CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

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)

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that naltrexone hydrochloride plus bupropion hydrochloride not be reimbursed for chronic weight management.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that naltrexone hydrochloride plus bupropion hydrochloride (NB) not be reimbursed for chronic weight management.

Reasons for the Recommendation

1. In four double-blind randomized controlled trials (RCTs) in adults who were obese or overweight with at least one weight-related comorbidity (COR-I, COR-II, COR-BMOD, and COR-DM), those allocated to receive NB experienced an average of 3% to 5% reduction in body weight after 28 or 56 weeks compared with placebo. The relevance of a 3-5% weight loss over a short time period on obesity, a chronic long-term condition, and on clinical conditions such as diabetes, hypertension, other cardiovascular disease or other conditions such as sleep apnea remains uncertain.
2. None of the aforementioned trials demonstrated that treatment with NB resulted in clinically meaningful improvements in weight-related comorbidities, symptoms of importance to patients (fatigue, pain, and impaired productivity, sleep, and mobility), or health-related quality of life.
3. Sustained weight loss over many years is necessary to influence many chronic disease outcomes. Given the short duration of the included trials and the early termination of a long-term cardiovascular safety study, the long-term benefits and risks of NB are unknown.

Discussion Points

- The committee noted that there is uncertainty with respect to the magnitude of short-term weight loss achieved with NB, given the high proportion of study non-completers (greater than 40%) and the approach to data analysis. There is also uncertainty with respect to the generalizability of the results for the co-primary end point of percentage of patients with at least 5% weight loss to the real-world setting. The committee heard the opinion of a clinical expert that patients generally require weight loss of at least 10% to 15% to be satisfied with efficacy and continue treatment in the real-world setting. The committee noted that obesity is a heterogeneous chronic long-term condition that results from complex interactions with many socio-psycho-biologic factors that requires individualized treatments and support. Due to the use of 5% weight loss as a co-primary end point in the pivotal trials, the generalizability of the weight loss results in the trials to clinical practice is unclear.
- The committee considered the absence of effectiveness data beyond 56 weeks, particularly with respect to clinically meaningful improvement in comorbidities, to be a major limitation, given that being overweight and obesity are both chronic conditions for which patients could remain on treatment indefinitely. In addition, the committee discussed that the long-term cardiovascular safety of NB is uncertain, noting that NB in the trials was associated with a higher risk of increased heart rate and blood pressure in some patients. The LIGHT study, which was designed to demonstrate that the risk of cardiovascular events does not adversely affect the benefit-risk profile of NB, was terminated early and a subsequent safety study, requested by regulatory authorities, is not expected to report until 2022.
- The committee noted that there may be subgroups of patients who might experience benefit from NB; however the available clinical trials did not provide relevant subgroup data to assist in identifying a subpopulation that would most benefit from treatment with NB nor did they provide evidence for long-term clinically meaningful outcomes for treatment with NB. Although additional subgroup analyses were presented as part of the reconsideration request by the sponsor, the committee noted that these were post hoc analyses that were not part of the a priori determined statistical hierarchy nor were the analyses included as part of the original clinical evidence submission for NB.
- Based on input from the clinical expert, CDEC discussed that patients who might be prescribed NB are those with pre-existing comorbidities, as part of a strategy to ameliorate the effect of comorbidities on long-term health. However, it is unclear how

treatment with NB would compare with alternative approaches that directly address obesity-related comorbidities, such as intensified treatment with antihypertensive, lipid lowering, or antihyperglycemic drugs.

- Key limitations were identified with the economic model structure, model mechanics, clinical data, and exclusion of relevant comparators. These limitations precluded CADTH from being able to derive a reasonable estimate of the cost-effectiveness of NB in either the Health Canada–indicated population, or a population more likely to be treated with NB. As a result, the cost-effectiveness of NB in Canada is unknown.

Background

Contrave (naltrexone hydrochloride plus bupropion hydrochloride) has a Health Canada indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI 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).

Naltrexone is an opioid antagonist and bupropion is a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine. Contrave is available as a fixed-dose combination of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg extended-release tablets for oral administration and the Health Canada–approved dosage is two tablets twice daily for a total daily dose of 32 mg of naltrexone hydrochloride and 360 mg of bupropion hydrochloride.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH for the Common Drug Review: a systematic review of phase III and IV RCTs of NB, one indirect treatment comparison, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating overweight and obese patients and from information submitted by patient groups regarding outcomes and issues important to patients.

