CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

HALOBETASOL PROPIONATE AND TAZAROTENE (DUOBRII)

(Bausch Health, Canada Inc.)

Indication: Psoriasis, moderate-to-severe plaque

Service Line:	CADTH Common Drug Review
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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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Abbreviations

BD	betamethasone dipropionate
BSA	body surface area
CAL	calcipotriol
CDR	CADTH Common Drug Review
EQ-5D	EuroQol 5-Dimensions
HP	halobetasol propionate
ICER	incremental cost-effectiveness ratio
IGA	Investigator's Global Assessment
ITC	indirect treatment comparison
QALY	quality-adjusted life-year
TAZ	tazarotene
VHPC	very high potency corticosteroid
w/w	weight by weight
WTP	willingness to pay

Executive Summary

The executive summary comprises two tables (Table 1: Submitted for Review; Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Halobetasol propionate (0.01% w/w) and tazarotene (0.045% w/w) topical lotion (Duobrii)
Submitted price	HP/TAZ lotion, 100 g tube: $200.00
Indication	Proposed: Improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis
Health Canada approval status	Under review (pre-NOC)
Health Canada review pathway	Standard
NOC date	Anticipated: June 16, 2020
Reimbursement request	As per indication
Sponsor	Bausch Health, Canada Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance; w/w = weight by weight.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Individuals with moderate-to-severe plaque psoriasis, who are experiencing a psoriasis flare and are eligible to receive topical therapy This population is more specific than the reimbursement request for "improving the signs and symptoms of plaque psoriasis in adult patients with moderate to severe plaque psoriasis"
Treatment	HP 0.01% and TAZ 0.045% lotion (HP/TAZ); thin layer applied to affected skin once daily
Comparators	• 50 mcg/g CAL and 0.5 mg/g betamethasone dipropionate BD (BD/CAL; weighted mix of foam, gel, and ointment formulations) • VHPC; weighted mix of 0.01% BD cream, lotion, and ointment and 0.05% HP cream and ointment • VDAs; weighted mix of CAL and calcitriol ointments • TAZ; weighted mix of 0.05% and 0.1% cream and gels
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	5 years
Key data source	Pooled results from the sponsor's Study 301 and Study 302,[1] and the sponsor's indirect treatment comparison[2] were used to inform treatment response; Langley et al.[3] was used to inform the probability of relapse
Submitted results for base case	Base case: only BD/CAL and HP/TAZ remained on the cost-effectiveness efficiency frontier; other comparators (VHPC, TAZ, and VDA) were dominated by HP/TAZ The ICER for HP/TAZ vs. BD/CAL is $34,611 per QALY gained (0.001 incremental QALYs [approximately 9 quality-adjusted hours] and $39 incremental costs)
Key limitations	• Underlying clinical evidence from Study 301 and Study 302 may be biased in favour of HP/TAZ due to study limitations including minor imbalances in baseline characteristics, disproportionate discontinuation rates, and lack of multiplicity adjustments for efficacy outcomes. The comparative efficacy of HP/TAZ with active topical therapies based on the indirect treatment comparison is uncertain, and the durability of clinical efficacy is uncertain given likely issues with adherence in clinical practice. • The clinical pathway in the model only considered 1 line of topical monotherapy 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 biologic therapy). The model is also unable to account for discontinuations earlier than 8 weeks or reduced treatment associated with flare remission. • Comparator groups comprised a weighted mix of treatments that did not allow individual comparison with HP/TAZ. Relevant comparators such as phototherapy, clobetasol propionate, and foam formulation of BD/CAL were not addressed in the submitted analysis. • Incorporated health utility values had limited validity, including a utility value higher (0.9) than the maximum observed in the general Canadian population (0.885) and a nonresponder state utility value based on shorter term evidence which may not reflect the patient experience of trying other treatments over a longer term. • Drug wastage associated with unused drugs at treatment discontinuation was not considered.
CADTH reanalysis results	CADTH conducted reanalyses that limited health utility to the maximum value observed in Canada and assumed that patients in the nonresponder state would experience equal amounts of time in psoriatic flare and treatment response states. However, several limitations could not be addressed. In the CADTH estimate, only BD/CAL and HP/TAZ remained on the cost-effectiveness efficiency frontier; other comparators were dominated by BD/CAL. Compared to BD/CAL, HP/TAZ was associated with an ICER of $85,670 per QALY (0.0004 incremental QALYs, approximately 4 quality-adjusted hours and $37 incremental costs) and 46% probability of being the optimal treatment at a willingness-to-pay threshold of $50,000 per QALY.

Component	Description
	In additional scenario analyses, CADTH explored alternate nonresponder state health utility values, VHPC administration frequency, flare relapse rate, affected body surface area, and the price of HP/TAZ, which resulted in a wide range of cost-effectiveness outcomes from an ICER of $23,911 per QALY for HP/TAZ compared with BD/CAL to HP/TAZ being dominated by BD/CAL. The generalizability of the results to the population of interest is uncertain. Based on this range of potential cost-effectiveness results, uncertain comparative efficacy of HP/TAZ, and the remaining key limitations that could not be addressed by CADTH in the submitted model, the results of CADTH reanalysis should be interpreted with caution.

BD/ = betamethasone dipropionate; CAL = calcipotriol; HP = halobetasol propionate; ICER = incremental cost-effectiveness ratio; QALY= quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high–potency corticosteroid.

Conclusions

Based on the substantial limitations with the submitted economic evaluation identified by CADTH:

- It is unclear whether the clinical efficacy data (i.e., Study 301, Study 302, and indirect treatment comparison [ITC]) which appears to have assessed halobetasol propionate (HP) 0.01% weight by weight (w/w) plus tazarotene (TAZ) 0.045% w/w as monotherapy in patients with more mild plaque psoriasis could be generalized to patients with moderate-to-severe plaque psoriasis, who are likely to be concurrently on systemic or biologic therapies.
- The comparative efficacy of HP/TAZ compared with other active topical therapies (including betamethasone dipropionate [BD] 0.5 mg/g and calcipotriol [CAL] 50 mcg/g) is uncertain.
- The cost-effectiveness of HP/TAZ compared with relevant comparators for the treatment of patients with moderate-to-severe plaque psoriasis remains uncertain.

CADTH reanalyses estimated that HP/TAZ is associated with a gain of 0.0004 quality-adjusted life-years (QALYs) compared with BD/CAL, resulting in an incremental cost-effectiveness ratio (ICER) of $85,670 per QALY. This estimate of the cost-effectiveness may be more representative of patients with a milder plaque psoriasis than the proposed indication, who are eligible to receive topical monotherapy and do not have access to phototherapy. CADTH illustrated that the ICERs are highly sensitive to changes in parameter values, and thus, the cost-effectiveness estimates for HP/TAZ in this setting should be interpreted with caution.

While the drug cost of HP/TAZ is less than the cost of the individual components based on a per gram list prices, HP/TAZ is more expensive than other relevant comparators such as BD/CAL.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Three patient groups contributed to CADTH's appraisal of the sponsor's pharmacoeconomic analysis of HP/TAZ (Canadian Psoriasis Network, the Canadian Skin Patient Alliance, and the Canadian Association of Psoriasis Patients).

The patient group input described the experience of oscillating between aggravated periods of psoriatic flares, followed by a possible period of remission with decreased symptoms. The patient groups also voiced the impact of psoriasis on family members and caregivers as well, who also cope with intimacy challenges and cleaning up plaques shed around their home.

The patient group input reported that current treatments included phototherapies and non-prescription treatments including moisturizers, essential and coconut oils, and salt baths. Patients expressed difficulties with available treatment modalities (i.e., inconvenient, greasy, smelly, messy, and time-consuming) that impact treatment adherence. Patients identified transportation cost as a major barrier to accessing a limited number of phototherapy clinics. Although home-based phototherapies are available, expensive rental costs may be barriers to access according to the clinical expert consulted by CADTH.

Although patients generally described the resolution of plaques as the most important outcome, patients also identified easy access and administration and faster resolution of plaque psoriasis symptoms as desired treatment goals.

