301 had [redacted] in the HP/TAZ and vehicle treatment groups, respectively. In Study 302, the mean

change from baseline in the DLQI score was [redacted] for patients in the HP/TAZ and vehicle treatment groups, respectively. In the absence of formal statistical testing and between-group comparisons, no conclusions can be made regarding the effect of HP/TAZ on HRQoL.

The primary outcome in both studies was treatment success at week 8 based on IGA score. In Study 301, 35.8% and 7.0% of patients treated with HP/TAZ and vehicle, respectively, had treatment success at week 8. In Study 302, 45.3% and 12.5% of patients treated with HP/TAZ and vehicle had treatment success at week 8, respectively. In both trials, the difference between HP/TAZ and vehicle in the proportion of patients achieving treatment success ($P < 0.001$) was in favour of HP/TAZ. Treatment success based on IGA score was assessed at weeks 12, 6, 4, and 2 as secondary end points, which were analyzed following a gated sequential testing procedure in that order. The difference between HP/TAZ and vehicle in the proportion of patients with treatment success was in favour of HP/TAZ ($P < 0.05$) at weeks 12, 6, and 4 in both studies.

A descriptive subgroup analysis of treatment success based on IGA score at week 8 by baseline disease severity was reported in both trials. The proportion of patients with treatment success at week 8 was numerically greater for the HP/TAZ groups compared with the vehicle groups for both patients with moderate and severe disease at baseline. The subgroup results are consistent with the primary analysis; however, no firm conclusions can be drawn about any of the subgroups in the absence of formal pre-specified testing. The subgroup analyses are also limited by their sample size, as less than 20% of the overall population in each of the two trials were included in the subgroup analysis of patients with severe disease at baseline.

BSA outcomes were included as exploratory end points in both trials and only descriptive statistics were presented for this outcome. The mean percent of BSA affected by psoriasis in Study 301 was [redacted] with HP/TAZ and [redacted] with vehicle at baseline, and [redacted] with HP/TAZ and [redacted] with vehicle at week 8. This corresponded to a 32.8% (SD = 40.8%) and 2.3% (SD = 83.0%) change in the mean for the HP/TAZ group and vehicle group, respectively. In Study 302, the mean percent of BSA was [redacted] and [redacted] at baseline for the HP/TAZ and vehicle treatment groups, respectively, and [redacted] with HP/TAZ and [redacted] with vehicle at week 8. This corresponded to a change in the mean of 42.5% (SD = 37.7%) and 8.3% (SD = 27.2%) for the two treatment groups, respectively.

Harms (Safety)

- Overall, adverse events were more frequent with HP/TAZ compared with vehicle in Study 301 (36.8% versus 19.4% for the HP/TAZ and vehicle group, respectively) and in Study 302 (35.0% versus 23.3% with HP/TAZ versus vehicle, respectively). The most commonly reported adverse event in both studies was contact dermatitis, which only occurred in patients in the HP/TAZ treatment groups (5.3% in Study 301 and 9.5% in Study 302).
- Overall, 7.5% of patients in the HP/TAZ treatment group and zero patients in the vehicle treatment group reported a withdrawal due to an adverse event in Study 301. In Study 302, 5.1% of patients in the HP/TAZ group and 6.8% of patients in the vehicle group reported a withdrawal due to an adverse event.
- In Study 301, serious adverse events were reported by three (2.3%) patients in the HP/TAZ group and zero patients in the vehicle group. No serious adverse event was observed in more than one patient. No serious adverse events were reported in Study 302, and no deaths were reported in either of the trials.
- Pruritis, skin atrophy, folliculitis, burning sensation, skin irritation, hypersensitivity events, hypothalamic pituitary adrenal axis suppression, and severe dryness were included as notable harms in the CADTH review protocol. Of the these, pruritus was the most frequently occurring; in Study 301, it was reported among 3.0% of patients treated with HP/TAZ and zero patients treated with vehicle. In Study 302, pruritus was reported by 2.9% and 5.5% of patients in the HP/TAZ and vehicle treatment groups, respectively. Reporting of the other notable harms was infrequent, occurring in no more than 3.0% of patients in a treatment group.

Indirect Treatment Comparisons

One sponsor-submitted ITC was included, which was a systematic literature review (SLR) followed by a network meta-analysis (NMA) that compared HP/TAZ to the other topical therapies available in Canada for patients with moderate-to-severe plaque psoriasis, if possible. Studies that included adults with mild, moderate, or severe plaque psoriasis, including scalp psoriasis, were eligible for inclusion in the SLR. For studies with a population of mixed disease severity, the proportion of those with mild plaque psoriasis should have been less than 30% of the overall study population. The NMA was informed by the SLR but focused on evidence specific to those with moderate-to-severe disease. It was decided a priori that all comparators would be pooled by class.

Corticosteroids were pooled according to their potency and vehicle was used as reference. The NMA was conducted using a Bayesian approach and both fixed- and random-effects models were used for analyses. Treatment success at week 8, using the same definition as studies 301 and 302, was the only end point assessed in this NMA.

