PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]CONTRAVE®

Naltrexone hydrochloride 8 mg and Bupropion hydrochloride 90 mg
Extended-Release Tablets

Antiobesity agent
Weight Management

Bausch Health, Canada Inc.
2150 Blvd. St-Elzear West,
Laval, Quebec
H7L 4A8

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets / Naltrexone hydrochloride 8mg and Bupropion hydrochloride 90mg	Colloidal Silicon Dioxide, Crospovidone, Edetate Disodium, FD&C Blue No. 2 Indigo Carmine Aluminum Lake, Hydroxypropyl Cellulose, Hypromellose, Lactose Anhydrous, Lactose Monohydrate, L-Cysteine Hydrochloride, Macrogol/Peg, Magnesium Stearate, Microcrystalline Cellulose, Polyvinyl Alcohol-Part Hydrolyzed, Talc and Titanium Dioxide.

INDICATIONS AND CLINICAL USE

CONTRAVE is 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 (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).

Limitations of Use

- The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, Increase in Blood Pressure and Heart Rate).
- The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

Geriatrics (65 ≥ years of age)
Clinical studies of CONTRAVE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects but greater sensitivity of some older individuals cannot be ruled out. (See: **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**).

Pediatrics (18 < years of age)
The safety and efficacy of CONTRAVE have not been studied in pediatric populations. **CONTRAVE is not indicated for use in pediatric patients** (see **WARNINGS AND PRECAUTIONS**, **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF HARM**, and **Special Populations**, **Pediatrics**).

CONTRAINDICATIONS

CONTRAVE is contraindicated in:

- Uncontrolled hypertension (see **WARNINGS AND PRECAUTIONS**)
- Seizure disorder or a history of seizures
- Use of other bupropion hydrochloride-containing products (including, but not limited to, WELLBUTRIN® SR, WELLBUTRIN® XL, and ZYBAN®), because the incidence of seizure is dose dependent.
- With a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures
- Chronic opioid or opiate agonist (e.g., methadone) or partial agonists (e.g., buprenorphine) use, or acute opiate withdrawal
- Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines or other sedatives, and antiepileptic drugs
- Concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with CONTRAVE
- Concomitant administration of the antipsychotic thioridazine, since bupropion may inhibit thioridazine metabolism, thus causing an increase in thioridazine levels and a potential increased risk of thioridazine-related serious ventricular arrhythmias and sudden death
- Pregnancy (see **WARNINGS AND PRECAUTIONS**, **Special Populations**)
- Severe hepatic impairment
- End-stage renal failure
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, (see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section)**.**

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics: Placebo-Controlled Clinical Trial Data

Recent analyses of placebo-controlled clinical trial safety databases from SSRIs, bupropion, and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may

be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.

The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.

Adults and Pediatrics: Additional Data

There are clinical trial and post-marketing reports with SSRIs, bupropion, and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.

CONTRAVE contains bupropion; therefore, the following precautions pertaining to this product should be considered when treating patients with CONTRAVE.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages given an anti-depressant drug. This includes monitoring for agitation-type emotional and behavioural changes.

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

All patients being treated with antidepressants such as bupropion for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression

or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

In placebo-controlled clinical trials with CONTRAVE for the treatment of obesity in adult patients, no suicide or suicide attempts were reported in studies up to 56 weeks duration with CONTRAVE (equivalent to bupropion doses of 360 mg/day). In these same studies, suicidal ideation was reported by 3 (0.20%) of 1,515 patients treated with placebo compared with 1 (0.03%) of 3,239 treated with CONTRAVE; one event of suicidal ideation in each group led to discontinuation of study drug. Patients with a history of serious psychiatric illness, current serious psychiatric illness including current severe major depressive disorder, recent (previous 6 months) suicide attempt, current active suicidal ideation, recent hospitalization due to psychiatric illness and patients receiving antidepressant medications were excluded from CONTRAVE in phase 2/phase 3 clinical trials.

