

Naltrexone/Bupropion ER (Contrave)

Newly Approved Treatment Option for Chronic Weight Management in Obese Adults

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INTRODUCTION

Obesity is becoming an increasingly serious and costly health problem in the United States, with more than one-third of adults (34.9%) and 17% of children suffering from this condition.¹ Obesity is defined as having a body mass index (BMI) greater than 30, while being overweight is defined as having a BMI between 25 and 29.9.² Besides being a psychological burden on the patient, obesity is associated with increased risk of stroke, cardiovascular disease, type-2 diabetes, and the development of certain types of cancers, including esophageal, pancreatic, colon, and breast cancers.^{3,4} Obesity represents a huge burden to the U.S. health care system—\$147 billion was spent on obesity in 2008 alone. Health care costs for obese patients were on average \$1,429 higher than for patients of normal weight.⁵ The physiological, psychological, and financial effects associated with obesity have pushed health care professionals to come up with appropriate solutions to manage obesity and achieve better health outcomes.

The Food and Drug Administration (FDA) has recently added to the effort to curb obesity with the approval of medications for chronic weight management, including phentermine/topiramate

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extended release (Qsymia, VIVUS, Inc.), lorcaserin (Belviq, Eisai, Inc.), and naltrexone/bupropion extended release (Contrave, Orexigen Therapeutics, Inc.). Contrave's two active components, naltrexone and bupropion, are both approved by the FDA (naltrexone to treat alcohol and opioid dependence, and bupropion to treat depression and seasonal affective disorder and as an aid to smoking cessation treatment). Initially, Contrave was rejected by the FDA in February 2011 because of the need for long-term clinical trials evaluating the cardiovascular effects of the drug.⁶ Contrave was finally approved in September 2014 after subsequent clinical trials demonstrated its safety and efficacy.⁷

CHEMICAL PROPERTIES⁸

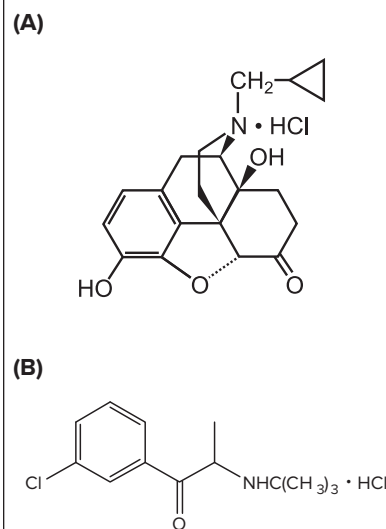
Contrave is an extended-release (ER), fixed-dose combination product containing naltrexone, an opioid antagonist, and bupropion, an aminoketone antidepressant, with chemical formulas of morphinan-6-one, 17-(cyclopropylmethyl)4,5-epoxy-3,14-dihydroxy-, hydrochloride, (5 α)- and (\pm)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propranone hydrochloride, respectively. It is available as a trilayer, film-coated, blue, round, biconvex, ER tablet debossed with NB-890 on one side and smooth on the other. Each tablet has a trilayer core composed of two drug layers containing 8 mg of naltrexone, 90 mg of bupropion, and excipients, which are separated by a rapid-dissolving inert layer. Inactive ingredients include edetate disodium, hydroxypropyl cellulose, microcrystalline cellulose, lactose anhydrous, magnesium stearate, L-cysteine hydrochloride, hypromellose, lactose monohydrate, crospovidone, Opadry II Blue, FD&C Blue #2 Aluminum Lake, and colloidal silicon dioxide. The structures of both drugs are illustrated in Figure 1.

MECHANISM OF ACTION

The exact neurochemical mechanism of the naltrexone/bupropion combination leading to weight loss is not fully understood.⁸ However, from preclinical study data, the combination is theorized to work synergistically in the hypothalamus and the mesolimbic dopamine circuit to promote satiety, reduce food intake, and enhance energy expenditure.^{9,10}

Pro-opiomelanocortin (POMC) cells found in the arcuate nucleus of the hypothalamus produce melanocyte-stimulating hormone (alpha-MSH) and beta-endorphin, an endogenous opioid.^{11,12} The alpha-MSH activates the melanocortin-4 receptor (MC4R), leading to decreased food intake, increased energy expenditure, and weight loss.^{13,14} Beta-endorphin reduces activity of POMC cells by binding to the inhibitory mu-opioid receptor (MOP-R).¹⁵ Bupropion, a weak dopamine and norepinephrine reuptake inhibitor, enhances POMC cell production and release of alpha-MSH and beta-endorphin

