CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

NALTREXONE HYDROCHLORIDE AND BUPROPION HYDROCHLORIDE (CONTRAVE)

(Bausch Health, Canada Inc.)

Indication: An adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).

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CADTH

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

AE	adverse event
BMI	body mass index
COR	Contrave Obesity Research
ICER	incremental cost-effectiveness ratio
NB	naltrexone and bupropion
NICE	National Institute for Health and Care Excellence
QALY	quality-adjusted life-year
SMC	Scottish Medicines Consortium
SM	standard management

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Naltrexone hydrochloride and bupropion hydrochloride (Contrave)
Study question	What is the cost-effectiveness of NB in combination with standard management (i.e., reduced-calorie diet and increased physical activity) compared to standard management alone for the treatment of obesity?
Type of economic evaluation	Cost-utility analysis
Target population	• Adults with a BMI ≥ 30 kg/m^2 with or without a comorbidity (base case) • Adults with a BMI ≥ 27 kg/m^2 in the presence of at least one comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia) (scenario analyses)[a]
Treatment	Two tablets of NB (8 mg/90 mg) twice daily
Outcome	Quality-adjusted life-year
Comparator	Standard management (i.e., reduced-calorie diet and increased physical activity)
Perspective	Canadian public health care payer
Time horizon	Lifetime (approximately 61 years)
Results for base case	ICER = $13,697 per QALY gained compared to standard management (Incremental costs: $18,627, incremental QALYs: 1.36)
Key limitations	• The submitted model lacked structural validity in the population most likely to be prescribed NB (BMI ≥ 27 kg/m^2 in the presence of at least one comorbidity), where the goals of treatment are focused on weight loss to alleviate existing comorbidities, and not the prevention of downstream comorbidities. CADTH requested an updated model in this population, but the sponsor indicated the data to populate such a model were unavailable. • The clinical effectiveness of NB is highly uncertain, particularly the long-term maintenance of weight loss achieved during the trial period, the use of BMI as the primary measure of treatment effects, and how changes in BMI were used as the link to downstream comorbidities given that the trials did not capture data on the impact of NB on comorbidities. This latter issue is highlighted in exploratory analyses, which also call into question the model mechanics. • Each 1 kg/m^2 increase in BMI was assumed to result in a 0.04 reduction in utility, independent of the impact on comorbidities, which appears to overestimate the impact of NB. Additionally, several utility values in the sponsor's model appeared to lack face validity. • Relevant comparators were not considered in the submitted pharmacoeconomic evaluation, thus the cost-effectiveness of NB + SM compared with pharmacologic treatments currently used for weight loss in Canada is unknown. • The sponsor's economic model was unnecessarily complex and lacked transparency, making it difficult to validate and evaluate the submitted model.
CADTH estimate	The limitations with the model structure, model mechanics, and available clinical data prevented CADTH from conducting reanalyses that provide a suitable basis to address the cost-effectiveness of NB in the Health Canada population, or populations most likely to be treated with NB. Although exploratory analyses were undertaken to highlight the key drivers of the model results, the true cost-effectiveness of NB in Canada is unknown.

BMI = body mass index; ICER = incremental cost-effectiveness ratio; NB = naltrexone and bupropion; QALY = quality-adjusted life-year; SM = standard management.

[a] Sections of the submitted pharmacoeconomic report inaccurately indicate that the submitted base case is for patients with a BMI of 27 kg/m^2 or greater.

Drug	Naltrexone hydrochloride and bupropion hydrochloride (Contrave)
Indication	Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of: • 30 kg/m^2 or greater (obese) or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia)
Reimbursement request	As per indication
Dosage form	Extended-release tablets of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg
NOC date	February 13, 2018
Sponsor	Bausch Health, Canada Inc.

Executive Summary

Background

Naltrexone and bupropion (NB; Contrave) is a fixed-dose combination oral tablet indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are obese (body mass index [BMI]: ≥ 30 mg/kg^2); or overweight (BMI: ≥ 27 mg/kg^2) with the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia). It is available in one combined strength: 8 mg naltrexone hydrochloride and 90 mg bupropion hydrochloride. The recommended dosage for NB is two tablets twice daily.[1] At the submitted price of $2.21 per tablet, the annual cost is expected to be $3,234.[2] The sponsor's reimbursement request was as per the indication.[2]

The sponsor submitted a cost-utility analysis comparing NB taken in conjunction with standard management (SM; defined as a reduced-calorie diet and increased physical activity) to SM alone. The model was conducted from the Canadian public health care payer perspective with a lifetime time horizon of approximately 61 years.[3] The submitted model was an event-driven decision analytic model, in which patients were assigned to one of three mutually exclusive weight categorizations: normal (BMI: 18.5 mg/kg^2 to 24.9 mg/kg^2), overweight (BMI: 25 mg/kg^2 to 29.9 mg/kg^2) and obese (≥ 30 mg/kg^2). A broad spectrum of comorbidities (e.g., myocardial infarction, chronic heart failure, stroke, diabetes, and various cancers) that are affected by weight were incorporated based on relative risks for each defined BMI-based weight category. Lower relative risks were applied to patients with a normal BMI, with the highest risk applied to patients who are obese (BMI ≥ 30 mg/kg^2). Risks were scaled linearly for each additional 1 kg/m^2 increase in BMI between each of the included weight categories. Patients in the model could experience a response (defined as a weight loss of at least 5% of body weight). Baseline patient characteristics and response rates were derived from pooling data from the Contrave Obesity Research (COR)-I and COR-II studies. Patients who responded to either NB + SM or SM alone experienced a decrease in their BMI (approximately 2 kg/m^2 for patients on NB + SM; 0.5 kg/m^2 for patients on SM alone) based on individual patient data from COR-I and COR-II. This one-time decrease in BMI was assumed to be maintained for the length of the time horizon and resulted in responding patients having a decreased risk of comorbidities, while those not responding to treatment would instead experience a constant increase in weight gain each

year (0.22 kg/m^2) and remain at higher, and increasing, risk of comorbidities. Mortality risk was included for each of the included comorbidities, regardless of treatment, based on rates identified in the literature. Bariatric surgery was included as an outcome in the sponsor's base case, as well as a comparator in a scenario analysis of patients with a BMI of 40 mg/kg^2 or greater. Patients accumulated costs related to treatment of obesity, adverse events, and comorbidities identified from the literature, while health-state utilities, as well as disutilities for adverse events and comorbidities, were identified in the literature.[3] Changes in BMI were associated with changes in utility values, independent of utility values associated with comorbid conditions.

In the sponsor's base case, over the lifetime time horizon, NB was associated with an incremental cost-effectiveness ratio of $13,697 per quality-adjusted life-year gained when compared to SM. In sponsor-conducted subgroup analyses of patients with a BMI of 27 mg/kg^2 or greater and at least one comorbidity, similar results were observed. Results were most sensitive to alternate assumptions regarding treatment effect over time, specifically, the utility of a 1 kg/m^2 increase in BMI and reducing the time horizon.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the sponsor's submission.