A total of 14 randomized controlled trials met the inclusion criteria for the NMA. The study findings showed that after eight weeks of treatment, both HP/TAZ and betamethasone dipropionate/vitamin D analogue combination (BD/VDA) were favoured over vehicle in achieving treatment success based on a relative risk of 4.72 (95% credible interval, 3.44 to 6.27) for HP/TAZ versus vehicle and 4.37 (95% credible interval, 3.31 to 5.72) for BD/VDA versus vehicle, respectively. However, there was no clear difference in treatment success between HP/TAZ and BD/VDA. In this NMA, the indirect comparisons were performed to examine the relative treatment effect between active topical therapies and vehicle, rather than between active therapies. This makes it difficult to draw conclusions about the comparisons between HP/TAZ and other active treatments. Safety was not assessed in the sponsor-submitted NMA. Limitations of the NMA include the inability to comprehensively assess the clinical heterogeneities across the included studies and their impact on the study results, the inability to perform subgroup analyses to explore the relative treatment effect of the topical therapies in various subgroups, the lack of long-term efficacy and safety data for the topical therapies of interest, and the generalizability of the patient population.

Cost and Cost-Effectiveness

HP/TAZ is available as a 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene lotion in a 100 g tube at the sponsor's submitted price of $200 per tube. The recommended use in adult patients with moderate-to-severe plaque psoriasis is to apply HP/TAZ to the affected area once daily.

The sponsor submitted a cost-utility analysis for patients with moderate-to-severe plaque psoriasis who are experiencing a psoriasis flare and are eligible to receive topical therapy. HP/TAZ was compared with BD/CAL, very high potency corticosteroid, and TAZ. The sponsor's four-state Markov model consisted of "initial psoriasis flare," "response to topical treatment," "flare relapse," and "non-responders." Patients were assumed to start in the initial psoriasis flare state with a topical treatment and could move between states at eight-week cycles. Treatment response was defined based on an IGA scale definition of clear or almost clear; these patients transitioned to the response to topical treatment state to continue treatment. Patients who did not achieve the treatment response criteria transitioned to the non-responder state, discontinued topical treatment, and received systemic or biologic treatments. Patients in the response to topical treatment state could relapse. Mortality and adverse events were not included in the sponsor's base-case analysis. IGA scale response was informed by the sponsor's ITC, which included the sponsor's Study 301 and Study 302. The probability of relapse was assumed to be the same for all treatments and was informed by a Canadian trial that compared BD/CAL gel with tacalcitol ointment and with gel vehicle. Health state utility values were informed by a post-hoc utility analysis of EuroQol 5-Dimensions values from the PSO-ABLE trial population, which reflected adult patients with moderate-to-severe psoriasis in France, the UK, and the US from 2014 to 2015.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- The underlying clinical evidence from Study 301 and Study 302 may be biased in favour of HP/TAZ due to the study limitations identified in the CADTH clinical review. The clinical efficacy of HP/TAZ compared with active topical therapies based on the ITC is uncertain.
- The clinical pathway in the model only considered one topical treatment use, as monotherapy, prior to systemic or biologic treatment and may not reflect patients with moderate-to-severe disease who are more likely to receive HP/TAZ in line with the proposed indication (i.e., with concurrent systemic or biology therapy). The model is also unable to account for discontinuations earlier than eight weeks, and reduced doses or administrations associated with flare remission.
- Relevant comparators such as phototherapy, clobetasol propionate, and foam formulation of BD/CAL were not included in the submitted analysis.
- The health state utility values used by the sponsor had limited validity.
- Drug wastage associated with unused drugs at treatment discontinuation was not considered, which underestimated the total treatment costs for all comparators.

CADTH conducted reanalyses that limited health utility to the maximum value observed in Canada, and assumed that patients in the non-responder state would experience equal amounts of time in the initial psoriasis flare and treatment response states. However, several limitations could not be addressed. Compared to BD/CAL, CADTH estimated that HP/TAZ was associated with an

incremental cost-utility ratio of $85,670 per quality-adjusted life-years (QALY; 0.0004 incremental QALYs; approximately four quality-adjusted hours; and a $37 incremental cost). All other comparators were dominated by BD/CAL. HP/TAZ had a 46% probability of being the optimal treatment at a willingness-to-pay threshold of $50,000 per QALY. This cost-effectiveness estimate may be more representative of patients with a milder plaque psoriasis than the proposed indication of those who are eligible to receive topical monotherapy and do not have access to phototherapy. Scenario analyses conducted by CADTH suggest that results are sensitive to input parameters (primarily utility values, flare relapse rate, and mean affected BSA) with the incremental cost-utility ratio ranging from $23,911 per QALY for HP/TAZ compared to BD/CAL, to HP/TAZ being dominated by (more costly and less effective than) BD/CAL.

Based on the range of potential cost-effectiveness results, the uncertain comparative efficacy of HP/TAZ, and other key limitations that could not be addressed by CADTH in the sponsor's model, the results of the CADTH reanalysis should be interpreted with caution.

June 17, 2020 Meeting (Initial)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None

October 21, 2020 Meeting (Reconsideration)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None