Summary of Patient Input

Two patient groups, Obesity Canada and the Canadian Spondylitis Association, provided input for this submission. Patient perspectives were obtained from online surveys, interviews, and one-on-one discussions with individuals living with obesity. The following is a summary of the key input from the perspective of the patient groups:

In addition to the numerous mental and physical health–related symptoms and conditions and chronic diseases that can result from obesity, patients also described difficulties with exercising, losing weight, performing daily activities, fatigue, low self-esteem due to perceived appearance, and a preoccupation with weight and depression. Patients struggle with varying degrees of success with available options to lose weight and often try several treatments, with weight regain identified as a significant issue.

Beyond weight loss, patients are interested in improvements in quality of life measures for issues such as productivity, energy level, sleep, activity, and mental health. In addition, an improvement in comorbidities, including diabetes, hypertension, and sleep apnea is also important to patients. Individuals living with a spondyloarthritic condition and obesity commented that weight loss would allow them to improve their mental and physical quality of life and, in turn, reduce or relieve pain and fatigue and improve mobility. Patients who take other medications — for example, for a spondyloarthritic condition — are looking for medications with fewer side effects.

Clinical Trials

The systematic review included five multi-centre, double-blind, parallel-group, placebo-controlled RCTs of patients with a BMI of 30 kg/m^2 to 45 kg/m^2 or a BMI of 27 kg/m^2 to 45 kg/m^2 with a weight-related comorbidity. There were four 56-week (four-week dose escalation phase and 52-week maintenance phase) pivotal phase III RCTs:

- The COR-I study (N = 1,742) randomized patients 1:1:1 to naltrexone 16 mg / bupropion 360 mg daily (not a recommended dosage in the product monograph), naltrexone 32 mg / bupropion 360 mg daily, or matching placebo.

- The COR-II study (N = 1,496) randomized patients 1:1 to naltrexone 32 mg / bupropion 360 mg daily or matching placebo. From week 28 to 44, patients who did not lose at least 5% of body weight were re-randomized to continue or to receive naltrexone 48 mg / bupropion 360 mg daily (not a recommended dosage in the product monograph). The primary analysis was at the week 28 time point.
- The COR-BMOD study (N = 793) randomized patients 3:1 to 32 mg naltrexone / 360 mg bupropion daily or matching placebo.
- The COR-DM study (N = 505) randomized patients with type 2 diabetes mellitus 2:1 to 32 mg naltrexone / 360 mg bupropion daily or matching placebo.

In the COR-I, COR-II, and COR-DM studies, all patients received instructions to follow a hypocaloric diet and a prescription for walking at least 30 minutes a day three days a week, while all patients in the COR-BMOD study participated in an intensive behaviour modification program that included dietary instruction, 28 closed-group sessions, and prescribed exercise. Patients in the COR-I, COR-II, and COR-BMOD studies were non-diabetic and had a BMI of 30 kg/m^2 to 45 kg/m^2 with uncomplicated obesity or a BMI of 27 kg/m^2 to 45 kg/m^2 with controlled hypertension and/or dyslipidemia. Patients in the COR-DM study had type 2 diabetes not treated with injectable antidiabetic medication or inhaled insulin and had a BMI of 27 kg/m^2 to 45 kg/m^2. The percentage of randomized patients discontinuing study treatment in the pivotal trials ranged from 41.2% to 50.1%.

The LIGHT study (N = 8,910) randomized patients 1:1 to 32 mg naltrexone / 360 mg bupropion daily or matching placebo and was a cardiovascular outcomes trial in patients with a BMI of 27 kg/m^2 to 45 kg/m^2 and cardiovascular disease or type 2 diabetes with at least two cardiovascular risk factors. All patients participated in a comprehensive, Web-based weight management program. The LIGHT study was a noninferiority trial assessing time to first confirmed occurrence of a major adverse cardiovascular event (MACE) using a noninferiority margin of 1.4 for the hazard ratio to rule out increased risk of MACE with NB. The required follow-up duration to accumulate the number of events in the statistical analysis plan was expected to be three to four years. Due to public release of the 25% interim results, the LIGHT study was terminated early by the investigators after 64% of anticipated events. The percentage of patients in the NB and placebo groups who discontinued study treatment for reasons other than sponsor decision (which included discontinuations due to study termination) were 77.1% and 84.7%, and MACE follow-up was not available for 11.6% of patients.