The model structure lacked validity. Feedback from the clinical expert consulted by CADTH suggested that patients with comorbidities were most likely to be prescribed NB, and the model structure did not reflect the goals of treatment for these patients. In such patients, the focus of treatment is to reduce weight to alleviate current comorbidities that result from weight gain.[4] CADTH requested revising the model to address this limitation or developing a model that considered different risk profiles for patients with and without comorbidities. However, the sponsor could not undertake these revisions. As a result, the cost-effectiveness of NB is highly uncertain, particularly in the population most likely to receive NB.

CADTH identified several key limitations relating to uncertainty regarding the clinical effectiveness of NB + SM compared to SM alone. Feedback from the clinical expert consulted by CADTH suggested that the use of BMI to model disease progression and risk of comorbidities is unlikely to be appropriate as other key factors were not considered. The link between BMI and the treatment goal of alleviating comorbidities is not linear as assumed by the sponsor. Because the model is highly sensitive to assumptions regarding changes in BMI, the model results are highly uncertain. Additionally, treatment response in practice would likely require weight loss of at least 10% to 15% to prevent discontinuation; these levels of response were achieved by few patients in the trials. Despite being informed by 56 weeks of trial data, treatment response was assumed to be maintained over a patient's lifetime. Feedback from the clinical expert suggested that while the majority of the benefit achieved in the first year by responders may be maintained for the first five years of treatment, no data suggest this benefit would be maintained over a longer duration. Furthermore, the data analyses used to inform the economic model may have biased the results in favour of NB, given limitations identified by the CADTH clinical reviewers with the sponsor's pooled trial results, and the use of modified intention-to-treat data analyses.

The sponsor assumed that each 1 kg/m^2 increase in BMI resulted in a reduction in utility of 0.04, independent of the impact on comorbidities. As noted, changes in BMI were identified as the key driver in the model. Given the limitations highlighted by the clinical expert, and the interrelationship of BMI and comorbidities, the sponsor's assumption appears to

overestimate the impact of NB. Furthermore, several utility values in the sponsor's model appear to lack face validity (e.g., a base utility value of 1 for obese people with no comorbidities, higher utility values for patients with comorbidities than the published general population utility values for Canada, and utility values greater than 1 for several comorbid conditions.

Relevant comparators were not included in the sponsor's pharmacoeconomic evaluation. The clinical expert consulted by CADTH noted that other treatments (e.g., orlistat) would likely be prescribed in practice to patients most likely to be prescribed NB. The cost-effectiveness of NB compared to other treatments is uncertain.

Finally, the sponsor's economic model was unnecessarily complex and lacked transparency, making it difficult to critically appraise the model and conduct reanalyses.

The aforementioned limitations associated with the structure of the submitted model, and lack of long-term data, limit CADTH 's ability to present a base case or best estimate. However, CADTH corrected errors in the sponsor's model, and undertook a series of exploratory analyses to highlight the drivers of the economic model to illustrate the impact of input parameters. The resulting exploratory analyses identified the key drivers of the cost-effectiveness of NB: change in quality-of-life impact of a 1 kg/m^2 increase in BMI and the impact of the assumed maintenance of treatment effect over time (assuming a shorter time horizon and increase in BMI after the first year for responders). The submitted model structure may be more applicable to patients with a BMI of 30 kg/m^2 or higher with no comorbidities given the identified limitation regarding the model structure. However, this population was not composed of the best candidates to receive treatment, based on clinical expert feedback (BMI ≥ 27 kg/m^2 and at least one pre-existing comorbidity). While a price reduction for NB would increase the likelihood that NB is cost-effective, the required magnitude of such a reduction is unknown.

Conclusions

The sponsor's analysis suggests that NB is cost-effective in patients with a BMI of 30 kg/m^2 or greater without a comorbidity, or patients with a BMI of 27 kg/m^2 or greater with a comorbidity. However, given the identified concerns with the application of the trial outcomes to the model and validity of several key model inputs and assumptions, CADTH was only able to conduct exploratory analyses that highlight that the model is most sensitive to the impact of a 1 kg/m^2 change in BMI on quality of life and the duration over which treatment effect is maintained. The CADTH clinical review concluded that it was unclear whether the weight-loss outcome observed in the trials translated to a clinically meaningful benefit given that improvement in, or prevention of, weight-related comorbidities was not assessed in the trials, and no evidence of a clinically meaningful benefit in health-related quality of life for NB was observed within the trials.

At the submitted price of $2.21 per tablet, the annual cost of NB is expected to be $3,234 per patient, which is higher than the price of orlistat, which is currently prescribed in clinical practice for obesity.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis comparing two tablets of the fixed-dose combination of NB (8 mg/90 mg) taken twice daily in conjunction with SM (i.e., reduced-calorie diet and increased physical activity) to SM alone. The model was conducted from the Canadian public health care payer perspective with a lifetime time horizon.[3] The sponsor's model was an event-driven decision-tree model with three mutually exclusive weight categorizations: normal (BMI: 18.5 mg/kg^2 to 24.9 mg/kg^2), overweight (BMI: 25 mg/kg^2 to 29.9 mg/kg^2) and obese (BMI ≥ 30 mg/kg^2) (Figure 1).

Patients characteristics upon entering the model were based on the COR-I and COR-II trials, with a mean age of 44 and a mean BMI of 36.8 kg/m^2 (although this was a subset of patients with a minimum BMI of 30 kg/m^2); 84.9% of patients were female. Patients may or may not have had comorbidities at baseline. After entry into the model, patients could move between the three mutually exclusive BMI-based weight categories based on treatment response. Treatment response was defined as a reduction in body weight of at least 5%, measured at 16 weeks and 56 weeks. The proportion of responders after the first year in the model time horizon was based on the proportion responding at week 56 multiplied by the number of patients responding at week 16 to obtain the proportion of initial responders from week 16 still responding at week 56, as those would be the patients receiving a benefit and continuing on NB indefinitely. This calculation was adjusted for patients who discontinued due to an adverse event (AE). In the model, 32% of patients receiving NB + SM and 15% of patients receiving SM alone were assumed to continue treatment beyond year 1. Patients deemed to be responders experienced a decrease in BMI and they would continue on NB indefinitely until they experienced an AE or mortality. Data from a pooled analysis of the COR-I and COR-II studies[5,6] were used to inform the treatment effectiveness of NB and SM. The proportion of patients experiencing a response saw a one-time mean decrease in BMI (approximately 2 kg/m^2 for patients on NB; 0.5 kg/m^2 for patients on SM alone) based on individual patient data collected during the trials but not part of the reported trial outcomes. Patients who did not respond were assumed to have an annual increase in BMI of 0.22 kg/m^2 according to a value identified in the literature.[7] In the base case, responders did not experience any weight gain at any point during the time horizon.