The sponsor's model accounted for some elements of the patient input identified above, although not all aspects of the patient input was captured in their model:

- The sponsor modelled cycles of flares, although treatment-independent remission was not modelled.
- The sponsor presented a scenario analysis for the societal perspective, although only indirect costs from lost wages while visiting a physician for psoriasis were included. Other relevant costs (e.g., transportation costs) were not incorporated in this scenario analysis.
- The sponsor's model did not consider non-prescription treatments identified to be used by patients.
- The sponsor's model did not incorporate treatment adherence.

Given structure limitations of the sponsor's model, CADTH could not incorporate the key elements of patient input that was not addressed by the submitted model in CADTH reanalyses.

Economic Review

The current review is for 0.01% w/w HP plus 0.045% w/w TAZ lotion (Duobrii) for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe psoriasis.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis that modelled "individuals with moderate-to-severe plaque psoriasis, who are experiencing a psoriasis flare and are eligible to receive topical therapy"[4] as monotherapy. This population is more closely aligned with the population studied in the sponsor's ITC than the proposed indication and may reflect a patient population with milder disease who is likely to receive HP/TAZ as a monotherapy. The analysis considered an initial line of a topical monotherapy followed by systemic or biologic treatments for nonresponders. For the initial topical monotherapy, the sponsor compared HP/TAZ to other mixed topical treatment comparator groups comprised of BD/CAL (weighted mix of foam, gel, and ointment formulations), very high–potency corticosteroid (VHPC, weighted mix of 0.01% BD cream, lotion, and ointment, and 0.05% HP cream and ointment), vitamin D analogue (VDA; weighted mix of calcipotriol and calcitriol ointments), and TAZ (weighted mix of 0.05% and 0.1% cream and gels).

HP/TAZ is recommended to be applied to affected area once daily, and is supplied at a submitted price of $200 per 100 g tube (i.e., $2 per g). Drug wastage, including the cost of unused drugs in the tube upon treatment discontinuation, was not considered in the sponsor's economic evaluation.

QALYs and costs associated with these treatment groups were captured from a Canadian publicly funded health care payer perspective over a five-year time horizon and were discounted at 1.5% per year.

Model Structure

The sponsor's economic evaluation was structured as a Markov cohort model consisting of four health states (Figure 1, Appendix 3): initial psoriasis flare, response to topical treatment, flare relapse, and nonresponders. Patients were assumed to start in the initial psoriasis flare state with a topical treatment and were modelled in eight-week cycles. Treatment response was defined based on the Investigator's Global Assessment (IGA) definition of *clear* or *almost clear*; these patients transitioned to response to topical treatment to continue treatment. Patients who did not meet the treatment response criteria transitioned to the nonresponder state, discontinued topical treatment, and received systemic or biologic treatments. Patients in the response to topical treatment state could relapse every eight weeks to the flare relapse state, from which the patient transitioned either to response to topical treatment or nonresponders state again after eight weeks depending on treatment response. As topical treatments were not assumed to have differing impact on mortality and adverse event-associated costs and disutilities, mortality and adverse events were not included in the sponsor's base-case analysis.

Model Inputs

Baseline characteristics were not explicitly considered by the sponsor, other than patients' affected body surface area (BSA, 5% assumed). The economic model appears to reflect a population of patients with milder plaque psoriasis, which may differ to the proposed Health Canada indication population of moderate-to-severe plaque psoriasis.[2,5]

The sponsor used 2019 IQVIA PharmaStat market share data to inform the distribution of treatment costs for the mixed comparator treatment groups.[4] These groups broadly corresponded with the treatment groups analyzed in the sponsor's ITC,[2] which was used to inform the relative risks of response in the model. However, the treatment groups from the market share data and the ITC differed in two key aspects: the VHPC group from the ITC did not include HP 0.05% gel and ointment and only included 0.01% lotion instead, and the BD/CAL group from the ITC did not include foam formulation of BD/CAL. The relative risks from the ITC were applied to the probability of response at eight weeks from the vehicle arms of the sponsor's Study 301 and Study 302 results.[1] The probability of relapse, defined as at least 50% loss of the Psoriasis Area and Severity Index improvement from baseline, was assumed to be treatment independent, and was informed by the eight-week relapse results in the BD/CAL gel arm of a 2011 Canadian trial which compared BD/CAL gel with tacalcitol ointment and with gel vehicle.[3]

Upon reaching the nonresponder state, 60% of the patients were assumed to have less than 10% BSA affected and were administered systemic treatments, and the remaining 40% of the patients with more than 10% BSA affected were assumed to either have a systemic treatment (40%) or a biologic treatment (60%). The composition of these treatments were informed by IQVIA CompuScript dermatologist prescription claims and IQVIA Good Manufacturing Practice psoriasis prescription data.[4] Systemic treatments included were acitretin, cyclosporine, and methotrexate, and biologic treatments included were adalimumab, etanercept, infliximab, infliximab biosimilar, ixekizumab, secukinumab, brodalumab, and ustekinumab. Apremilast, guselkumab, certolizumab pegol, and risankizumab were not included as the claims data did not indicate any use.

Health state utility values were informed by a post hoc utility analysis of EuroQol 5-Dimensions (EQ-5D) values from the PSO-ABLE trial population,[6] which reflects adult patients with moderate-to-severe psoriasis who were recruited from France, UK, and US from 2014 to 2015.[7] The 12-week PSO-ABLE trial compared BD/CAL foam, BD/CAL gel, foam vehicle, and gel vehicle.[7] The utility values for the initial psoriasis flare and flare relapse states reflect the baseline EQ-5D score for the BD/CAL foam arm (0.80), while the utility value for the response to topical treatment state reflected the EQ-5D score of patients who achieved 75% reduction in Psoriasis Area and Severity Index score at week 4 (0.90), and the utility value for the nonresponder state reflected the EQ-5D score of nonresponders at week 4 (0.83).[6]

Cost inputs were informed by Canadian sources from 2019. Health care resource use costs were assumed to be treatment independent and a proportion of patients would consult a general practitioner (35%), dermatologist (35%), or rheumatologist (10%) over the time horizon.[4] Patients were assumed to incur an initial consultation fee for these physicians in the initial psoriasis flare state and repeat consultation fee in the other states based on Ontario Schedule of Benefits.[8] For drug costs, the sponsor made a dermatologist-validated assumption that 30 g of any topical treatment would be required to cover 100% of a patient's BSA, and that patients would adhere to dosing schedule described in the product monographs.[4] Topical drug acquisition costs were based on Ontario Drug Benefit Formulary

list prices, except for HP/TAZ which were informed by British Columbia formulary list prices.[4] Systemic and biologic drug acquisition costs were informed by the CADTH Common Drug Review (CDR) report for risankizumab which reported these costs in its Appendix 1: Cost Comparison Table.[9]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (5,000 iterations) and are presented below.

Base-Case Results

The sponsor's base-case analysis (for individuals with moderate-to-severe plaque psoriasis, who are experiencing a psoriasis flare and are eligible to receive topical therapy) reported that HP/TAZ generated 0.001 incremental QALYs at an incremental cost of $39 compared to BD/CAL in a sequential analysis, resulting in an ICER of $34,611 per QALY gained (Table 3). Other comparators, including TAZ, VHPC, and VDAs, were dominated by BD/CAL and did not appear on the cost-effectiveness efficiency frontier.[4] The cost differences between comparators were based on drug costs (Table 11, Appendix 3). The sponsor's base case was associated with a notable degree of decision uncertainty as HP/TAZ had a 46% chance of being the optimal intervention at a willingness-to-pay (WTP) threshold of $50,000 per QALY.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,554	3.967	—
HP/TAZ	**18,593**	**3.968**	**34,611**

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Only treatments that are on the efficiency frontier are reported in the main body. Detailed results are reported in Appendix 3.