Seizures

Bupropion, a component of CONTRAVE, can cause seizures. The risk of seizure is dose-related. The incidence of seizure in patients receiving CONTRAVE in clinical trials was approximately 0.1% vs 0% on placebo. CONTRAVE should be discontinued and not restarted in patients who experience a seizure while being treated with CONTRAVE.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with CONTRAVE. CONTRAVE is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs, or using other bupropion-containing products. Caution should be used when prescribing CONTRAVE to patients with predisposing factors that may increase the risk of seizure including:

- history of head trauma or prior seizure, severe stroke, arteriovenous malformation, central nervous system tumor or infection, or metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia)
- excessive use of alcohol or sedatives, addiction to cocaine or stimulants, or withdrawal from sedatives
- patients with diabetes treated with insulin and/or oral diabetic medications (sulfonylureas and meglitinides) that may cause hypoglycemia
- concomitant administration of medications that may lower the seizure threshold including antipsychotics, tricyclic antidepressants, theophylline, systemic steroids

Recommendations for Reducing the Risk of Seizure: Clinical experience with bupropion suggests that the risk of seizure may be minimized by adhering to the recommended dosing recommendations [see **DOSAGE AND ADMINISTRATION**], in particular:

- the total daily dose of CONTRAVE does not exceed 360 mg of the bupropion component (i.e., four tablets per day)
- the daily dose is administered in divided doses (twice daily)
- the dose is escalated gradually
- no more than two tablets are taken at one time

- co-administration of CONTRAVE with high-fat meals should be avoided (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**)
- if a dose is missed, a patient should wait until the next scheduled dose to resume the regular dosing schedule

If a Seizure Occurs: Patients should be warned that if they experience a seizure while taking CONTRAVE, they should contact their doctor or be taken to a hospital emergency ward immediately and should stop taking CONTRAVE. Treatment should not be restarted if a patient has experienced a seizure while taking CONTRAVE.

General

Interference with the Action of Opioid Containing Drug Product

Patients taking CONTRAVE may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. Where a non-opioid containing alternative is available, it should be used.

Patients Receiving Opioid Analgesics

Vulnerability to Opioid Overdose: CONTRAVE should not be administered to patients receiving chronic opioids, due to the naltrexone component, which is an opioid receptor antagonist (see **CONTRAINDICATIONS**). If chronic opiate therapy is required, CONTRAVE treatment should be stopped. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and lower doses of opioids may be needed. Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after CONTRAVE treatment is discontinued.

An attempt by a patient to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is especially dangerous and may lead to a fatal overdose or life-threatening opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Precipitated Opioid Withdrawal

The symptoms of spontaneous opioid withdrawal, which are associated with the discontinuation of opioid in a dependent individual, are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly, the resulting withdrawal syndrome can be severe enough to require hospitalization. To prevent occurrence of either precipitated withdrawal in patients dependent on opioids or exacerbation of a pre-existing subclinical withdrawal symptoms, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting CONTRAVE treatment.

An opioid-free interval of a minimum of 7 to 10 days is recommended for patients previously dependent on short-acting opioids, and those patients transitioning from buprenorphine or methadone may need as long as two weeks. Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use.

Cardiovascular

Increase in Blood Pressure and Heart Rate

CONTRAVE can cause an increase in systolic and/or diastolic blood pressure as well as an increase in resting heart rate. In clinical practice with other bupropion-containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. The clinical significance of the increases in blood pressure and heart rate observed with CONTRAVE treatment is unclear, especially for patients with cardiac and cerebrovascular disease, since patients with a history of myocardial infarction or stroke in the previous 6 months, life-threatening arrhythmias, or congestive heart failure were excluded from CONTRAVE clinical trials. Blood pressure and pulse should be measured prior to starting therapy with CONTRAVE and should be monitored at regular intervals consistent with usual clinical practice (see **DOSAGE AND ADMINISTRATION**). If patients experience clinically relevant and sustained increases in blood pressure or pulse rate as a result of CONTRAVE treatment, it should be discontinued. CONTRAVE should not be given to patients with uncontrolled hypertension (see **CONTRAINDICATIONS**) and should be used with caution in patients with controlled hypertension.