No trials comparing NB with an active comparator met the review criteria.

The main limitation of all the trials was the large proportion of treatment and study discontinuations. Additionally, rates of discontinuation due to adverse event (AE) or lack of efficacy were imbalanced between treatment groups in each trial. Discontinuation due to AE was more common in the NB groups and discontinuation due to lack of efficacy was more common in the placebo groups. Primary analyses for all efficacy outcomes in the pivotal trials were performed in the full analysis set (all randomized patients with a baseline weight measurement and at least one post-baseline weight measurement while on study drug) using the last observation carried forward method to impute missing data. The use of the full analysis set rather than a true intention-to-treat set meant that any patients who discontinued treatment before the week 4 visit were excluded. Due to substantial, imbalanced discontinuations during the first four weeks, using the full analysis set instead of the set of all randomized patients likely biased the results in favour of NB as patients who discontinued in the first four weeks were less likely than the rest of the patients to receive treatment benefit. Clinical expert input indicated that patients who discontinue treatment are expected to return to their baseline weight and that there is no evidence for an overall benefit from temporary weight loss; therefore, the baseline observation carried forward (BOCF) imputation method, which assigned no overall benefit in weight loss to patients who discontinue treatment and was performed in the set of all randomized patients (or the full analysis set in the COR-BMOD study), was the most appropriate method of analysis for the primary end points.

The results from the COR-I, COR-II, and COR-DM are likely more generalizable to the Canadian clinical setting than the results from the COR-BMOD study, given that the co-interventions in the COR-BMOD study were more intensive than patients in Canada would generally receive, according to clinical expert input.

The major limitation in the LIGHT study was its early termination and the inability to draw conclusions based on the 50% interim analysis or the final data cut-off analysis. In addition, the large proportions of patients discontinuing treatment early may have biased the results toward the null (problematic in a noninferiority study) as the risk of cardiovascular events could be positively associated with duration of treatment exposure and/or negatively associated with time since treatment discontinuation.

The pivotal trials did not provide efficacy results beyond one year of treatment and most patients in the LIGHT study discontinued treatment after less than one year. Therefore, evidence for the long-term efficacy of NB past one year of treatment is limited.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed weight loss (including percent change in weight loss and percentage of patients with at least 5% and at least 10% weight loss), disease-specific health-related quality of life using the Impact of Weight on Quality of Life – Lite version (IWQOL-Lite), and MACE. The co-primary outcomes in the four pivotal trials were per cent change in weight loss from baseline and percentage of patients with at least 5% weight loss, both assessed at week 56 (week 28 in the COR-II study). In addition, the percentage of patients with at least 10% weight loss at week 56 (week 28 in the COR-II study) was assessed as a secondary outcome. The primary outcome in the LIGHT study was time to first occurrence of MACE (defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Secondary end points were part of a sequential hierarchical closed testing procedure in the pivotal trials.

Improvement in weight-related comorbidities was identified in the patient input submissions and by clinical expert input as an outcome that is important to patients with obesity and it was not assessed comprehensively in the studies. Symptoms of depression were assessed in the pivotal trials using the Inventory of Depressive Symptomology – Self Report, but the scale's validity in this patient population is unclear. Changes in antidiabetic medications were assessed in the COR-DM study, but were not statistically tested in accordance with the closed testing procedure. Changes in medication for other weight-related comorbidities were not assessed. Improvement in food craving was also identified as an important outcome, but there were issues with the validity of the scales used to assess food craving in the pivotal trials. Other outcomes important to patients according to the patient input received (fatigue, pain, productivity, sleep, and mobility) were not assessed in the trials.