Source: Sponsor's pharmacoeconomic submission.[4]

Sensitivity and Scenario Analysis Results

The sponsor conducted a number sensitivity and scenario analyses (Table 12), which considered alternate assumptions for: flare relapse rate (23% to 81%), BSA affected (3% to 12%), time horizon (1 year to 10 years), adverse events (included), and treatment in the nonresponse state (patients assumed to receive biologic; 36% of moderate patients [< 10% BSA affected] and 30% of severe patients [> 10% affected] did not receive any treatment). ICER was found to increase with increasing relapse rate ($26,686 to $79,951 per QALY) and the affected BSA (HP/TAZ dominant to $230,900 per QALY), and with decreasing time horizon ($43,865 to $118,451 per QALY) and treatment costs in the nonresponse state (HP/TAZ dominant to $66,194 per QALY). ICER decreased with the inclusion of adverse events ($14,527 per QALY).

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Uncertain comparative clinical efficacy:** The CADTH clinical reviewers deemed the sponsor's evidence for the comparative efficacy of HP/TAZ to be uncertain due to limitations associated with the sponsor's Study 301, Study 302, and ITC.

The CADTH review team identified concerns regarding the generalizability of the studied patient population (i.e., used to inform the ITC, which may have included more mild patients than covered in the sponsor's proposed Health Canada indication), and the uncertainty associated with the maintenance of the eight-week efficacy observed from these sources over the patient's lifetime; these concerns are discussed in subsequent limitations. According to the clinical expert consulted by CADTH, treatment adherence is associated with treatment efficacy and may affect the durability of treatment response. The clinical reviewers considered that the efficacy of HP/TAZ compared to vehicle in Study 301 and Study 302 may be biased in favour of HP/TAZ due to limitations associated with the studies, including minor imbalances in baseline demographic and disease characteristics, the disproportionate discontinuation rates, and lack of multiplicity adjustment for efficacy outcomes. The evidence from these trials were further incorporated into the sponsor's ITC, which included studies of various disease durations and severities, but did not assess for potential biases from heterogeneity. CADTH clinical reviewers concluded that although the efficacy of HP/TAZ and BD/CAL was superior to vehicle, the efficacy of HP/TAZ compared to other active topical therapies was inconclusive for the study population. The concerns regarding the population studied and comparative clinical efficacy are reflected in the following limitation regarding the patient population and clinical pathway of disease.

- Alternative clinical data to populate the model was not identified. Given the uncertainty regarding the comparative efficacy of HP/TAZ, the results of the economic analysis should be interpreted with caution.

- **The model may not accurately reflect the population and the clinical pathway associated with moderate-to-severe psoriasis:** The sponsor's model considered only one line of topical monotherapy before switching to systemic or biologic therapies over a time horizon of five years. Feedback from the clinical expert consulted by CADTH indicated that patients who are on topical monotherapy are likely to try multiple lines of topical therapy before progressing to use systemic or biologic therapies, while the five-year time horizon does not consider the chronic nature of the disease and patients' experiences with flares and extended use of topical treatments over a longer time period in patients who did not respond.

  - Given the structural limitations of the submitted model, CADTH was unable to conduct additional reanalyses to consider a more appropriate clinical pathway or time horizon. Although CADTH observed that at the end of the five-year time horizon greater than 99% of patients were in the absorbing nonresponder state, the unresolved limitations result in limited validity in the model structure, and thus the sponsor's results should be interpreted with caution.

Furthermore, the clinical expert indicated that moderate-to-severe plaque psoriasis patients would likely receive topical therapy as an adjunctive treatment with systemic or biologic therapy rather than as a monotherapy, which would be considered for milder cases. This feedback also appears to be consistent with the submitted clinical evidence as CADTH clinical reviewers noted lower mean affected BSA (6%) in a pooled analysis of the pivotal trials (Study 301 and Study 302) compared to a common trial inclusion criteria for moderate-to-severe psoriasis patients (≥ 10%) reported by a Canadian clinical guideline,[10] and the inclusion of a mild psoriasis population in a number of trials that were incorporated into the sponsor's ITC. Therefore, the clinical evidence used to inform the sponsor's model may better reflect a patient population with a milder psoriasis.

- CADTH explored scenario analyses that considered a more severe population in terms of the affected BSA. Scenario analyses considered alternate estimates of affected BSA in line with a commonly used trial inclusion criteria for moderate-to-severe psoriasis reported in a Canadian clinical guideline,[10] or that broadly reflected baseline affected BSA of trial populations in previous CDR submissions for moderate-to-severe plaque psoriasis.[11-13] Given the lack of clinical data available for patients with more severe psoriasis who are on concurrent systemic or biologic therapy, the results of the economic analysis are of limited validity based on the modelled (and

indicated) population and should be interpreted with caution. Of note, the product monograph for HP/TAZ specifies that the efficacy and safety of HP/TAZ in patients with more than 12% of BSA affected by plaque psoriasis has not been established.[5]

The sponsor reported that an eight-week cycle length was used in the model due to the lack of more granular IGA end points. However, this cycle length does not allow the model to capture events that occur within a shorter time frame. The clinical expert consulted by CADTH reported that patients may discontinue topical treatments due to an adverse event arising within the first four weeks of treatment.

- Given the lack of clinical data for patients with more severe psoriasis and the lack of flexibility in the model to use a shorter cycle length, CADTH was unable to conduct additional reanalyses to consider a more appropriate cycle length which impacts the clinical pathway.

The model structure does not accurately capture the relapsing and remitting nature of psoriasis. According to patient input and the clinical expert consulted by CADTH, periods of remission were expected after flares, when topical therapies would not be expected to contribute significantly to differences in quality of life and would be either stopped or reduced in frequency as maintenance therapy.

- Given the lack of clinical data for patients with more severe psoriasis and the lack of flexibility in the model to address the relapsing-remitting nature of flares, CADTH was unable to conduct additional reanalyses to consider a more appropriate population and clinical pathway.

Furthermore, the modelled flare relapse rate was also based on an eight-week trial result and it is uncertain whether this estimate is reflective of the long-term relapse rate in the indicated population. Collectively, the generalizability of the sponsor's model to the indicated population for HP/TAZ is unclear.

- CADTH explored alternate flare relapse rate assumptions in scenario analysis 3a (30%) and 3b (50%) due to the uncertainty associated with this parameter estimate.

- Inappropriately modelled comparators: The sponsor used a weighted mix of treatment comparators and did not consider all relevant comparators individually, increasing the uncertainty regarding the generalizability and the validity of the results. The sponsor's use of mixed treatment comparators also aggregated potentially heterogenous efficacy across active ingredients and formulations. In addition, key relevant comparators such as phototherapy, clobetasol, and the foam formulation of BD/CAL were excluded as their comparative efficacy to HP/TAZ could not be addressed by the sponsor's ITC which informed the economic model. Of note, the clinical expert consulted by CADTH identified that the foam formulation of BD/CAL is more effective than other formulations,14 and it is unclear whether the inclusion of the foam formulation in the sponsor's ITC would have reduced the observed difference between the relative risk of response between HP/TAZ and BD/CAL or allowed BD/CAL to surpass HP/TAZ. Given that the incremental QALY difference between HP/TAZ and BD/CAL is small (0.001) in the sponsor's base case, this has the potential to substantially alter the results of the cost-utility analysis. Furthermore, the sponsor's use of a different mix of treatments for cost and efficacy inputs further contributed to uncertainty in the results of the analysis.

  - Given the available clinical information and the structural limitations of the submitted model, CADTH was unable to conduct reanalyses to assess the cost-effectiveness of HP/TAZ compared with relevant comparators.

    Although the sponsor modelled VHPC treatments as twice daily administration based on product monographs, VHPC is commonly prescribed as once daily administration according to the clinical expert consulted by CADTH.

  - As the clinical expert consulted by CADTH indicated that VHPC treatments are commonly prescribed as once daily administration rather than the twice daily

administration in the sponsor's model, CADTH explored modelling once daily VHPC administration in scenario analysis 2.