Based on their weight categorization in the model, patients were at different risks of comorbidities associated with elevated BMI (e.g., myocardial infarction, chronic heart failure, stroke, diabetes, and various cancers); patients with a higher BMI were at greater risk of experiencing a comorbidity than patients with a lower BMI. Assuming patients in the normal BMI range as the reference, a relative risk of comorbidity was applied to patients classified as having a BMI in the overweight or obese ranges. The relative risks were obtained from a report by the Health Research Council of New Zealand, and these values were adjusted using linear regression to account for the continuous nature of BMI gain and loss.[8] The same risks of comorbidity were applied regardless of baseline comorbidity status (i.e., patients with a BMI of 27 kg/m^2 or greater with a comorbidity at baseline had the same risk of subsequent comorbidity as patients with a BMI of 30 kg/m^2 or greater without a comorbidity at baseline). Additionally, 1% of patients were assumed to require bariatric surgery based on clinical expert opinion. Mortality risk was included for all causes based on Canadian life

tables adjusted for age and sex,[9] and adjusted for each comorbidity, regardless of treatment, based on rates identified in the literature.[8]

The baseline utility value for normal BMI patients was assumed to be 1 (i.e., perfect health). A utility increment or disutility was applied for each 1 kg/m^2 gain or loss in BMI, respectively, with different magnitudes for increases and decreases based on published literature,[10] while additional disutilities were applied for AEs,[11,12] as well as each comorbidity experienced. Different disutility values were identified for the first year and subsequent years for comorbidities, based on literature that suggested lower quality of life is experienced after the first year of diagnosis or occurrence of an event compared to subsequent years.[3]

Patients accumulated costs related to the intervention, AEs, and comorbidities. The sponsor assumed patients would require monitoring every three months by a nurse, psychologist, and general practitioner, while a general practitioner visit (via telephone call) was assumed in the case of AEs, based on clinical expert opinion. The costs for these resources were obtained from the Ontario Schedule of Benefits.[13] Costs for bariatric surgery and associated complications were identified from Sheppard et al.,[14] and costs related to comorbidities were identified from a variety of sources in the literature.

Sponsor's Base Case

In the sponsor's base case, incorporating changes based on a request by CADTH to address limitations identified with the clinical pathway and over the lifetime time horizon, NB + SM was associated with higher costs ($574,337 versus $555,751) and quality-adjusted life-years (QALYs) (23.37 versus 21.02) for incremental costs of $18,627 and QALYs of 1.36 when compared to SM alone. This resulted in an incremental cost-effectiveness ratio (ICER) of $13,697 per QALY gained. NB + SM was also associated with 0.41 incremental life-years gained (28.17 versus 27.77). At a willingness-to-pay threshold of $50,000 per QALY, NB + SM had a 100% probability of being cost-effective. Proxy information on the disaggregate results is presented in Table 10.

Table 2: Summary of Results of the Sponsor's Base Case

	Total life-years	Incremental life-years	Total costs ($)	Incremental cost ($)	Total QALYs	Incremental QALYs	Incremental cost per QALY ($)
Standard management	27.77		555,751		21.01		
NB + standard management	28.17	0.41	574,337	18,627	22,37	1.36	13,697

QALY = quality-adjusted life-years; NB = naltrexone and bupropion.

Source: Sponsor's pharmacoeconomic submission.

Summary of Sponsor's Sensitivity Analyses

The sponsor presented several scenario analyses. Subgroup analyses were conducted for the indicated subpopulations, and for patients with a BMI greater than 27 kg/m^2 with each of the following comorbidities at baseline: dyslipidemia, myocardial infarction, stroke, hypertension and type 2 diabetes mellitus. The results for patients with dyslipidemia were similar to those observed in the base case, while in patients with a history of stroke, myocardial infarction, diagnosis of diabetes or hypertension, the ICERs rose to $19,495,

$21,013, $37,304, and $17,535 per QALY gained, respectively, for NB + SM compared with SM alone (Table 11). In these analyses, the ICERs rose due to decreases in the incremental QALYs that were likely a result of the presence of a comorbidity at baseline. In a subgroup analysis of patients with a BMI of 40 kg/m^2 or greater, NB + SM was dominant over bariatric surgery.

Additional scenario analyses were conducted to assess the impact of alternate assumptions on results. These included alternate assumptions varying the time horizon (10, 25, and 30 years), altering model entry age (65 years instead of 44), incorporating type 2 diabetes mellitus at baseline, applying alternative utility values related to BMI gains and losses, excluding oncology-related comorbidities, and basing mortality rates on obesity instead of complications.

The model was most affected by reducing the time horizon, the age of patients at model entry, and utility values used for changes in BMI, and assuming patients responding to therapy experienced a weight increase in subsequent years (Table 12).

Limitations of Sponsor's Submission

- **The model structure lacks validity and does not accurately reflect goals of treatment:** The sponsor's model focused on the use of weight loss to prevent the occurrence of future comorbidities. However, it did not address another key treatment focus for patients with obesity; alleviating comorbidities that result from weight gain by losing weight.[4] While the submitted model structure is potentially applicable to patients with a BMI of 30 kg/m^2 or greater without a comorbidity, feedback from the clinical expert consulted by CADTH indicated that this population is unlikely to be prescribed NB in clinical practice in Canada — NB would most likely be prescribed in clinical practice only to patients with a BMI of 27 kg/m^2 or greater with at least one comorbidity — and the model therefore does not accurately reflect the clinical pathway of disease for patients most likely to receive NB. Feedback from the clinical expert was aligned with published literature, which noted that patients with a pre-existing comorbidity would be at different risks of subsequent comorbidities than patients with a BMI of 30 kg/m^2 or greater and no prior comorbidities.[4]

  The model allowed for stratification of patients by certain subgroups, including those stated in the Health Canada indication. However, this stratification only affected inputs related to the probability of the relevant comorbidity at baseline (set to 100% for each of the potential baseline comorbidities), revised treatment effects, and change in BMI values when compared to the base-case population incorporating data for patients with a BMI of at least 30 kg/m^2.

  As a result, serious limitations with the model structure remain, particularly in regard to the population most likely to receive the submitted drug (patients with a BMI of 27 kg/m^2 or greater and at least one comorbidity). The cost-effectiveness of NB in the population most likely to take it is uncertain and this issue could not be addressed in the CADTH reanalyses.

  Additional concerns with model validity arose when assessing the model structure. For example, attempting to make changes specific to the number of patients on NB + SM in the model, which should have only affected the results of the NB + SM arm of the trial, led to changes in results for patients receiving SM only (based on the deterministic analysis). Furthermore, assuming the relative risk of all comorbidities for overweight and obese people are the same as for people with a normal BMI did not have a substantial impact on

the incremental benefits associated with NB + SM (as determined by QALYs). These issues highlight concerns with the submitted model mechanics and increase the uncertainty of the modelled results.