Efficacy

The co-primary end points were met in all four pivotal trials; therefore, superiority of NB over placebo for weight loss was demonstrated:

- Least squares mean differences in percentage change in body weight from baseline to week 56 (week 28 in the COR-II study) for NB versus placebo were: –4.81% (95% confidence interval [CI], –5.63% to –3.99%) in the COR-I study, –4.56% (95% CI, –5.19% to –3.93%) in the COR-II study, –4.21% (95% CI, –5.56% to –2.86%) in the COR-BMOD study, and –3.28% (–4.34% to –2.22%) in the COR-DM study. Results using BOCF imputation were consistent with the primary analysis, though effect sizes were consistently smaller in the BOCF analyses.
- Odds ratios for the percentage of patients with at least 5% weight loss from baseline to week 56 (week 28 in the COR-II study) for NB versus placebo were: 4.86 (95% CI, 3.60 to 6.57) in the COR-I study, 6.61 (95% CI, 4.95 to 8.84) in the COR-II study, 2.89 (95% CI, 2.02 to 4.13) in the COR-BMOD study, and 3.44 (95% CI, 2.15 to 5.50) in the COR-DM study. Results using BOCF imputation were consistent with the primary analysis, though effect sizes were consistently smaller in the BOCF analyses. The percentage of patients with at least 5% weight loss in the BOCF analyses ranged from 11.5% to 14.1% in the placebo groups and 28.1% to 42.1% in the NB groups in the COR-I, COR-II, and COR-DM studies.

The percentage of patients with at least 10% weight loss from baseline to week 56 (week 28 in the COR-II study), which was a secondary end point, was also statistically significantly different between groups in the COR-I, COR-II, and COR-BMOD studies. Odds ratios for this outcome for NB versus placebo were: 4.19 (95% CI, 2.82 to 6.23) in the COR-I study, 5.36 (95% CI, 3.60 to 7.98) in the COR-II study, and 2.89 (95% CI, 2.02 to 4.13) in the COR-BMOD study. The percentage of patients with at least 10% weight loss using LOCF imputation in the full analysis set ranged from 5.7% to 7.4% in the placebo groups and 18.5% to 27.3% in the NB groups in the COR-I, COR-II, and COR-DM studies. The end point was not statistically tested in the COR-DM study and BOCF analyses were not performed for this end point.

Change in IWQOL-Lite total score from baseline to week 56 (week 28 in the COR-II study), a secondary end point, was statistically significantly different between treatment groups in favour of NB in the COR-I, COR-II, and COR-BMOD studies. The end point was not statistically tested in the COR-DM study. The between-group differences in all the pivotal trials did not meet the lower end of the range of minimally important differences identified for the IWQOL-Lite total score. In addition, the clinical expert did not consider the between-group differences to be clinically meaningful.

Besides the IWQOL-Lite total score, the only other outcome in the pivotal trials for which a statistically significant between-group difference was found was for the item 19 score for the Control of Eating questionnaire in the COR-I study; the validity of using a single item score for this scale is unknown.

In the LIGHT study, the hazard ratio for the primary end point for NB versus placebo using the final data cut-off was 0.95 (99.7% CI, 0.65 to 1.38) with a *P* value of 0.0013 for ruling out a hazard ratio of 1.4 or greater and a *P* value of 0.6953 for demonstrating superiority.

Harms (Safety)

In the pivotal trials, AEs were more common in the NB group than in the placebo group. AEs that consistently occurred more commonly in the NB group versus the placebo group were constipation, dry mouth, nausea, vomiting, dizziness, headache, and insomnia. Serious adverse events (SAEs) were reported in fewer than 5% of each treatment group in the pivotal trials. SAEs reported in more than 1% of a treatment group were angina pectoris and atrial fibrillation, each occurring in two patients in the placebo group of the COR-DM study. In the LIGHT study, 9.7% of patients in the placebo group and 10.4% in the NB group reported an SAE. No specified SAEs were reported in at least 1% of either treatment group.

Gastrointestinal disorders and psychiatric disorders were identified in the systematic review protocol as notable harms and were more common in the NB group than in the placebo group in the pivotal trials. In all the pivotal trials, increases from baseline at two consecutive visits in pulse rate (of at least 5 bpm or 10 bpm), systolic blood pressure (of at least 10 mm Hg or 15 mm Hg), and diastolic blood pressure (of at least 5 mm Hg or 10 mm Hg) were more common in patients receiving NB than in patients receiving placebo.

Indirect Treatment Comparisons

One relevant published network meta-analysis (NMA) was included in the review. The NMA, which included 28 RCTs, compared weight loss and discontinuations due to AE between FDA-approved weight loss drugs for long-term use in patients with obesity (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) with at least one weight-related comorbidity. Of the comparators in the evidence network, orlistat and liraglutide were relevant to the systematic review. The primary efficacy outcome for the NMA was the proportion of patients with at least 5% weight loss at one year of follow-up, relative to baseline weight. Other efficacy outcomes assessed were the proportion of patients with at least 10% weight loss and the change in weight in kilograms relative to baseline weight in excess of placebo after one year of follow-up.