- **Health utility values of limited validity:** The health utility values used in the sponsor's economic evaluation do not reflect the Canadian patient population. While the maximum observed EQ-5D Canadian utility value in the general population is 0.885,[15] the sponsor's model allowed a utility value up to 0.9 in the response to topical treatment state. Furthermore, the sponsor used a utility value for nonresponder which reflects BD/CAL nonresponders at four weeks post-treatment.[6] As the nonresponder state in the model is an absorbing state reflective of a long-term patient state, the generalizability of this utility value from four-week evidence is uncertain, especially as the nonresponders are assumed to move on to other treatments that they may respond to.
    - CADTH applied a Canadian general population utility value estimate for the response to topical treatment health state (0.885) within the undertaken reanalyses. An alternate estimate for the utility value of the nonresponder health state was also applied, reflective of the assumption that patients spend half of the time in flare relapse and the other half of the time in the response state (0.8425). Extreme assumptions for the utility value of this health state were explored in scenario analyses.
- **Unaccounted cost of topical treatment wastage:** The sponsor did not account for the potential cost of wasted drugs upon topical treatment discontinuation. HP/TAZ for example, is supplied in 100 g tubes and approximately 59% of patients discontinuing treatment after the first eight-week cycle due to lack of response would not be using the remaining 16 g in the tube. As the impact of accounting for drug wastage would depend on the size of the topical treatment tube and the cycle at treatment discontinuation, the direction of its impact is uncertain.
    - Due to the structural limitations of the submitted model, CADTH was unable to conduct reanalyses that considered the cost of drug wastage. Given small incremental differences in cost and QALYs between the comparators, the impact of accounting for drug wastage on cost-effectiveness outcomes is expected to be substantial.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (See Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
Flare relapse is treatment independent	Acceptable. According to the clinical expert consulted by CADTH, topical treatments are likely to reduce the quality of life impact of flare relapses rather than the frequency of relapses.
Mortality was not modelled	Acceptable. According to the clinical expert consulted by CADTH, topical treatments are unlikely to impact mortality.
Cost and health impacts of adverse events do not substantially impact cost-effectiveness results	Acceptable. According to the clinical expert, differences in treatment-emergent adverse events between the comparators are negligible.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case: none		
Changes to derive the CADTH estimate		
1. Limit maximum health utility value to reflect observed Canadian values	Mean utility value of the response to topical treatment state: 0.9 (SE = 0.012)	Mean utility value of the response to topical treatment state: 0.885 (SE = 0.017) from Bansback et al.[15]
2. Nonresponder state health utility value reflective of long-term health state assuming patients experience equal durations of relapse and response	Mean utility value of the nonresponder state: 0.83	Mean utility value of the nonresponder state = 0.85; CADTH assumed these patients would have a utility value that would reflect spending half of their remaining life in relapse and the other half in response (50% × 0.8 + 50% × 0.9 = 0.85)
CADTH estimate		Sponsor's base case + reanalyses 1 and 2 (mean utility value of the nonresponder state: 50% × 0.8 + 50% × 0.885 = 0.8425).

SE = standard error.

CADTH undertook a stepped analysis (Table 13) to highlight the impact of each change that was applied to the sponsor's base case (Table 5). The summary of results of the CADTH estimate is presented in Table 6, and detailed results are available in Table 14. Details regarding QALYs and costs accrued in each health state were unavailable as the sponsor did not provide this disaggregated information in the submitted model. Only BD/CAL and HP/TAZ remained on the cost-effectiveness efficiency frontier and all other comparators were dominated by BD/CAL. HP/TAZ had an ICER of $85,670 per QALY compared to BD/CAL. At a WTP threshold of $50,000 per QALY, HP/TAZ had 46% probability of being the optimal treatment.

Table 6: Summary of the CADTH Reanalysis Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
CADTH estimate			
BD/CAL	18,564	4.0167	-
HP/TAZ	18,601	**4.0171**	85,670

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places. Note: Only treatments that are on the efficiency frontier are reported in the main body. Detailed results are reported in Appendix 4.

Scenario Analysis Results

Although many of the identified limitations could not be explored in reanalyses, CADTH identified that utility value of the nonresponder state was a key driver of model results. Given the uncertainty associated with the estimate of this state's utility value, CADTH conducted scenario analyses (1a and 1b) that reflected extreme assumptions associated with this state.

CADTH also explored other parameter uncertainties inherent in the submitted model. In the scenario analysis 2, CADTH explored a scenario with once daily administration of VHPC instead of the twice daily administration assumed in the CADTH estimate as the clinical expert consulted by CADTH indicated that once daily administration is commonly prescribed in practice. Alternate assumptions for flare relapse rate (scenario analyses 3a and 3b) and affected BSA (scenario analyses 4a and 4b) were also explored as the uncertainties associated with these parameters substantially impacted cost-effectiveness outcomes in the sponsor's scenario analyses. For the relapse rate, estimates that were approximately 10% lower and 10% higher compared to the base-case value of 41.8% were explored (30% in scenario analysis 3a and 50% in scenario analysis 3b). For the affected BSA, higher estimates than the base assumption of 5% were explored to consider populations with more severe disease. Scenario analysis 4a explored a BSA estimate of 10% in line with a commonly used trial inclusion criteria for moderate-to-severe psoriasis reported in a Canadian clinical guideline,[10] while scenario analysis 4b explored a BSA estimate of 25% that broadly reflected baseline affected BSA of trial populations in previous CDR submissions for moderate-to-severe plaque psoriasis.[11-13] However, scenario analysis 4b should be interpreted with caution given that the efficacy and safety of HP/TAZ in patients with more than 12% of BSA affected by plaque psoriasis has not been established.[5] Lastly, the impact of a 3% price reduction in HP/TAZ was explored in scenario analysis 5 given that cost-effectiveness outcomes are likely to be sensitive to changes in cost due to a small incremental QALY difference (0.0004 QALYs in CADTH estimate).

A summary of the explored scenario analyses is presented below:

Scenario analysis 1a: Patients in the nonresponder state was assumed to experience health utility equivalent to a relapsed psoriatic flare (mean 0.8).

Scenario analysis 1b: Patients in the nonresponder state was assumed to experience health utility equivalent to the response to topical treatment state health state (mean 0.885, SE: 0.017).

Scenario analysis 2: The frequency of VHPC administration was reduced from twice daily to once daily.

Scenario analysis 3a: Mean eight-week psoriatic flare relapse rate was reduced from 41.8% to 30%.

Scenario analysis 3b: Mean eight-week psoriatic flare relapse rate was increased from 41.8% to 50%.

Scenario analysis 4a: Mean affected BSA of patients was increased from 5% to 10%.

Scenario analysis 4b: Mean affected BSA of patients was increased from 5% to 25%.

Scenario analysis 5: The price of HP/TAZ was reduced by 3%.

Detailed results of the scenario analyses are presented in Table 15 (scenario 1a), Table 16 (scenario 1b), Table 17 (scenario 2), Table 18 (scenario 3a), Table 19 (scenario 3b), Table 20 (scenario 4a), Table 21(scenario 4b), and Table 22 (scenario 5). The results showed that cost-effectiveness outcomes varied widely depending on utility values (ICER range: $23,900 per QALY to dominated), flare relapse rate (ICER range: $55,562 per QALY to $109,105 per QALY), and mean affected BSA (ICER range: $377,093 per QALY to $1,443,890 per QALY). Although reducing VHPC administration frequency to once daily did not have

substantial impact on cost-effectiveness results, reducing the price of HP/TAZ by only 3% resulted in a lowering of the ICER to $37,276 per QALY.

Collectively, these scenario analyses reflect a substantial uncertainty in the economic analysis. Even in the most favourable scenario 1a, HP/TAZ was associated with 51% probability of being the optimal treatment at a WTP threshold of $50,000 per QALY.

Issues for Consideration

- According to the clinical expert consulted by CADTH, prescribing practices vary across Canada and may contribute to uncertainty regarding the selection of comparators.
- According to the clinical expert consulted by CADTH, HP/TAZ has the potential to be used as off-label treatment in patients with milder psoriasis.
- According to the clinical expert consulted by CADTH, HP/TAZ would not be used in psoriatic patients experiencing non-plaque flares with the exception of possible use in patient with localized pustular flares.
- On a per gram basis, HP/TAZ is less costly ($2.00/g) than its individual components (HP [cream: $0.9766, ointment: $1.0811/g] and TAZ [cream or gel: $1.3887/g] sum to a range between $2.3653 to $2.4698 per g). However, as HP/TAZ is only available in a tube size (100 g) larger than HP (cream or ointment: 50 g) and TAZ (cream or gel: 30 g), initial drug cost may be more expensive.