- **The clinical effectiveness of NB is highly uncertain:** While the CADTH clinical review noted that NB + SM results in greater weight loss than SM alone based on the co-primary end points meeting statistical significance, it was unclear whether the weight-loss outcome observed in the trials translated to a clinically meaningful benefit, given that improvement in, or prevention of, weight-related comorbidities was not assessed in the trials. Given these findings, there are several limitations with the interpretation of the clinical results and the implementation of these data within the model.

  The COR trials did not assess the occurrence of comorbidities between treatment arms as an outcome. Therefore, the sponsor used BMI as the primary measure of disease progression in the model (derived from individual participant data in the trials). The clinical expert consulted by CADTH noted several limitations with the use of BMI to model disease progression and the risk of downstream comorbidities. First, BMI is only one indicator among several, including visceral fat and waist circumference, that should also be considered to determine the impact of obesity treatment as well as the risk of developing subsequent comorbidities. Second, the link between subsequent comorbidity and BMI is assumed to be linear, even though the link is generally not linear in practice. Third, the assumption that comorbidities are independent of one another is inappropriate, as many comorbidities are interrelated or occur in clusters.[15-17] The model is highly sensitive to changes in BMI over time and the assumed impact of a 1 kg/m^2 change in BMI on quality of life and risk of comorbidities.

  Furthermore, the data used in the model to define response included the proportion of patients achieving at least a 5% reduction in body weight from baseline. Feedback from the clinical expert consulted by CADTH for this review noted that patients may be more likely to discontinue a therapy for weight loss if they do not experience at least 10% or 15% weight loss. Fewer patients experienced at least 10% weight loss in the COR trials compared to the proportion of patients losing at least 5% of their weight, although the relative impact between the treatment arms appeared to be similar.[5,6] Additionally, the data were sourced from the modified intention-to-treat population using imputation of the last observation carried forward, and the CADTH clinical review noted that imputation of the baseline observation carried forward in the population of all randomized patients would have been more appropriate. Using more appropriate values in the model does not appear to have a notable impact on the results given the model structure.

  The primary goal of treatment for obesity is not simply weight loss, but also maintaining the weight loss. The sponsor assumed that the weight loss experienced after 56 weeks in the COR trials was maintained indefinitely. This assumption is highly uncertain due to a lack of supporting data, as well as the trend of weight regain from week 16 to week 56. Given more patients receiving NB responded to treatment, assuming maintenance of treatment effect for the patient's lifetime biased the results in favour of NB. This assumption was tested by the sponsor in a scenario analysis that assumed patients responding to treatment experienced weight gain after the first year of the time horizon at the same rate as nonresponders. Feedback from the clinical expert indicated that responders may be expected to maintain the majority of the benefit they received initially over the first five years of treatment, but there is no evidence to suggest this benefit would be maintained over a longer period.

  Additionally, changes in patient BMI were informed by a pooled analysis of individual patient data on BMI measured in the COR trials. This analysis could not be validated by

the CADTH clinical review team. The CADTH review team noted that pooling individual patient data from the COR-I and II trials as if they were a single trial was likely inappropriate and that a study-level meta-analysis of the two trials would have been more appropriate. While the pooling may not have been appropriate, the impact this approach had on the treatment effect inputs used in the model appeared to be limited as values from the individual COR trials were able to be assessed.

In summary, the CADTH clinical reviewers caution that it is unclear whether there is a clinical benefit associated with the use of NB, given that improvement in, or prevention of, weight-related comorbidities was either not assessed in the trials, or no evidence was found for a clinically meaningful benefit from NB over placebo in health-related quality of life. The clinical review report identified limitations with the clinical data for NB, noted differences in results between body-weight outcome measures assessed, and commented on the generalizability of the results, including the impact of different forms of SM that may have been used in the trial compared with current Canadian SM practices.

- **Not all appropriate comparators of interest were included:** The sponsor did not include a comparator regimen that incorporated both lifestyle modification and an additional active treatment in the model for patients with a BMI below 40 kg/m^2. The clinical expert consulted by CADTH for this review noted that this would be appropriate for patients indicated for NB without a comorbidity, given that such patients are unlikely to receive pharmacologic treatment for obesity in clinical practice as noted above. But for patients with a BMI of 27 kg/m^2 or greater and a comorbidity, orlistat would be a relevant treatment often prescribed for this indication. The sponsor noted in its pharmacoeconomic submission that orlistat was not considered a comparator due to its limited use in Canada, although it is listed on the formularies of participating CADTH jurisdictions and is therefore an appropriate comparator. No comparative analysis of the effectiveness of NB and orlistat was provided by the sponsor. This limitation could not be addressed in the CADTH reanalyses and the cost-effectiveness of NB compared to orlistat in patients with a BMI of 27 kg/m^2 or greater with a comorbidity remains unknown.

  The CADTH clinical review identified and appraised a published network meta-analysis that compared weight loss and AEs among NB, orlistat, lorcaserin, phentermine-topiramate, and liraglutide, but due to several limitations, including substantial amounts of missing data and heterogeneity, no conclusions on the comparative effectiveness of NB to these other pharmacologic agents could be drawn.

- **The utility values and their application in the model were questionable:** The baseline utility value used by the sponsor in its base case was 1, which is not appropriate, given that a value of 1 corresponds to perfect health and patients in the model would have some baseline impact of morbidity on quality of life. A more appropriate value would have been one representative of the general Canadian population, such as the one identified in a study by the Alberta PROMS and EQ-5D Research and Support Unit, in which the mean utility for patients 45 to 65 years of age was 0.83 (standard deviation: 0.16).[18] However, this value is greater than utility values used for certain comorbid conditions within the submitted model. Therefore, to maintain a logical hierarchy of utility values in the model and prevent utilities for comorbid conditions from exceeding this value, all utilities included by the sponsor for comorbidities were modified by identifying the relative difference between the value as incorporated in the sponsor's base case and the value of 1.0, then subtracting this difference from the new baseline utility to identify the updated comorbidity utility value.

The sponsor assumed each 1 kg/m^2 increase in BMI was associated with a reduction in utility of 0.04.[10] This increase was assumed to be independent of any specific comorbid condition and therefore any utility value associated with that comorbid condition. This assumption is highly uncertain, given the previous limitations that highlight the goals of obesity treatment. A scenario analysis was presented by the sponsor assuming a 0.017 reduction in utility.[19] Other published literature appears to suggest the 0.04 value from Lane et al.[10] may overestimate the impact,[20] particularly without considering comorbid conditions, and that this constant application regardless of baseline BMI is inappropriate.[21] The magnitude of the impact on utility values of a 1 kg/m^2 increase in BMI for patients is uncertain, based on the modelled population (i.e., patients with a baseline BMI of approximately 36 kg/m^2).