In the main analyses of the three efficacy outcomes, the 95% credible intervals (CrIs) excluded one for odds ratios and zero for mean differences for the comparisons of NB versus placebo and NB versus orlistat (and not for the comparison of NB versus liraglutide) and between-group differences favoured NB. In the main analyses of the safety outcome (discontinuations due to AE), the 95% CrIs excluded one for the odds ratios for the comparisons of NB versus placebo and NB versus orlistat (and not for the comparison of NB versus liraglutide) and between-group differences did not favour NB.

The main limitations affecting the interpretation of the NMA results were the high risk of attrition bias in all the primary RCTs due to the proportions of study discontinuations ranging from 30% to 45%, bias in favour of NB for efficacy and against NB for harms due to use of the full analysis set compared with the modified intention-to-treat set in the other RCTs, and variation in study design characteristics and potential effect modifiers that may have undermined the assumption of clinical similarity between pairwise comparisons. Inconsistencies between the main analyses and worst-case scenario sensitivity analyses for the 5% and 10% weight loss outcomes (i.e., 95% CrIs for odds ratios no longer excluding 1), coupled with the identified limitations, meant that superior efficacy of NB over orlistat could not be concluded. Similarly, the identified limitations meant that superiority of orlistat over NB in discontinuations due to AE could not be concluded. There was no evidence for a difference in any of the outcomes between NB and liraglutide.

Cost and Cost-Effectiveness

NB (Contrave) is available as a tablet comprising 8 mg naltrexone hydrochloride and 90 mg bupropion hydrochloride. The recommended dose for NB is two tablets twice daily. At the submitted price of $2.21 per tablet, the annual cost is $3,234.

The sponsor submitted a cost-utility analysis comparing NB in conjunction with standard management (SM; defined as a reduced-calorie diet and increased physical activity) with SM alone. The model was conducted from the Canadian public health care payer perspective with a lifetime time horizon (approximately 61 years). The submitted model was an event-driven decision analytic model where patients were within one of three mutually exclusive weight categorizations: normal weight (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 or more). Comorbidities impacted by weight (e.g., myocardial infarction, chronic heart failure, stroke, diabetes, various cancers) were incorporated based on relative risks for each weight category. Lower relative risks were applied to patients with a normal BMI, with the highest risk in patients who are obese. Baseline patient characteristics and response rates were derived from pooling data from COR-I and COR-II. Patients who experienced a response to either NB + SM or SM alone (defined as a weight loss 5 % or more of body weight) 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 duration of the time horizon and resulted in responders 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. Changes in BMI were associated with changes in utility values, independent of utility values associated with comorbid conditions. In the sponsor's base case, NB was associated with an incremental cost-effectiveness ratio of $13,697 per quality-adjusted life-year gained when compared with 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. The results were sensitive to alternate assumptions regarding the time horizon, utility values for BMI change, and post-response weight change.

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

- The submitted model lacked structural validity in the population most likely to be prescribed NB (BMI of 27 kg/m^2 or greater in the presence of at least one comorbidity), where the goals of treatment are focused on weight loss to alleviate existing comorbidities.
- The clinical effectiveness of NB is highly uncertain. Particularly, the assumption of long-term maintenance of weight loss observed during the short-term trial period, and the use of BMI to model disease progression and the risk of downstream comorbidities have not been substantiated.
- 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 benefit of NB.
- Relevant comparators were not considered in the submitted pharmacoeconomic evaluation; therefore, the comparative cost-effectiveness of NB with relevant comparators is unknown.
- The sponsor's economic model was unnecessarily complex and lacked transparency, which made it difficult to validate and evaluate.

Given the identified concerns with the application of the trial outcomes to the model, exclusion of relevant comparators, and uncertainty regarding the validity of several key model inputs and assumptions, CADTH was unable to undertake an appropriate base-case analysis. CADTH conducted 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. As a result, the cost-effectiveness of NB in Canada is unknown.

CDEC Members

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

January 15, 2020 Meeting

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None.

May 20, 2020 Meeting

Regrets

None.

Conflicts of Interest

None.