Overall Conclusions

CADTH identified several key limitations with the submitted economic evaluation that could not be addressed given the lack of more appropriate model structure and model inputs. This limits the applicability of the results in providing information on the likely cost-effectiveness of HP/TAZ compared with relevant comparator treatments for patients with moderate-to-severe plaque psoriasis.

In line with the findings of the CADTH clinical reviewers, the CADTH economic reviewers determined that it is uncertain whether the population used to inform key clinical data for the submitted economic model (i.e., Study 301, Study 302, and ITC) is generalizable to patients with moderate-to-severe plaque psoriasis, who are more likely to be concurrently on systemic or biologic therapies. Furthermore, the modelled clinical pathway did not reflect clinical expert feedback on Canadian clinical management nor the feedback from patients with moderate-to-severe plaque psoriasis. Moreover, the ITC omitted relevant comparators and was performed to examine the relative treatment effect of active topical therapies to vehicle (as opposed to between active therapies), which lead CADTH clinical reviewers to conclude that the efficacy of HP/TAZ compared with other active topical therapies (including BD/CAL) cannot be determined for the study population.

CADTH reanalyses highlight the volatility of the results due to several other areas of uncertainty. CADTH estimated an ICER of $85,670 per QALY for HP/TAZ compared with BD/CAL for a patient population representative of milder plaque psoriasis than the proposed indication, who are eligible to receive topical monotherapy and do not have access to phototherapy; HP/TAZ is associated with small incremental QALY benefits (at the level of quality-adjusted hours of life). The ICER varied widely in CADTH scenario analyses (in some analyses HP/TAZ maintained a small QALY benefit compared with other treatments, in others HP/TAZ accrued fewer QALYs than other treatments) and was most sensitive to the flare relapse rate, the proportion of affected BSA, the price of HP/TAZ, and health utility

values associated with the long-term nonresponder state. Due to the identified limitations with the submitted model, population and comparators, and uncertain comparative efficacy, the value of HP/TAZ compared to relevant comparators in the Canadian setting is uncertain and the cost-effectiveness estimates presented should be viewed with caution.

While the drug cost of HP/TAZ is less than the cost of the individual components (HP and TAZ) based on per gram list prices, HP/TAZ is more expensive than other relevant comparators such as BD/CAL.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 7: CADTH Cost Comparison Table of Topical Treatments for Plaque Psoriasis

Treatment	Strength	Package form	Dosage form	Price per g or mL ($)	Recommended dosage
Halobetasol propionate + tazarotene (Duobrii)	**0.01% + 0.045%**	**100 g**	**Lotion**	**2.0000[a]**	**Apply to affected area once daily**
Other combination treatment					
Betamethasone dipropionate + calcipotriol (Dovobet, Enstilar)	0.5 mg/g + 50 mcg/g	60 g 30 g, 60 g, 120 g 30 g, 60 g, 120 g	Foam Gel Ointment	1.5760 1.6311 1.5929	Apply to affected area once daily up to 4 weeks; daily maximum 15 g, weekly maximum 100 g
Corticosteroids					
Amcinonide (generic)	0.1%	60 g 60 mL 60 g	Cream Lotion Ointment	0.1955 0.2997[b] 0.3069[b]	Apply to affected area twice daily; maximum 5 days on face, axillae, scrotum, or scalp, 2 to 3 weeks elsewhere
Betamethasone dipropionate (generic)	0.05%	50 g 75 mL 50 g	Cream Lotion Ointment	0.2048 0.1980 0.5186	Apply to affected area twice daily, reassess need at least every 4 weeks
Betamethasone valerate (generic)	0.1%	450 g 30 mL, 60 mL 450 g	Cream Lotion Ointment	0.0889 0.3125 0.0889	No recommended daily dose; use as directed by clinicians
Clobetasol propionate (generic)	0.05%	15 g, 50 g, 450 g 15 g, 50 g 59 mL	Cream Ointment Spray	0.2279 0.2279 1.9259[c]	Apply to affected area twice daily; weekly maximum 50 g, and limited to 2 consecutive weeks
Desonide (generic)	0.05%	15 g, 60 g, 454 g 60 g	Cream Ointment	0.2650 0.2647	Apply to affected area twice daily, may be increased in refractory cases
Desoximetasone (Topicort)	0.05% 0.25% 0.05% 0.25%	20 g 60 g 60 g 60 g	Cream Gel Ointment	0.5129[b] 0.7340[b] 0.5540[b] 0.7142[b]	Apply to affected area twice daily
Fluocinonide (Lyderm, Lidex)	0.05%	15 g, 60 g, 400 g 15 g, 60 g 15 g, 60 g	Cream Gel Ointment	0.2378 0.3076 0.3035	Apply to affected area twice daily; weekly 45 g, and limited to 2 weeks

Treatment	Strength	Package form	Dosage form	Price per g or mL ($)	Recommended dosage
Fluocinolone acetonide (Synalar)	0.01% 0.025%	60 mL, 118 mL 60 g	Solution Ointment	0.2979[b] 0.4875[b]	Solution: Apply 2 to 4 times daily Ointment: Apply 2 to 3 times daily
Fluocinonide (Tiamol)	0.05%	25 g 100 g	Cream	0.1980	Apply 2 to 4 times daily
Halobetasol propionate (Ultravate)	0.05%	50 g 50 g	Cream Ointment	0.9766[d] 1.0811[d]	Apply to affected area twice daily; limited to 50 g weekly and 2 weeks without re-evaluation
Hydrocortisone/ Hydrocortisone acetate (various)[e]	0.5% 1% 2.5% 10% 1% 2.5% 10% 0.5% 1%	15 g, 28 g, 45 g 30 g,45 g,120 g, 225 g, 454 g, 500 g 45 g, 225 g 100g 60 mL, 120 mL, 150 mL 60 mL 250 mL 15 g 454 g	Cream Lotion Ointment	0.1907[b] 0.0859[b] 0.3322[b] 0.1881[f] 0.1010[f] 0.1656[f] 0.1045[f] 0.1400 0.0390	Use as directed by clinicians
Hydrocortisone valerate (Hydroval)	0.2%	15 g, 45 g, 60 g 15 g, 60 g	Cream Ointment	0.1313	Apply to affected area twice daily; discontinue as soon as lesions heal or if no response
Mometasone furoate (generic)	0.1%	15 g, 50 g 15 g, 50 g	Cream Ointment	0.5542 0.2252	Apply to affected areas twice daily
Prednicarbate (Dermatop)	0.1%	20 g, 60 g 60 g	Cream Ointment	1.7098[c]	Apply to affected areas twice daily; reassess if no response within a few days to a week, maximum two weeks
Triamcinolone acetonide (various)	0.1%	30 g 15 g	Cream Ointment	0.0533	No recommended for daily use; use as directed by clinicians
Calcineurin inhibitor					
Pimecrolimus (Elidel)	1%	10 g, 30 g	Cream	2.4157	Apply to affected area twice daily, discontinue when resolved or after three weeks if no improvement or exacerbation
Tacrolimus (Protopic)	0.03% 0.10%	30 g	Ointment	2.4928 2.6667	Apply to affected area twice daily; discontinue after 6 weeks if no improvement or exacerbation

Treatment	Strength	Package form	Dosage form	Price per g or mL ($)	Recommended dosage
Vitamin D analogue					
Calcipotriol (Dovonex)	50 mcg/g	15 g, 60 g, 120 g, 240g	Ointment	0.9077	Apply 1 to 2 times daily; maximum of 100 g per week
Calcitriol (Silkis)	3 mcg/g	5 g, 30 g, 100 g	Ointment	1.3625	Apply twice daily; no more than 30 g daily
Retinoid					
Tazarotene (Tazorac)	0.05% 0.1%	30 g	Cream/Gel Cream/Gel	1.3887[b]	Start with 0.05% once daily, increase to 0.1% if tolerated and medically indicated; apply once a day in the evening

Note: Ontario Drug Benefit Formulary (accessed March 2020)[16] list prices unless otherwise indicated, and do not include dispensing fees. Recommended doses from respective product monographs unless otherwise indicated.