Several of the included utility values were greater than 1 and are therefore invalid. The original literature sources cited by the sponsor were assessed and the appropriate corresponding values from these sources were used in the CADTH base case. These included values for rectal, colon, breast, prostate, kidney, esophageal, and endometrial cancer.

- **The sponsor's submission was unnecessarily complex and lacked transparency:** The model calculations relied on nested formulas and tracing values through sheets with limited commentary as to what information was being reported.

Additionally, inappropriate statistical distributions were used when specifying parameter uncertainty for costs. Beta distributions were used when gamma distributions would have been more appropriate. Gamma distributions were applied in the CADTH base case.

CADTH Common Drug Review Reanalyses

The aforementioned limitations restricted the ability of CADTH to undertake reanalyses that provide a suitable basis to address the cost-effectiveness of NB in the Health Canada population, or the population most likely to be treated with NB.

CADTH addressed errors from the submitted model, and then conducted a series of exploratory analyses to highlight limitations with the submitted model and identify the key drivers in the model. These exploratory results may be less reflective of patients with a pre-existing comorbidity due to the model structure limitations.

CADTH identified errors in the sponsor's model (utility values greater than 1 for various comorbid conditions and application of utility values in subsequent years; use of a more appropriate distribution for costs (gamma); and the removal of distributions for known cost components such as the cost of NB, physician visits, and psychologist visits), and revised the population data to better align with the Health Canada indication ("all subjects"). These revisions had limited impacts on the model (Table 13).

The sponsor's scenario analyses may be consulted when considering several relevant scenarios and their impact on the model (e.g., assuming responders regained 90% of weight lost after year 5 of the model time horizon instead of maintaining weight loss for the entirety of time horizon, clinical data based on COR-I, clinical data based on COR-II, BMI utility based on Hakim, and reduced time horizons). CADTH undertook several exploratory analyses based on the corrected model. The results of key exploratory analyses that combine alternate BMI utility values based on Hakim, and a shorter time horizon to address the concerns regarding maintenance of treatment effect are reported in Table 3. In these analyses, if a decision-maker's willingness to pay was $50,000 per QALY, NB would not be

considered cost-effective. Additional exploratory analyses were undertaken, the results of which are reported in Table 14 (e.g., alternate relative-risk assumptions, alternate data-source assumptions, and alternate utility-value assumptions).

Table 3: Summary of the CADTH Scenario Analysis Results

Scenario analysis	Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($ per QALYs)
5-year time horizon, Hakim BMI utility values	Standard management	13,438		4.00		
	NB + standard management	18,699	5,261	4.07	0.07	78,815
10-year time horizon, Hakim BMI utility values	Standard management	39,129		7.35		
	NB + standard management	47,926	8,797	7.48	0.13	66,781

BMI = body mass index; ICER = incremental cost-effectiveness ratio; NB = naltrexone and bupropion; QALY = quality-adjusted life-year.

A price reduction for NB would increase the likelihood that NB is cost-effective. However, the magnitude of the price reduction required for NB to be cost-effective is unknown.

Issues for Consideration

- Treatment effect depends significantly on accompanying lifestyle modification, and the effect of lifestyle modification may vary greatly based on intensity and form of activity. As noted in the key limitations, the lifestyle modifications used in the trials, and/or their intensity, may not align with those likely to be used in clinical practice.
- The indicated population may not align with clinical practice. The clinical expert consulted by CADTH noted the presence of a comorbidity would likely be necessary in clinical practice for NB to be prescribed to a patient. As a result, patients without comorbidities may not be prescribed NB. As noted in the limitation section, the cost-effectiveness of NB in patients with existing comorbidities at baseline is highly uncertain.
- Patients most likely to be prescribed NB would have a pre-existing comorbidity, with many patients taking medications to treat the comorbidity(ies). Concomitant medication for treatment of comorbidities of interest in patients who are either overweight or obese may alter the treatment effects of NB.
- Neither of the components of NB (naltrexone hydrochloride or bupropion hydrochloride) have been reviewed by CADTH at this time, though they have been reviewed by international health technology assessment bodies for other conditions.

Patient Input

Input for this review was received from two patient groups, the Canadian Spondylitis Association and Obesity Canada. Feedback from the Canadian Spondylitis Association indicated there are patients for whom weight gain is due to a pre-existing condition that makes exercise and other activities difficult to undertake, as well as due to medication for pre-existing treatments. This is important to note, given that NB is intended to be an adjunct to SM, which includes increased exercise, and all data used to inform the model for NB was in addition to SM. The impact of the drug in a population in whom activity is limited is

uncertain, particularly given the presence of other comorbidities due to the underlying condition, which may not be completely resolved due to weight loss.

The submission by Obesity Canada noted the difficulty with access to bariatric surgery, which was included as a comparator in a severely obese scenario, as well as an outcome for a small portion of patients in the base case. This submission also noted the impact of downstream comorbidities due to obesity, all of which were included as events in the submitted model. The group also noted that obesity is a heterogeneous chronic disease, and that there is likely no solution that will work for everyone. This is potentially reflected in the economic submission via treatment efficacy data from the pivotal trials.

Conclusions

The sponsor's analysis suggests that NB is cost-effective in patients with a BMI of 30 kg/m^2 or greater without a comorbidity, or patients with a BMI of 27 kg/m^2 or greater with a comorbidity. However, given the identified concerns with the application of the trial outcomes to the model and validity of several key model inputs and assumptions, CADTH was only able to conduct exploratory analyses that reveal the model is most sensitive to the impact of a 1 kg/m^2 change in BMI on quality of life and the duration over which treatment effect is maintained. The CADTH clinical review concluded that it was unclear whether the weight-loss outcome observed in the trials translated to a clinically meaningful benefit, given that improvement in, or prevention of, weight-related comorbidities was not assessed in the trials, and no evidence was found for a clinically meaningful benefit from NB over placebo in health-related quality of life.

The submitted model structure may be more applicable to patients with a BMI of at least 30 kg/m^2 with no comorbidities. However, this population is not composed of the best candidates to receive treatment (those with a BMI of 27 kg/m^2 or greater and at least one pre-existing comorbidity), based on clinical expert feedback.

At the submitted price of $2.21 per tablet, the annual cost of NB is expected to be $3,234 per patient, which is higher than the price of orlistat, which is currently prescribed in clinical practice for obesity.

Appendix 1: Cost Comparison

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are sponsor list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such the figures may not represent the actual costs to public drug plans.

Table 4: CDR Cost Comparison Table for Interventions Used to Treat Obesity

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
Submitted drug						
Naltrexone hydrochloride/ bupropion hydrochloridede (Contrave)	8 mg/90 mg	Tablet	2.2149[a]	Two tablets twice daily	8.86	3,234
Comparator drugs and interventions						
Liraglutide (Saxenda)	6 mg/mL	3 mL pre-filled injection pen	73.6221	3 mg per day	12.27	4,479
Orlistat (Xenical)	120 mg	Capsule	1.6525	One capsule, three times daily	4.96	1,809
Bariatric surgery	NA	NA	13,870[b]	NA	NA	13,870

CRD = CADTH Common Drug Review; NA = not applicable.