Figure 1 Structural Formula of Naltrexone (A) and Bupropion (B)⁸



in vitro.¹⁰ Naltrexone, an opioid antagonist, blocks the MOP-R, therefore disrupting beta-endorphin inhibitory feedback on POMC cells.¹⁰ The naltrexone/bupropion combination enhances the effect of POMC signaling more than either drug alone.¹⁶

In addition, a preclinical study in hungry mice showed that direct injection of naltrexone and bupropion into the ventral tegmental area of the mesolimbic circuit produced a reduction in food intake.¹⁷ The reduction in food intake was notably larger than the reduction seen with either agent alone, suggesting that these drugs have independent yet synergistic actions in the mesolimbic dopamine circuit.¹⁷

INDICATION AND DOSAGE⁸

Naltrexone/bupropion is indicated as an adjunct to increased physical activity and a reduced-calorie diet for chronic weight management in obese adults (BMI of 30 kg/m² or greater) or in overweight adults (BMI of 27 kg/m² or greater) with at least one weight-related comorbid condition, such as hypertension, type-2 diabetes, or dyslipidemia.

Dosing recommendations are based on the number of tablets, which contain 8 mg of naltrexone and 90 mg of bupropion. Contrave should initially be prescribed as one tablet taken by mouth in the morning for one week. At the start of week 2, another tablet should be added to the regimen in the evening. This titration should continue weekly until the optimal dosing of two tablets twice daily is reached at week 4 for a total daily dose of 32 mg of naltrexone and 360 mg of bupropion.

After 12 weeks of treatment with naltrexone/bupropion, a patient should have achieved at least a 5% weight loss since initiation of therapy. If this result is not attained within 12 weeks, then naltrex-

Table 2 Pharmacokinetic Profile of Contrave⁸

	Naltrexone	Bupropion
Mean apparent volume of distribution at steady state (V _{ss} /F)	5,697 L	880 L
Protein binding	21%	84%
Metabolism	Noncytochrome-mediated dehydrogenase	Extensively hepatic via CYP2B6
Inhibition or induction of cytochrome P450 isozymes	None	Strong CYP2D6 inhibition
Metabolic first pass	Yes	No
Major metabolites	6-beta-naltrexol (active)	Hydroxybupropion, erythrohydrobupropion, threo hydrobupropion
Half-life	<ul style="list-style-type: none"> Naltrexone: 5 hours 6-beta-naltrexol: 13 hours 	<ul style="list-style-type: none"> Bupropion: ~21 hours Hydroxybupropion: 20 ± 5 hours Erythrohydrobupropion: 33 ± 10 hours Threo hydrobupropion: 37 ± 13 hours
Excretion	Urine	Urine, feces

one/bupropion should be discontinued because it is unlikely that the patient will derive benefit from it.

The drug has not been evaluated in patients with renal or hepatic impairment. The manufacturer's dosing recommendations are based on data for naltrexone and bupropion individually (Table 1).

Too few trial participants were 65 years of age or older to determine if this age group responds differently than younger patients. Patients older than 65 years of age may be more sensitive to naltrexone/bupropion's central nervous system adverse effects. No specific dose adjustments are recommended based solely on age, but using caution is advised. Safety and efficacy studies for patients younger than 18 years of age have not been performed, and the drug is not recommended for this age group.

DRUG INTERACTIONS⁸

The naltrexone component of Contrave may prevent patients from achieving full benefit from opioid-containing medications such as cough suppressants, anti-diarrheal drugs, or opioid analgesics. If a patient requires intermittent treatment with opioids, Contrave should be discontinued and standard doses of the opioid should not be exceeded. If a patient uses opioids chronically, the opioid should be

discontinued for seven to 10 days before Contrave is initiated to prevent precipitation of opioid withdrawal.⁸

The concomitant use of bupropion with a monoamine oxidase inhibitor (MAOI) is contraindicated due to risk of hypertensive reactions. A 14-day washout period should elapse before the initiation of Contrave or an MAOI after the discontinuation of the other medication.¹⁸

Bupropion is a strong inhibitor of cytochrome P450 (CYP 450) 2D6 isozyme and is primarily metabolized by CYP2B6 isozyme to the active metabolite hydroxybupropion.¹⁹ When initiating medications metabolized by CYP2D6 in a patient already receiving Contrave, start the concurrent medication at the lower end of its dosage range and titrate cautiously. Conversely, when initiating Contrave in a patient already receiving a drug metabolized by CYP2D6, a dose reduction of the original medication should be considered. Contrave should not exceed one tablet in the morning and evening when used concomitantly with CYP2B6 inhibitors.²⁰ Avoiding the use of Contrave with CYP2B6 inducers is recommended as well.¹⁹