[a] Sponsor's submitted price.[17]

[b] Saskatchewan Formulary list price (March 2020).[18]

[c] Ontario wholesale price, as reported by IQVIA DeltaPA (March 2020).[19]

[d] Alberta Formulary list price (March 2020).[20]

[e] Includes compounds with camphor, menthol, pramoxine, and urea.

[f] British Columbia Formulary list price (March 2020).[21]

Table 8: CADTH Cost Table of Phototherapy Treatments for Plaque Psoriasis

Treatment	Strength	Dosage form	Price per unit ($)	Recommended dosage	Weekly cost ($)
Phototherapy					
Ultraviolet light therapy	NA	NA	7.85 per treatment[a]	Administered 2 to 3 times per week; maintenance therapy may be tapered to once weekly[b]	8 to 24
Methoxsalen[c] (various)	10 mg 1%	Capsule Lotion	0.5580 per mg 1.94 per mL[d]	30 mg[b] 1 mL mixed with 2 L of water soaked into hands and feet	17 to 50 2 to 6

NA = not applicable.

Note: Ontario Drug Benefit Formulary list prices unless otherwise indicated (accessed March 2020),[16] and do not include dispensing fees. Assumed patient weight of 90 kg.

[a] Assumed to be reimbursed private clinic treatment cost: Ontario Schedule of Benefits for Physician Services, code G470 "Ultraviolet Light Therapy" (accessed March 2020).[22] Can also be administered as public outpatient or as home therapy.

[b] 2019 American Academy of Dermatology and National Psoriasis Foundation guidelines for care for the management and treatment of psoriasis with phototherapy.[23]

[c] Administered as the psoralen component in a psoralen plus ultraviolet A light therapy.[23]

[d] British Columbia Formulary list price (March 2020).[21]

Table 9: CADTH Cost Comparison Table of Systemic Treatments for Moderate-to-Severe Plaque Psoriasis

Treatment	Strength	Dosage form	Price ($)	Recommended dosage	Annual cost ($)
Biologics					
Adalimumab (Humira)	40 mg/0.8 mL	Syringe or pen	769.9700	80 mg initial dose, 40 mg every other week starting 1 week after initial dose	First year: 21,559 Subsequent years: 20,019
Brodalumab (Siliq)	210 mg/1.5 mL	Pre-filled syringe	645.0000	210 mg SC at weeks 0, 1, and 2, followed by every 2 weeks thereafter	First year: 17,415 Subsequent years: 16,770
Certolizumab pegol (Cimzia)	200 mg 400 mg	Pre-filled syringe or autoinjector	664.5100[a] 1,329.0200[a]	400 mg initial dose at weeks 0, 2, and 4, followed by 400 mg or 200 mg every 2 weeks	First year: 19,271 to 34,555 Subsequent years: 17,277 to 34,555
Etanercept (Enbrel)[b]	50 mg/mL 25 mg/vial	Syringe or pen vial	405.9850 202.9300	50 mg twice weekly for 12 weeks, then 50 mg weekly	First year: 25,975 to 25,983 Subsequent years: 21,105 to 21,111
Guselkumab (Tremfya)	100 mg/mL	Pre-filled syringe	3,059.7400[c]	100 mg SC at weeks 0 and 4, followed by every 8 weeks thereafter	First year: 21,418 Subsequent years: 19,888
Infliximab (Remicade)	100 mg/vial	Vial	977.0000[d]	5 mg/kg/dose, for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks	First year: 39,080 Subsequent years: 31,753
Infliximab (Renflexis, SEB)			493.0000		First year: 19,720 Subsequent years: 16,023
Ixekizumab (Taltz)	80 mg/ 1mL	Pre-filled syringe	1,582.2400	160 mg initial dose, 80 mg at 2, 4, 6, 8, 10, and 12 weeks, followed by 80 mg every 4 weeks	First year: 26,898 Subsequent years: 20,569
Risankizumab (Skyrizi)	75 mg/0.83 mL	Pre-filled syringe	2,467.5000[e]	150 mg at week 0 and 4, followed by 150 mg every 12 weeks thereafter	First year: 24,675 Subsequent years: 21,385
Secukinumab (Cosentyx)	150 mg/mL	Pre-filled syringe or pen	831.1100	300 mg SC injection at weeks 0, 1, 2, and 3, then monthly injections starting at week 4	First year: 24,933 Subsequent years: 19,947
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1 mL	Pre-filled syringe	4,593.1400	< 100 kg patients: 45 mg at weeks 0 and 4, followed by 45 mg every 12 weeks thereafter (same for > 100 kg, at 90 mg)	First year: 22,966 Subsequent years: 19,904
Non-biologic systemic treatments					
Acitretin (generics)	10 mg 25 mg	Capsule	1.2965 2.2770	25 mg to 50 mg daily	829 to 1,658
Apremilast (Otezla)	30 mg	Tablet	18.9041[f]	30 mg twice daily	13,762

Treatment	Strength	Dosage form	Price ($)	Recommended dosage	Annual cost ($)
Cyclosporine (generics)	10 mg 25 mg 50 mg 100 mg 100 mg/mL	Capsule Oral solution	0.6520 0.9952 1.9400 3.8815 3.7707	2.5 mg to 5 mg/kg daily, in 2 divided doses	3,106 to 6,212
Methotrexate (generics)	2.5 mg 10 mg 20 mg/2 mL 50 mg/2 mL	Tablet Tablet Vial Vial	0.6325 2.7000[d] 12.5000 8.9200	10 mg to 25 mg by mouth or IM weekly	140 to 347 464

IM = intramuscular; SC = subcutaneous; SEB = subsequent entry biologic.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed March 2020),[16] unless otherwise indicated, and do not include dispensing fees. Recommended doses from respective product monographs unless otherwise indicated. Annual cost assumed 52 weeks or 364 days. Assumed patient weight of 90 kg and wastage of excess medication in vials, if applicable.

[a] Sponsor's submitted price.[24]

[b] Two biosimilars of etanercept are currently available in Canada but are not currently approved for the treatment of psoriasis.

[c] Ontario wholesale price, as reported by IQVIA DeltaPA (March 2020).[19]

[d] Saskatchewan formulary (March 2020).[18]

[e] Sponsor's submitted price.[9]

[f] Quebec formulary, as reported by IQVIA DeltaPA (March 2020).[19]