Note: All prices are wholesale acquisition prices from IQVIA Delta PA (accessed June 2019) unless otherwise indicated and do not include dispensing fees.

[a] Sponsor-submitted price.

[b] Mean cost of bariatric surgery at an institution in Alberta, not including complications. Price obtained from a study in published literature.[14]

Appendix 2: Additional Information

Table 5: Submission Quality

	Yes/good	Somewhat/average	No/poor
Are the methods and analysis clear and transparent?			X
Comments	The sponsor's model was poorly commented, and there were discrepancies within the submitted pharmacoeconomic report regarding the base-case population.		
Was the material included (content) sufficient?			X
Comments	CADTH requested a revised pharmacoeconomic submission that appropriately stratified the two indicated populations (BMI ≥ 27 kg/m^2 with at least one weight-related comorbidity; and BMI ≥ 30 kg/m^2 with or without at least one weight-related comorbidity); i.e., one that incorporates the difference in risk for subsequent comorbidities between the two populations. Additionally, a revised model structure representative of the clinical pathway in patients with a pre-existing comorbidity should be considered. The sponsor indicated that a model structure incorporating the reversal of complications of obesity resulting from a reduction in BMI specifically in relation to patients with comorbid type 2 diabetes at baseline would be too weak without hard outcomes on actual reversal of type 2 diabetes by NB. It is unclear if this justification is applicable to all other subgroups with comorbidities at baseline, but the revised model did not incorporate the reversal of any of the other potential baseline comorbidities.		
Was the submission well organized and was information easy to locate?			X
Comments	See previous comments		

BMI = body mass index; NB = naltrexone and bupropion.

Table 6: Authors' Information

Authors of the pharmacoeconomic evaluation submitted to CADTH
☐ Adaptation of global model/Canadian model done by the sponsor
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis		X	

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

The cost-effectiveness of NB has been assessed by the National Institute for Health and Care Excellence (NICE) in the UK,22 and the Scottish Medicines Consortium (SMC) in Scotland.23 No information on the economic submission was provided by the SMC. A summary from NICE is available in Table 7.

From the available guidance documents, NICE did not recommend reimbursement of NB, nor did the SMC.

The Institute for Clinical and Economic Review in the US developed a simulation model to evaluate the cost-effectiveness of several interventions for the management of obesity, including NB.24 They found an ICER of greater than $100,000 per quality-adjusted life-year gained for NB compared to SM (i.e., lifestyle modification) for the treatment of obesity, although, given that the institute's modelling approach was substantially different, the results are not comparable to those from this review.

Table 7: Other Health Technology Assessment Findings

	NICE (July 2017)[22]
Treatment	Two oral tablets containing 8 mg naltrexone hydrochloride and 90 mg bupropion hydrochloride, twice daily
Price	£73 per pack of 112 tablets; £0.65 per tablet
Similarities with CADTH submission	Primary comparator (standard management) and baseline characteristics
Differences with CADTH submission	Also included orlistat as a comparator; model structure (discrete event simulation was submitted to NICE); model did not include transition to bariatric surgery; accounting for currency conversion, the drug cost of NB was substantially less in the submission to NICE
Sponsor's results	Not provided
Issues noted by the review group	Model did not include episodes of re-treatment and transition to bariatric surgery; implementation of discrete event simulation caused slow model run times; baseline characteristics used may not reflect population under consideration; inappropriate use of time to treatment discontinuation data; incremental cost-effectiveness ratios not sufficiently reliable for decision-making
Results of reanalyses by the review group	£23,750 per QALY gained compared to standard management, noted to be highly uncertain
Recommendation	Not recommended for reimbursement due to unknown long-term effectiveness and uncertainty with modelling assumptions

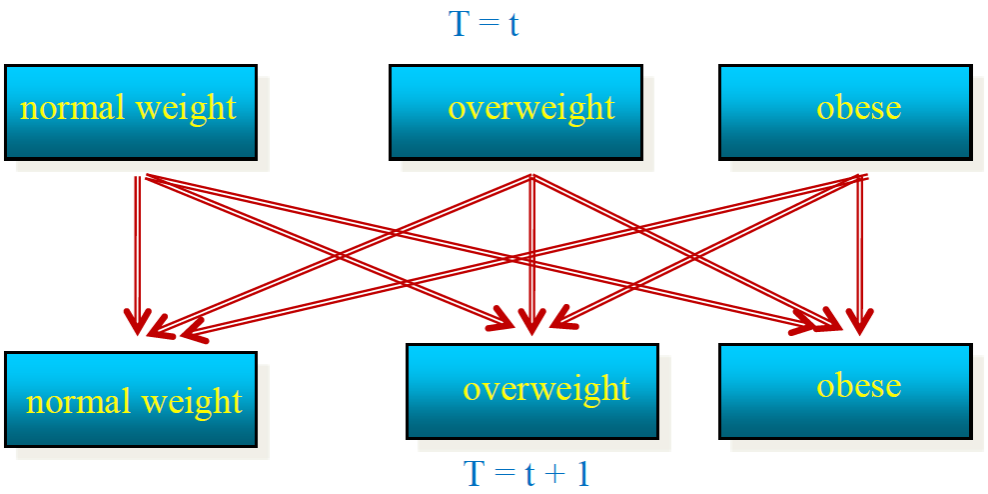
NICE = National Institute for Health and Care Excellence; NB = naltrexone and bupropion; QALY = quality-adjusted life-year.

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

The submitted model was an event-driven, decision analytic model, in which patients were assigned to one of three mutually weight categorizations: normal (BMI: 18.5 mg/kg2 to 24.9 mg/kg2), overweight (BMI: 25 mg/kg2 to 29.9 mg/kg2) and obese (≥ 30 mg/kg2), Figure 1. Each of the three mutually exclusive weight categories were associated with a risk of comorbidities associated with weight (e.g., myocardial infarction, chronic heart failure, stroke, diabetes, and various cancers), with the lowest risk in patients with normal BMI and highest risk in obese patients. Based on response to treatment, patients could experience a mean decrease in their BMI, which was assumed to be maintained for the length of the time horizon, and move into a lower BMI health state, effectively decreasing their risk of comorbidities, while those not responding to treatment would not lose weight and remain at a higher risk of comorbidities.

Figure 1: Sponsor's Model Structure



Source: Sponsor's pharmacoeconomic submission.[3]

Table 8: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Based on patient characteristics from the sponsor's COR-I[5] and COR-II[6] studies.	Appropriate.
Efficacy	For the base-case population and subgroup (except for the type 2 diabetes population) efficacy was pooled from the COR-I and COR-II pivotal studies for both NB and standard management.[5,6] Efficacy for the type 2 diabetes scenario was obtained from the COR-DM trial.[25]	Limitations were identified with the implementation of response to treatment in the model via change in BMI. The raw BMI data used by the sponsor were not provided to CADTH and could not be appraised.