Among patients treated with CONTRAVE in placebo-controlled clinical trials, mean systolic and diastolic blood pressure was approximately 1 mmHg higher than baseline at Weeks 4 and 8, similar to baseline at Week 12, and approximately 1 mmHg below baseline between Weeks 24 and 56. In contrast, among patients treated with placebo, mean blood pressure was approximately 2 to 3 mmHg below baseline throughout the same time points, yielding statistically significant differences between the groups at every assessment during this period. The largest mean differences between the groups were observed during the first 12 weeks (treatment difference +1.8 to +2.4 mmHg systolic, all $p<0.001$; +1.7 to +2.1 mmHg diastolic, all $p<0.001$; last-observation-carried-forward).

In subgroups who experienced significant weight loss (at least 5% weight loss from baseline at Week 16 of treatment), mean systolic and diastolic pressure were approximately 1 mmHg above baseline at Week 4 in patients treated with CONTRAVE and approximately 2 mmHg below baseline in patients treated with placebo. Between weeks 8 and 56 of treatment, mean systolic blood pressure levels varied from no change to approximately 3 mmHg below baseline in patients treated with CONTRAVE and approximately 3-5 mmHg below baseline for those treated with placebo; and mean diastolic blood pressure levels varied from no change to approximately 2 mmHg below baseline in patients subgroups treated with CONTRAVE and approximately 3-4 mmHg below baseline in those treated with placebo.

In subgroups who did not experience significant weight loss, systolic and diastolic blood pressure levels in patients treated with CONTRAVE were approximately 1 mmHg higher than baseline at Week 4 and 8, and similar to baseline between week 12 and 56 of the study. In patients treated with placebo, blood pressure levels were approximately 1-2 mmHg below baseline through the 56 weeks of study.

The differences in blood pressure in CONTRAVE compared to placebo treated patients were larger in the subgroup of patients with significant weight loss than in the subgroup without significant weight loss.

For heart rate, at both Weeks 4 and 8, mean heart rate was statistically significantly higher (2.1 bpm) in the CONTRAVE group compared with the placebo group; at Week 52, the difference between groups was +1.7 bpm ($p<0.001$; last-observation-carried-forward).

In subgroups who experienced significant weight loss (at least 5% weight loss from baseline at Week 16 of treatment), throughout the 56 weeks study, the mean heart rate varied from no change to approximately 2 bpm higher than baseline in patients treated with CONTRAVE compared to approximately 1-3 bpm below baseline in patients treated with placebo.

In subgroups who did not experience significant weight loss, mean heart rates varied between approximately 1-3 bpm higher than baseline in CONTRAVE, and from no change to approximately 2 bpm higher than baseline in placebo throughout the 56 weeks study.

The differences in heart rate in CONTRAVE compared to placebo treated patients were larger in the subgroup of patients with significant weight loss than in the subgroup without significant weight loss.

In an ambulatory blood pressure monitoring sub study of obese patients (CONTRAVE N=79, placebo N=38), the mean change from baseline in the average 24-hr systolic blood pressure after 52 weeks of treatment was -0.2 mmHg for the CONTRAVE group and -2.8 mmHg for the placebo group (treatment difference, +2.6 mmHg, p=0.08); the mean change in the average 24-hr diastolic blood pressure was +0.8 mmHg for the CONTRAVE group and -2.1 mmHg for the placebo group (treatment difference, +2.9 mmHg, p=0.004).

A greater percentage of subjects in the CONTRAVE group compared to the placebo group had adverse reactions of hypertension/blood pressure increased (5.9% vs 4.0%, respectively) and of tachycardia (0.7% vs. 0.2%, respectively). Greater incidences of these events in CONTRAVE versus placebo were observed in both patients with and without evidence of pre-existing hypertension, and in both patients with or without significant weight loss (i.e. loss of at least 5% of baseline weight by Week 16 of treatment). In a trial that enrolled individuals with diabetes, 12.0% of patients in the CONTRAVE group and 6.5% in the placebo group had a hypertension/blood pressure increased adverse reaction; also, a greater incidence of subjects in CONTRAVE than placebo had adverse reactions of heart rate increased (0.6% vs. 0%, respectively), tachycardia (1.2% vs. 0%, respectively), and sinus tachycardia (0.3% vs. 0%, respectively).

The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established.