Additionally, bupropion has a dose-related propensity to cause seizures. Extra caution should be exercised when administering Contrave with anti-

Table 1 Renal and Hepatic Impairment Dosing Recommendations⁸

Renal Impairment

- Mild: No dosage adjustment recommended
- Moderate to severe: One tablet in the morning and evening
- End stage renal disease: Use is not recommended

Hepatic Impairment

- Mild to severe: One tablet in the morning

psychotics, antidepressants, theophylline, or systemic corticosteroids because of an enhanced risk of seizure. The use of bupropion with levodopa or amantadine has been reported to cause restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness due to combined dopamine agonistic effects.⁸ Use caution and monitor the patient for similar adverse events if Contrave is concurrently administered with these drugs.

PHARMACOKINETICS⁸

Following oral administration in healthy subjects, the peak concentrations (C_{max}) and time to C_{max} (T_{max}) were 1.4 ng/mL in two hours and 168 ng/mL in three hours for naltrexone and bupropion, respectively. Naltrexone/bupropion administration is not recommended following a high-fat meal due to a significant increase in systemic exposure. Naltrexone demonstrated a 1.7-fold increase in area under the curve (AUC) and a 1.9-fold increase in C_{max}. Bupropion exhibited a less significant 1.1-fold increase in AUC and 1.3-fold increase in C_{max}.⁸ The increase in AUC and C_{max} for both drugs is even more pronounced prior to reaching steady state. For more information on bioavailability, distribution, metabolism, and excretion, see Table 2.

EFFICACY IN CLINICAL TRIALS²¹⁻²⁴

The Contrave Obesity Research-I (COR-I) study, the Contrave Obesity Research-II (COR-II) study, the Contrave Obesity Research-Intensive Behavior Modification study (COR-BMOD), and the Contrave Obesity Research-Diabetes study (COR-Diabetes) were four 56-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 trials enrolling 4,536 patients to evaluate the efficacy and safety of naltrexone/bupropion. The first three trials focused mainly on weight reduction in uncomplicated obesity or obesity with controlled hypertension and/or dyslipidemia. The COR-Diabetes study evaluated overweight and obese patients with type-2 diabetes.²⁴ COR-I was the only study of the four that compared naltrexone/bupropion 16 mg/360 mg to naltrexone/bupropion 32 mg/360 mg and to placebo.²¹ All the studies combined low-intensity lifestyle modification counseling with naltrexone/bupropion or placebo except COR-BMOD. COR-BMOD utilized more intensive lifestyle modification counseling by exercise specialists, dietitians, and psychologists over 28 sessions.²³ Interventions included strategically planned hypocaloric diets, calorie counting, maintaining food diaries, and gradual titration of exercise requirements. A full list of inclusion and

exclusion criteria for the studies can be found in Table 3.

In all four studies, naltrexone/bupropion was started at one-fourth of the full maintenance dose and titrated weekly until reaching the full maintenance dose at week 4. Efficacy analyses included an intention-to-treat (ITT) and modified intention-to-treat (mITT) approach with the last observation carried forward.

Baseline characteristics were similar among treatment arms in each of the four studies. In three of the four studies, the patient populations' mean age was 44 to 46 years, the BMI was 36 kg/m², more than 85% were women, and more than 68% were Caucasian. The COR-Diabetes trial, however, had a mean age of 54 years and 54% of the participants were female. These baseline characteristics could limit the external validity of these phase 3 studies.

Patients treated with naltrexone/bupropion 32 mg/360 mg achieved statistically and clinically significant weight reduction when compared with placebo in all four phase 3 studies. Additionally, the weight loss was maintained throughout the 56 weeks of all the trials. See Table 4 for overall weight loss percentage ranges. Patients in both arms of the COR-BMOD study lost on average more weight than patients in the other trials, most likely due to the more intensive lifestyle modification training.²³

Table 3 Inclusion and Exclusion Criteria for the Contrave Obesity Research (COR) Trial Program