Data input	Description of data source	Comment
Natural history	An annual increase (0.22 kg/m^2) in BMI was included for patients not responding to treatment based on a study from the literature.[7] The relative risk of comorbidities based on being overweight or obese compared to a normal BMI was obtained from a report by the Health Research Council of New Zealand.[8] Additionally, these risks were adjusted using linear regression to account for the increased risk of comorbidities as BMI increased within each of the health states. It was assumed 1% of patients would undergo bariatric surgery based on clinical expert opinion.	The natural increase in BMI was appropriate. The use of BMI to model natural history of disease and treatment impact is highly uncertain. The implementation of the relative risks in the submitted model is unlikely to be appropriate. The generalizability of the data from this patient population to the Canadian setting is uncertain.
Utilities	Baseline utility value was assumed to be 1.0 for patients without comorbidities. Utility values from Lane et al. (2014), were identified for each 1 kg/m^2 gain and loss of BMI,[10] which was applied exclusive of utility implications for comorbidities. Disutilities for adverse events were obtained from studies by Nafees et al. (2008)[11] and Restelli et al. (2017).[12] Utilities for each comorbidity were identified from a variety of sources in the literature, with separate values identified for the first year and subsequent years.	Not appropriate. A value representative of the general Canadian population at age 44 (0.887) was used.[26] Patients with obesity or excess weight with a comorbidity would have some reduction in utility at baseline. Lane et al. (2014) values were derived from a small population of type 2 diabetes mellitus patients using a time trade-off approach, reporting a 0.04 utility change per 1 kg/m^2 increase in BMI. Published literature suggests this may be an overestimate, particularly given the model structure, and alternate values may be more appropriate. Several utilities noted were greater than 1 and thus not appropriate. Other utility values for comorbidities used in the model suggest higher utility than published Canadian general population values, and therefore are highly uncertain. Alternate values were tested and appeared to have limited impact on the cost-effectiveness results.
Adverse events (nausea, headache, dizziness, vomiting)	Safety for both comparators was obtained from five double-blind placebo-controlled trials, four of which were phase III studies.[5,6,25,27,28]	Acceptable, although the trials do not appear to have been powered to assess adverse events.
Mortality	Baseline mortality risk was based on Canadian age and gender-specific lifetables.[9] The Health Research Council of New Zealand report was also used to estimate the increased risk of mortality associated with having each of the comorbidities.[8]	Appropriate. The generalizability of the relative risk of mortality to the Canadian population is uncertain.

Data input	Description of data source	Comment
Resource use and costs		
Drug	Sponsor submission.	Appropriate.
Administration	Monitoring every three months by a nurse, psychologist, and general practitioner was assumed based on clinical expert opinion. Costs for such resource use was obtained from the Ontario Schedule of Benefits.[13]	Appropriate.
Event	Costs related to bariatric surgery were obtained from a study by Sheppard et al. (2013), and included costs of the initial surgery, as well as associated complications.[14] Costs and resource use related to comorbidities from excess weight or obesity were obtained from a number of sources in the literature.	Inappropriate distributions were used for cost inputs in the sponsor's base case. These were correct to gamma distribution in CADTH reanalyses.
Adverse events	One telephone call to a general practitioner was assumed for each adverse event based on clinical expert opinion. Costs for such resource use was obtained from the Ontario Schedule of Benefits.[13]	Appropriate.

BMI = body mass index; NB = naltrexone and bupropion.

Table 9: Sponsor's Key Assumptions

Assumption	Comment
The model structure appropriately captures the clinical pathway of disease for overweight and obese patients.	Not appropriate, particularly for the population with a BMI of 27 kg/m^2 or greater with at least one weight-related comorbidity. Feedback from the clinical expert consulted by CADTH for this review noted that NB would be prescribed in clinical practice primarily to patients with comorbidities that could be alleviated through weight loss. CADTH requested a model that reflected the clinical pathway of obesity in such patients, one that not only incorporated downstream comorbidities, but comorbidities at baseline that may be alleviated via weight loss. The model reviewed did not incorporate such a pathway.
The submitted pharmacoeconomic report and model provided enough information to depict the interactions between inputs in the model to appropriately appraise and validate results of the economic evaluation.	The submitted model lacked transparency, making it difficult to appraise and validate the model and its results. The cost-effectiveness of NB + SM compared to SM alone is highly uncertain.
It was assumed in the model that a patient with a BMI between 27 and 30 kg/m^2 and comorbidity had the same risk of developing further comorbidities as a patient with a BMI of 30 kg/m^2 and no comorbidities.	This assumption is not appropriate, as the clinical expert consulted by CADTH indicated that patients with comorbidities at baseline would have different risks of subsequent comorbidities, and potentially different responses to treatment.
Weight loss directly correlates with reduction in risk of developing all comorbidities in the model.	Weight loss is one of many factors that may have an impact on the risk of developing comorbidities included in the model that may be associated with being overweight or obese. As a result, changes in these values alone may not directly affect the risk of developing such a comorbidity.
Association of risk of comorbidities is linear between the intervals of normal weight, overweight and obese.	Feedback from the clinical expert consulted by CADTH indicated this may be the case for some comorbidities, but not all. In some cases, comorbidities may cluster, while in others there may be a threshold effect.

Assumption	Comment
Patients on treatment are assumed to maintain the reduction in BMI achieved. There is no future gain or waning of treatment effects while on treatment.	This is an appropriate assumption for the first five years following treatment, according to the clinical expert consulted by CADTH. Beyond this point, there are no data in support of maintained benefit, and it is uncertain how long treatment effects would last, particularly given the high probability of nonadherence following several years with no weight loss.
Increases and decreases in BMI lead to differing magnitudes of utility gains and losses.	The sponsor applied utility-value increments and decrements with different magnitudes for corresponding increases in BMI and decreases in BMI. While feedback from the clinical expert consulted by CADTH suggested that an increase in BMI may have a greater impact on a patient's quality of life than decrease in BMI, the way BMI is implemented in the model, as the primary marker of disease progression, potentially leads to illogical values for patient quality of life. Using these values, two patients with the same starting BMI could end up with vastly different utility values, holding all other factors equal. For example, a patient with a decrease in BMI in the first model cycle and a subsequent return to baseline BMI in a later cycle would have a different utility value applied than a patient with a constant BMI and otherwise identical characteristics. The uncertainty in the magnitude of impact of BMI on patient quality of life (via utility values) is highlighted in the CADTH exploratory analyses.
Nonresponders experience a natural increase in BMI of 0.22 kg/m^2 per year.	The assumption that nonresponders experience an increase in BMI is appropriate, although the magnitude of the increase is associated with some uncertainty.
1% of patients not responding to treatment undergo bariatric surgery.	Acceptable; feedback from the clinical expert suggested only a small number of patients would undergo bariatric surgery.
Costs and utilities for certain comorbidities were assumed to be applicable for year 1 only.	Not appropriate. No justification was provided for this assumption, and for several comorbidities (e.g., breast cancer), this assumption lacks face validity.