Appendix 2: Submission Quality

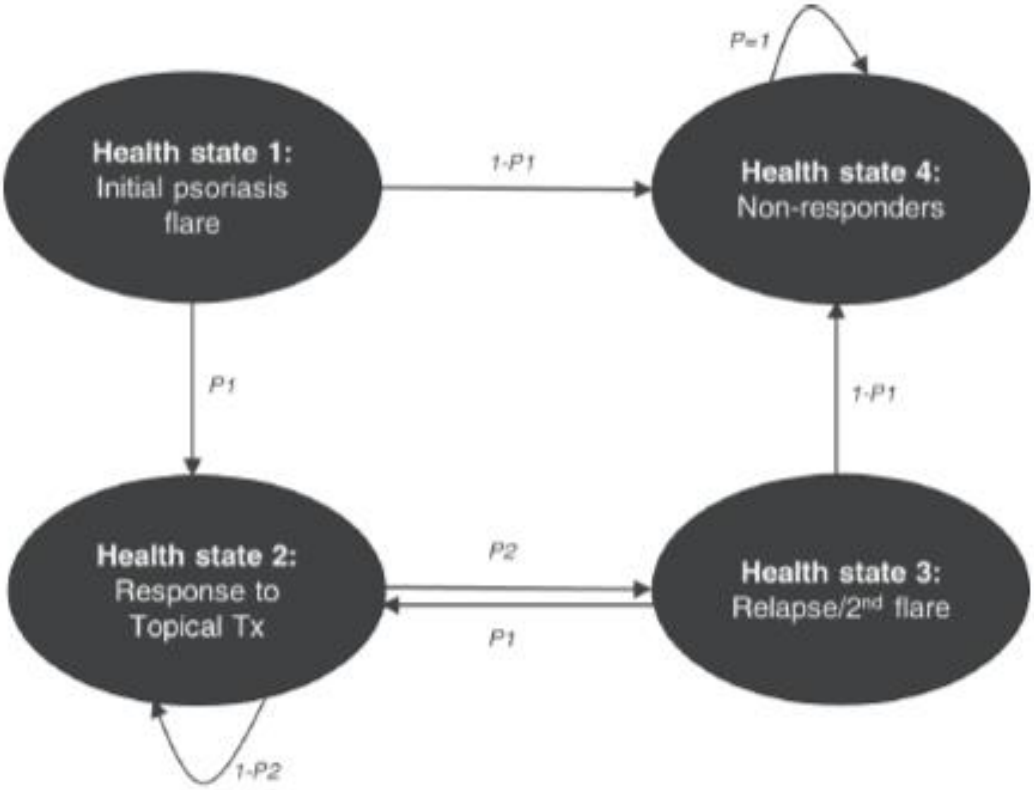
Table 10: Submission Quality

	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☐	☒	Sponsor modelled patient population with milder disease receiving topical monotherapy. Population with higher affected BSA is expected for the proposed indication, and this population is also likely to be on concurrent systemic or biologic therapy.
Model has been adequately programmed and has sufficient face validity	☒	☐	
Model structure is adequate for decision problem	☐	☒	Sponsor used grouped comparators consisting of weighted mix of treatments and did not consider relevant comparators. Model did not sufficiently capture the relapsing and remitting nature of the disease, the clinical management that allows for reduced treatment, and the nonresponder state health utility value that is reflective of a long-term patient experience.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	Although some parameter uncertainty was explored in the sponsor's scenario analyses, many structural limitations were not explored as additional analyses.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☒	☐	

BSA = body surface area.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Health state 1: Patients with moderate-to-severe plaque psoriasis enter the model after experiencing an initial psoriasis flare

Health state 2: Patients that respond to topical treatment after 8-weeks, enter the response health state

Health state 3: After response to topical treatment patients can experience a relapse or second flare; following their relapse patients either respond to topical treatment or do not respond and move to the post-topical treatment options

Health state 4: Patients that do not respond to topical treatments and move to post-topical treatment options

P1: Probability of IGA response to topical treatment
P2: Probability of relapse

IGA = Investigator's Global Assessment; Tx = treatment.

Source: Sponsor's pharmacoeconomic submission.[4]

Detailed Results of the Sponsor's Base Case

Table 11: Detailed Results of the Sponsor's Base Case

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,554	17,737	817	3.967	-
HP/TAZ	**18,593**	**17,775**	**817**	**3.968**	**34,611**
Dominated treatments					
VHPC	18,741	17,923	817	3.962	Dominated by BD/CAL
TAZ	19,382	18,564	817	3.956	Dominated by BD/CAL
VDA	19,407	18,590	817	3.957	Dominated by BD/CAL

BD/CAL = 50.5 mg/g betamethasone dipropionate and 0 mcg/g calcipotriol; HP = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

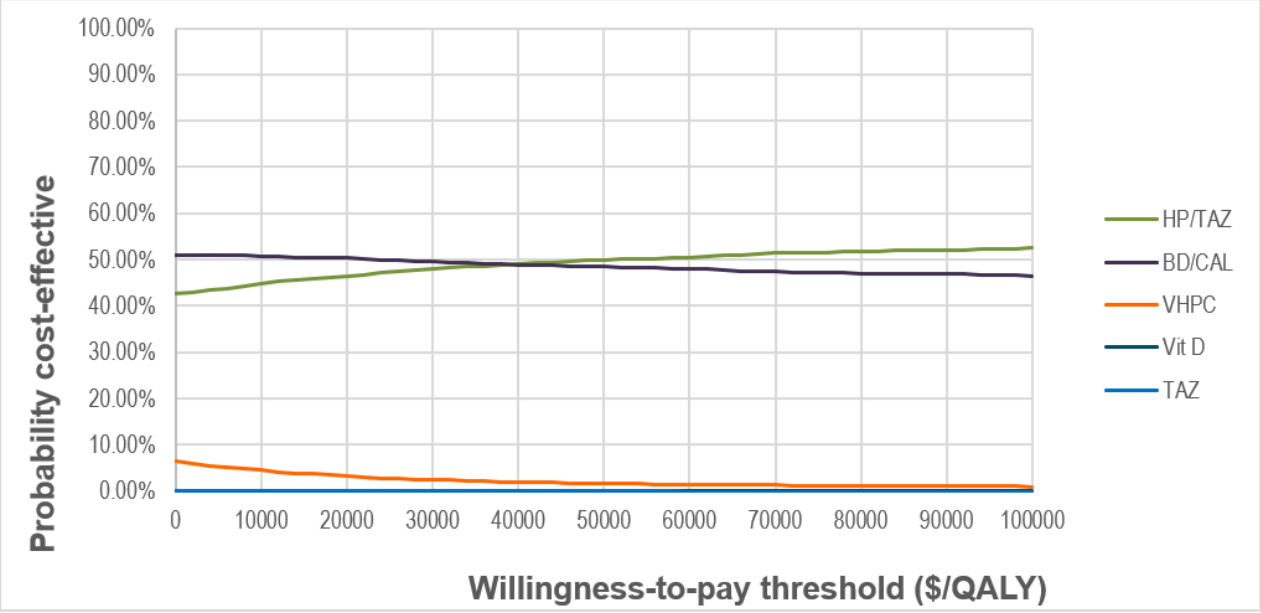
Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Source: Sponsor's pharmacoeconomic submission.[4]

The cost-effectiveness acceptability curve for HP/TAZ and other comparators in the sponsor's base case is presented in Figure 2. The probability of HP/TAZ to be the optimal treatment increased with increasing WTP thresholds, and increased above the probabilities associated with other treatments beyond the threshold of $40,000 per QALY. At the threshold of $50,000 per QALY, HP/TAZ had a 46% chance of being the optimal intervention.

Figure 2: Cost-Effectiveness Acceptability Curve of the Sponsor's Base Case



BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; QALY = quality-adjusted life-year; TAZ = tazarotene; VHPC = very high potency corticosteroid; vit D = vitamin D analogue.

Source: Sponsor's pharmacoeconomic submission.[4]

The sponsor also tested the following key scenarios in Table 12; all scenarios resulted in a sequential ICER for HP/TAZ between $26,686 per QALY to $230,900 per QALY.

Table 12: Key Sponsor's Sensitivity and Scenario Analyses

Scenario	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Relapse rate 23%	BD/CAL	17,906	3.983	—
	HP/TAZ	**17,955**	**3.984**	**26,686**
Relapse rate 81%	BD/CAL	18,934	3.959	—
	HP/TAZ	**18,972**	**3.960**	**79,951**
Time horizon 1 year	BD/CAL	2,650	0.770	—
	HP/TAZ	**2,668**	**0.767**	**118,451**
Time horizon 3 years	BD/CAL	10,542	2.395	—
	HP/TAZ	**10,585**	**2.396**	**43,865**
Time horizon 10 years	BD/CAL	37,937	7.754	—
	HP/TAZ	**37,974**	**7.755**	**35,899**
3% BSA affected	**HP/TAZ**	**18,352**	**3.969**	**Dominant**
12% BSA affected	VHPC	18,910	3.962	—
	BD/CAL	19,219	3.967	56,350
	HP/TAZ	**19,457**	**3.968**	**230,900**
Adverse events included	BD/CAL	18,570	3.950	—
	HP/TAZ	**18,608**	**3.953**	**14,527**
Societal perspective	BD/VDA	19,145	3.966	—
	HP/TAZ	**19,184**	**3.967**	**36,866**
All patients in nonresponder state receive biologic treatments	**HP/TAZ**	**87,261**	**3.968**	**—**
In nonresponder state, 36% of patients with < 10% BSA affected and 30% of patients with > 10% BSA affected do not receive any treatments	BD/CAL	13,227	3.967	—
	HP/TAZ	**13,297**	**3.968**	**66,194**