	Inclusion Criteria	Exclusion Criteria
COR-I Trial ²¹	Men and women ages 18–65 years, a BMI 30–45 kg/m ² with uncomplicated obesity, or a BMI of 27–45 kg/m ² with controlled hypertension and/or dyslipidemia	Pregnancy or lactation, type-1 or type-2 diabetes, obesity of known endocrine origin, cerebrovascular disease, cardiovascular disease, hepatic disease, renal disease, history of seizures, history of psychiatric illness, drug or alcohol misuse, previous surgical or device intervention for obesity, treatment with bupropion or naltrexone in the previous 12 months, loss or gain of more than 4 kg within 3 months prior to randomization
COR-II Trial ²²	Same as COR-I plus a lack of any opioid medication for at least 7 days prior to randomization	Same as COR-I
COR-BMOD Trial ²³	Same as COR-I	Same as COR-I except that patient cannot have used tobacco or nicotine within 6 months of study
COR-Diabetes Trial ²⁴	Men and women ages 18–70 years with type-2 diabetes, a BMI of 27–45 kg/m ² , an HbA _{1c} of 7%–10%, a fasting blood glucose < 270 mg/dL, systolic and diastolic blood pressures < 145 and < 95 mm Hg, respectively; either no diabetes medications or stable doses of oral antidiabetic medications for ≥ 3 months prior to randomization	Type-1 diabetes, poorly controlled diabetes, diabetes deemed secondary to pancreatitis or pancreatectomy, severe microvascular or macrovascular complications of diabetes, serious medical conditions, loss or gain of > 5 kg weight within the previous 3 months, obesity of known endocrine origin, history of surgical or device intervention for obesity, history of seizures, history of serious psychiatric illness, history of drug or alcohol misuse, clinically significant cardiac abnormalities, receipt of prohibited concomitant medications

BMI = body mass index; BMOD = behavioral modification; COR = Contrave Obesity Research; HbA_{1c} = hemoglobin A1c.

Table 4 Body Weight Changes at 56 Weeks in Contrave Obesity Research (COR) Clinical Trials

	COR-I ²¹		COR-II ^{22,a}		COR-BMOD ²³		COR-Diabetes ²⁴	
	Naltrexone/ Bupropion 32/360 mg	Placebo	Naltrexone/ Bupropion 32/360 mg	Placebo	Naltrexone/ Bupropion 32/360 mg	Placebo	Naltrexone/ Bupropion 32/360 mg	Placebo
Intent-to-Treat^b	n = 538	n = 536	n = 820	n = 474	n = 565	n = 196	n = 321	n = 166
Percent change in body weight from baseline, LS mean	-5.4% ^d	-1.3%	-5.6% ^d	-1.2%	-8.1% ^d	-4.9%	-3.7% ^d	-1.7%
Patients with ≥ 5% weight loss	42% ^d	17%	47.9% ^d	16.9%	57% ^d	43%	36% ^d	18%
Patients with ≥ 10% weight loss	21% ^d	7%	28.1% ^d	6.1%	35% ^d	21%	15% ^e	5%
Completers^c	n = 296	n = 290	n = 434	n = 267	n = 301	n = 106	n = 175	n = 100
Percent change in body weight from baseline, LS mean	-8.1% ^f	-1.8%	-8.2% ^d	-1.4%	-11.5% ^d	-7.3%	-5.9% ^d	-2.2%
Patients with ≥ 5% weight loss	62% ^f	23%	64.9% ^d	21.7%	80.4% ^d	60.4%	53.1% ^d	24%
Patients with ≥ 10% weight loss	34% ^f	11%	39.4% ^d	7.9%	55.2% ^d	30.2%	26.3% ^d	8.0%

BMOD = behavioral modification; COR = Contrave Obesity Research; LS = least squares.

^a 56-week data was a secondary endpoint in the COR-II trial.

^b Includes all randomized patients with one baseline weight measurement and at least one post-baseline weight measurement during the defined treatment phase with the last observation carried forward.

^c Includes all randomized patients who completed 56 weeks of treatment.

^d Difference from placebo, *P* < 0.001.

^e Difference from placebo, *P* < 0.01.

^f Difference from placebo, *P* < 0.0001.

In the ITT population, the only cardio-metabolic and glycemic parameters to show statistically significant improvements at 56 weeks after treatment with naltrexone/bupropion were waist circumference in COR-I and COR-BMOD and hemoglobin A1c (HbA_{1c}) in the COR-Diabetes trial. When the analysis was changed to mITT, treatment with naltrexone/bupropion was associated with statistically significant improvements in waist circumference, triglycerides, and high-density lipoprotein-cholesterol (HDL-C). Moreover, in the COR-Diabetes trial, there was a clinically significant improvement in HbA_{1c} and a lower portion of patients required rescue medications for glycemic control.²⁴

Active treatment in the COR-I and COR-II trials was associated with significant improvements in eating control. Additionally, self-reported weight-related quality of life significantly improved in the COR-I, COR-II, and COR-Diabetes trials in the naltrexone/bupropion treatment arms.