BMI = body mass index; NB = naltrexone and bupropion; SM = standard management.

Sponsor's Results

Table 10: Expected Discounted Costs by Treatment and Cost Categories, Sponsor's Base Case

	Drug cost	Resource utilization	Adverse events	Comorbidities	Nonresponders
Standard management (a)	0	5,278	0	512,440	14,439
NB + standard management (b)	28,536	2,725	15	507,354	12,050
Difference (b − a)	28,536	−2,553	15	−5,086	−2,389

Note: Disaggregated costs from the last simulation of the probabilistic sensitivity analysis. Not presented for the full simulated population.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 11: Sponsor's Subgroup Analyses

		Total costs ($)	Incremental cost of naltrexone HCl/bupropion HCl ($)	Total QALYs	Incremental QALYs of naltrexone HCl/bupropion HCl	Incremental cost per QALY ($)
BMI ≥ 27 kg/m^2 with hypertension	Standard management	295,085		6.31		
	NB + standard management	304,819	9,734	6.86	0.55	17,535
BMI ≥ 27 kg/m^2 with dyslipidemia	Standard management	557,689		21.01		
	NB + standard management	576,717	19,029	22.43	1.42	13,391
BMI ≥ 27 kg/m^2 with previous myocardial infarction	Standard management	497,473		5.97		
	NB + standard management	509,135	11,662	6.53	0.56	21,013
BMI ≥ 27 kg/m^2 with previous stroke	Standard management	218,196		3.65		
	NB + standard management	223,101	4,905	3.90	0.25	19,495
BMI ≥ 27 kg/m^2 with Type 2 Diabetes Mellitus	Standard management	478,884		23.09		
	NB + standard management	505,824	26,940	23.80	0.71	37,304
BMI ≥ 40 kg/m^2	Bariatric surgery	631,259		19.71		
	NB + standard management	613,416	−17,843	21.39	1.68	Dominant

BMI = body mass index; NB = naltrexone and bupropion; QALY = quality-adjusted life-year.

Table 12: Sponsor's Scenario Analyses

Scenario	Base-case value	Scenario analysis value	Incremental costs ($)	Incremental QALYs	Incremental cost per QALY (vs. standard management)
Base case			18,537	1.36	$13,619
Perspective	Health care	Societal	−$6,514	1.35	Dominant
Time horizon	Lifetime	10 years	$8,642	0.32	$27,433
		25 years	$12,412	0.79	$15,816
		30 years	$12,408	0.92	$13,506
Discount rate	1.5%	0%	$26,473	2.38	$11,146
		3%	$14,127	0.84	$16,800
Age	44 years	65 years	$18,117	0.80	$22,803
Efficacy source data	Pooled COR-I and COR-II	COR-I	$18,874	1.55	$12,196
		COR-II	$18,210	1.24	$14,701
Baseline characteristics	Aligned with COR-I and COR-II	Based on Canadian averages for	$18,140	1.16	$15,605

Scenario	Base-case value	Scenario analysis value	Incremental costs ($)	Incremental QALYs	Incremental cost per QALY (vs. standard management)
		BMI, age and % female			
BMI threshold	COR-I and COR-II 36 kg/m^2	Canadian population 40.7 kg/m^2	$18,046	1.31	$13,776
BMI utility	Lane et al. (2014)[10]	Hakim time trade-off	$18,133	0.67	$27,215
		Hakim visual analogue scale	$18,089	0.77	$24,082
Annual BMI increase	Responders: no increase Nonresponders: 0.22 kg/m^2 per year bariatric surgery: no increase	Responders: increase by 0.22 kg/m^2 per year	$19,663	0.70	$28,179
BMI	Mild	Severe	$18,058	1.32	$13,664
Comorbidities	Recurrent	Once only	$25,191	1.44	$17,416
Oncology	Included	Excluded	$18,549	1.38	$13,447
Mortality	Due to complications	Due to obesity	−$4,997	1.73	Dominant
Mortality	Included	Excluded	−$12,272	1.83	Dominant

BMI = body mass index; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[3]

CADTH Reanalyses

Table 13: Corrected Sponsor's Model

Stepped analysis	Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($ per QALYs)
Correction: No utility value for comorbidity ≥ 1	Standard management	557,977		20.82		
	NB + standard management	576,272	18,295	22.17	1.35	13,516
Correction: gamma distribution for costs	Standard management	557,977		20.97		
	NB + standard management	576,272	18,295	22.33	1.36	13,455
Correction: no distribution for certain costs	Standard management	557,977		20.97		
	NB + standard management	576,272	18,295	22.33	1.36	13,455
Correction: population = "all subjects"	Standard management	557,932		20.96		
	NB + standard management	576,293	18,361	22.34	1.38	13,288
Combined corrections	Standard management	557,932		20.81		
	NB + standard management	576,293	18,361	22.18	1.38	13,348
	Standard management	557,627		20.80		

Stepped analysis	Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($ per QALYs)
Combined corrections, scenario: population BMI ≥ 27, with comorbidities (expected population)	NB + standard management	576,239	18,612	22.20	1.40	13,276

BMI = body mass index; ICER = incremental cost-effectiveness ratio; NB = naltrexone hydrochloride/bupropion hydrochloride; QALY = quality-adjusted life-year.

Note: Currently based on deterministic analyses.

Table 14: CADTH Exploratory Analyses

Scenario	Base-case value	Scenario analysis value	Incremental costs ($)	Incremental QALYs	Incremental cost per QALY (vs. standard management)
Sponsor base case			18,537	1.36	$13,619
CADTH-corrected base case			18,361	1.38	$13,348
Response data at 56 weeks	mITT	Baseline carried forward	16,963	1.18	$14,406
BMI utility	Lane et al. (2014)[10]	No impact (i.e., change in utility of 0.001)	18,361	0.35	$52,053
Relative risks for comorbidities	Van Baal et al. (2008)[29]	No impact (RR = 1)	33,963	1.38	$24,500
Utility values for comorbid conditions	Based on published literature	No impact (i.e., utility value of 1)	18,361	1.45	$12,637
Base-case utility value	1	0.83[18] (other utility values scaled to 0.83 baseline)	18,361	1.32	$13,912
Population	"all subjects" (per CADTH-corrected base case)	BMI > 30, no comorbidities	16,974	1.40	$12,099
		BMI > 30, with comorbidities	18,682	1.34	$13,992
		BMI > 30, with or without comorbidities	18,295	1.35	$13,516

BMI = body mass index; mITT = modified intention-to-treat; NB = naltrexone and bupropion; QALY = quality-adjusted life-year. RR = relative risk.

Note: Currently based on deterministic analyses.

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