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; BSA = body surface area; HP/TAZ = 0.01% w/w halobetasol propionate and tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Only treatments that are on the efficiency frontier are reported. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

Source: Sponsor's pharmacoeconomic submission.[4]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 13: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)
Sponsor's base case	BD/CAL	18,554	3.967	—
	HP/TAZ	**18,593**	**3.968**	**34,610**
	Dominated treatments			
	VHPC	18,741	3.962	Dominated by BD/CAL
	TAZ	19,382	3.956	Dominated by BD/CAL
	VDA	19,407	3.957	Dominated by BD/CAL
CADTH reanalysis 1: Canadian maximum utility value	BD/CAL	18,560	3.9626	—
	HP/TAZ	**18,598**	**3.9633**	**49,662**
	Dominated treatments			
	VHPC	18,746	3.9585	Dominated by BD/CAL
	TAZ	19,385	3.9544	Dominated by BD/CAL
	VDA	19,410	3.9547	Dominated by BD/CAL
CADTH reanalysis 2: Modified nonresponder health state value	BD/CAL	18,551	4.0533	—
	HP/TAZ	**18,590**	**4.0538**	**75,550**
	Dominated treatments			
	VHPC	18,739	4.0504	Dominated by BD/CAL
	TAZ	19,381	4.0477	Dominated by BD/CAL
	VDA	19,406	4.0478	Dominated by BD/CAL
CADTH estimate Sponsor's base case + CADTH reanalyses 1 and 2	BD/CAL	18,564	4.0167	—
	HP/TAZ	**18,601**	**4.0171**	**85,670**
	Dominated treatments			
	VHPC	18,748	4.0143	Dominated by BD/CAL
	TAZ	19,386	4.0119	Dominated by BD/CAL
	VDA	19,411	4.0121	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

Detailed Results of CADTH Estimate

Table 14: Detailed Results of CADTH Estimate

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,564	17,746	818	4.0167	—
HP/TAZ	**18,601**	**17,782**	**818**	**4.0171**	**85,670**
Dominated treatments					
VHPC	18,748	17,930	818	4.0143	Dominated by BD/CAL
TAZ	19,386	18,567	818	4.0119	Dominated by BD/CAL
VDA	19,411	18,593	818	4.0121	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Scenario Analyses

The following scenario analyses of the CADTH estimate are presented in the tables below:

Scenario analysis 1a: Patients in the nonresponder state were assumed to experience health utility equivalent to a relapsed psoriatic flare (mean 0.8).

Scenario analysis 1b: Patients in the nonresponder state were assumed to experience health utility equivalent to the response to topical treatment state health state (mean 0.885, SE: 0.017).

Scenario analysis 2: The frequency of VHPC administration was reduced from twice daily to once daily.

Scenario analysis 3a: Mean eight-week psoriatic flare relapse rate was reduced from 41.8% to 30%.

Scenario analysis 3b: Mean eight-week psoriatic flare relapse rate was increased from 41.8% to 50%.

Scenario analysis 4a: Mean affected BSA of patients was increased from 5% to 10%.

Scenario analysis 4b: Mean affected BSA of patients was increased from 5% to 25%.

Scenario analysis 5: The price of HP/TAZ was reduced by 3%.

Table 15: Detailed Results of the CADTH Scenario Analysis 1a: Low Nonresponder State Utility Value

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,558	17,746	818	3.8378	—
HP/TAZ	**18,596**	**17,782**	**818**	**3.8394**	**23,911**
Dominated treatments					
VHPC	18,745	17,930	818	3.8298	Dominated by BD/CAL
TAZ	19,386	18,567	818	3.8219	Dominated by BD/CAL
VDA	19,411	18,593	818	3.8224	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 16: Detailed Results of the CADTH Scenario Analysis 1b: High Nonresponder State Utility Value

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,558	17,746	818	4.1959	—
VHPC	18,744	17,930	818	4.1991	58,301
TAZ	19,385	18,567	818	4.2022	203,755
Dominated treatments					
HP/TAZ	**18,596**	**17,782**	**818**	**4.1953**	**Dominated by BD/CAL**
VDA	19,410	18,593	818	4.2020	Dominated by TAZ

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 17: Detailed Results of the CADTH Scenario Analysis 2: Once Daily VHPC Administration

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,559	17,738	821	4.0163	—
HP/TAZ	**18,597**	**17,776**	**821**	**4.0167**	**87,674**
Dominated treatments					
VHPC	18,687	17,866	821	4.0138	Dominated by BD/CAL
TAZ	19,386	18,565	821	4.0114	Dominated by BD/CAL
VDA	19,412	18,590	821	4.0115	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 18: Detailed Results of the CADTH Scenario Analysis 3a: 30% Relapse Rate

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,227	17,407	820	4.0211	—
HP/TAZ	**18,270**	**17,450**	**820**	**4.0218**	**55,562**
Dominated treatments					
VHPC	18,482	17,662	820	4.0172	Dominated by BD/CAL
TAZ	19,276	18,456	820	4.0133	Dominated by BD/CAL
VDA	19,300	18,481	820	4.0136	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 19: Detailed Results of the CADTH Scenario Analysis 3b: 50% Relapse Rate

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,693	17,873	821	4.0148	—
HP/TAZ	**18,731**	**17,911**	**821**	**4.0151**	**109,105**
Dominated treatments					
VHPC	18,851	18,030	821	4.0130	Dominated by BD/CAL
TAZ	19,429	18,608	821	4.0113	Dominated by BD/CAL
VDA	19,454	18,634	821	4.0114	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 20: Detailed Results of the CADTH Scenario Analysis 4a: 10% Affected BSA

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
VHPC	18,864	18,042	822	4.0142	—
BD/CAL	19,031	18,210	821	4.0166	70,245
HP/TAZ	**19,212**	**18,390**	**822**	**4.0170**	**377,093**
Dominated treatments					
TAZ	19,609	18,787	822	4.0118	Dominated by VHPC
VDA	19,697	18,875	822	4.0120	Dominated by VHPC

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; BSA = body surface area; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 21: Detailed Results of the CADTH Scenario Analysis 4b: 25% Affected BSA

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
VHPC	19,206	18,390	816	4.0142	—
BD/CAL	20,436	19,621	816	4.0167	490,007
HP/TAZ	**21,044**	**20,228**	**816**	**4.0171**	**1,443,890**
Dominated treatments					
TAZ	20,268	19,452	815	4.0117	Dominated by VHPC
VDA	20,544	19,728	816	4.0119	Dominated by VHPC

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; BSA = body surface area; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places. As the efficacy and safety of HP/TAZ in patients with greater than 12% of BSA affected by plaque psoriasis has not been established,[5] the results of this analysis should be interpreted with caution.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

Table 22: Detailed Results of the CADTH Scenario Analysis 5: 3% HP/TAZ Price Reduction

Drug	Total costs ($)	Drug costs[a] ($)	Health services costs ($)	Total QALYs	Sequential ICER ($/QALY)
BD/CAL	18,558	17,739	819	4.0161	—
HP/TAZ	**18,577**	**17,759**	**819**	**4.0167**	**37,276**
Dominated treatments					
VHPC	18,744	17,925	819	4.0138	Dominated by BD/CAL
TAZ	19,385	18,566	819	4.0114	Dominated by BD/CAL
VDA	19,409	18,590	819	4.0116	Dominated by BD/CAL

BD/CAL = 0.5 mg/g betamethasone dipropionate and 50 mcg/g calcipotriol; HP/TAZ = 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; VHPC = very high potency corticosteroid.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as QALYs were only rounded up to three decimal places.

[a] Drug costs include both comparator drug costs and the systemic and biologic drug costs in the nonresponder health state.

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