The COR trial series provides adequate support for the efficacy of naltrexone/bupropion in chronic weight management, combined with lifestyle modifications.

SAFETY AND TOLERABILITY

Naltrexone/bupropion has been administered to 3,475 patients with more than 2,300 patient-years of exposure.²⁵ The most common side effects experienced during the placebo-controlled trials are presented in Table 5. Contrave carries the antidepressant-class boxed warnings for suicidality and neuropsychiatric reactions in patients taking bupropion for smoking cessation, even though Contrave is not approved for depression or smoking cessation.⁸

Naltrexone/bupropion has been associated with increases in resting heart rate and average blood pressure.^{8,25,26} In clinical trials, naltrexone/bupropion was not associated with a clinically significant change in blood pressure or electrocar-

diogram parameters.²⁵ The number of cardiovascular events reported in clinical trials was considered to be too low to exclude a potential risk.^{25,26}

P&T COMMITTEE CONSIDERATIONS

In February 2011, the FDA declined to approve Contrave due to concerns about the long-term cardiovascular safety profile; this was a substantial setback for Orexigen.⁶ Since that time, Orexigen has worked closely with the FDA and completed two additional studies. The FDA determined the additional studies were sufficient to grant approval of Contrave if Orexigen agreed to conduct post-marketing trials, including a long-term cardiovascular study called the LIGHT trial.²⁷ However, Orexigen recently announced the termination of the LIGHT trial upon the recommendation of the lead researcher.²⁸ Orexigen stated that the study is not being terminated due to the finding of superiority or harm but

because protocol was breached.²⁸ Interim study data was prematurely released in March 2015 indicating that naltrexone/bupropion may reduce cardiovascular risks, but these claims cannot be substantiated.²⁸ Study protocol for a second post-marketing requirement, a cardiovascular outcomes trial, received FDA acceptance in April 2015, but Takeda and Orexigen have since entered into a legal dispute affecting the start date of the new trial.

Contrave's approval came in the wake of the 2012 approvals of Qsymia and Belviq, and it is the fourth medication approved as an adjunct for chronic weight management. In the absence of head-to-head comparative studies, only data from the approved labeling can be used to determine general similarities and differences among products.

All currently approved antiobesity medications for chronic weight management have met the minimum FDA requirement of a 5% placebo-corrected weight loss and seem to have similar efficacy rates. While 5% to 10% weight loss in obese patients may appear to be only marginally beneficial, if at all, clinical benefits have been shown to exist even with modest reductions in weight. For example, weight loss of 5% to 10% is associated with reduced sleep apnea symptoms, improved mobility, and improvement in urinary stress incontinence.²⁹ In patients with type-2 diabetes, weight loss of 5% to 10% is associated with reduced need for diabetes medications and a 0.6% to 1.0% reduction in HbA_{1c}.³⁰

Contrave, Qsymia, and Belviq have similar adverse effect profiles, which are rela-

tively mild. Contrave has not been shown to have abuse potential and therefore is not a Schedule IV controlled substance like Qsymia and Belviq. Although Contrave has not been approved for any indication other than chronic weight management, it may have an advantage over weight-loss medications in patients who are overweight and concomitantly suffer from major depressive disorder, seasonal affective disorder, or attention-deficit disorder or who want to quit smoking. Conversely, it would be the last option, if used at all, in patients with uncontrolled hypertension, history of seizures, bulimia or anorexia nervosa, and chronic opioid use.

CONCLUSION

In recent years, obesity has evolved far beyond a simple cosmetic issue. It is now recognized at all levels of government as a major national health threat contributing significantly to many health conditions and mortality.³⁰ In 2013, the American Medical Association passed a resolution that resulted in reclassification of obesity as a disease with physiological impairments requiring a range of medical interventions for treatment and prevention.³¹ Identification and treatment of underlying conditions contributing to obesity as well as intensive counseling on lifestyle modifications should remain first-line treatment. When first-line options provide unsatisfactory results, Contrave may serve as a valuable treatment adjunct to lifestyle modifications by promoting satiety, reducing feeding, enhancing energy expenditure, and ultimately helping patients achieve weight loss goals.

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Table 5 Common Adverse Events Reported⁸

Adverse Reactions	Naltrexone/ Bupropion 32/360 mg n = 2,545	Placebo n = 1,515
Nausea	32.5%	6.7%
Constipation	19.2%	7.2%
Headache	17.6%	10.4%
Vomiting	10.7%	2.9%
Dizziness	9.9%	3.4%
Insomnia	9.2%	5.9%
Dry mouth	8.1%	2.3%
Diarrhea	7.1%	5.2%

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