Dependence/Tolerance

Abuse

CONTRAVE (naltrexone HCl and bupropion HCl) has not been systematically studied in

humans for its potential for abuse, tolerance, or physical dependence. However, in outpatient clinical studies of up to 56 weeks in duration, there was no evidence of euphoric drug intoxication, physical dependence, diversion, or abuse. There was no evidence of an abstinence syndrome following abrupt or tapered drug discontinuation after 56 weeks of double-blind, placebo-controlled, randomized treatment.

Naltrexone is a pure opioid antagonist. It does not lead to physical or psychological dependence. Tolerance to the opioid antagonistic effect is not known to occur.

Controlled clinical trials of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed subjects showed some increase in motor activity and agitation/excitement. In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability. Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers.

The inhalation of crushed tablets or injection of dissolved bupropion has been reported. Seizures and/or cases of death have been reported when bupropion has been administered intranasally or by parenteral injection. CONTRAVE (naltrexone HCl and bupropion HCl) extended-release tablets are intended for oral use only.

Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

Endocrine and Metabolism

Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Antidiabetic Therapy

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). CONTRAVE has not been studied in combination with insulin in phase 2/phase 3 clinical trials.

Measurement of blood glucose levels prior to starting CONTRAVE and during CONTRAVE treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications which are non-glucose-dependent should be considered to mitigate the

risk of hypoglycemia. If a patient develops hypoglycemia after starting CONTRAVE, appropriate changes should be made to the antidiabetic drug regimen.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Cases of hepatitis and clinically significant liver dysfunction were observed in association with naltrexone exposure during naltrexone clinical trials and in postmarketing reports for patients using naltrexone. Transient, asymptomatic hepatic transaminase elevations were also observed. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs. Although clinically significant liver dysfunction is not typically recognized as a manifestation of opioid withdrawal, opioid withdrawal that is precipitated abruptly may lead to systemic sequelae, including acute liver injury.

CONTRAVE is contraindicated in severe hepatic impairment (see **CONTRAINDICATIONS**). Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of CONTRAVE should be discontinued in the event of symptoms and/or signs of acute hepatitis.

In CONTRAVE clinical trials, there were no cases of elevated transaminases greater than three times the upper limit of normal (ULN) in conjunction with an increase in bilirubin greater than two times ULN; however, 1/4455 CONTRAVE-treated subjects in a randomized, double-blind, placebo-controlled trial in overweight and obese subjects with cardiovascular risk factors experienced a serious event of drug-induced liver injury leading to discontinuation.

Drugs Metabolized by CYP2D6

Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g. tamoxifen), may have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Therefore, CONTRAVE should not be used in combination with tamoxifen and other treatment options should be considered (see **DRUG INTERACTIONS**).

Ophthalmologic

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion, a component of CONTRAVE, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Psychiatric

Activation of Mania

Bupropion, a component of CONTRAVE, is a drug used for the treatment of depression. Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder.

Prior to initiating CONTRAVE, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). CONTRAVE is not approved for use in treating bipolar depression. No activation of mania or hypomania was reported in the clinical trials evaluating effects of CONTRAVE in obese patients; however, patients receiving antidepressant medications and patients with a history of bipolar disorder or recent hospitalization because of psychiatric illness were excluded from CONTRAVE clinical trials.

Hallucinations
Patients with major depression treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance, paranoia and confusion.

In a long-term multicentre, randomized, double-blind, placebo-controlled trial in overweight and obese subjects with cardiovascular risk factors, treatment-emergent adverse events of hallucination (including events of auditory hallucination and visual hallucination) led to premature discontinuation in 14/4455 (0.3%) of patients in the CONTRAVE group and 0/4450 subjects in the placebo group. In the Phase 2/3 trials of CONTRAVE, treatment-emergent hallucination events were reported for 2/2545 (<0.1%) subjects in CONTRAVE group, one of them discontinued due to the event, and 0/1515 subjects in the placebo group.

Sensitivity/Resistance

Allergic Reactions
Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue CONTRAVE and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, or shortness of breath) during treatment.

Arthralgia, myalgia, fever with rash, and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Special Populations

Pregnant Women
CONTRAVE is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

Clinical Considerations
A minimum weight gain, and no weight loss, is currently recommended for all pregnant women,

including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Human Data
There are no adequate and well-controlled studies of CONTRAVE in pregnant women. The extent of exposure in pregnancy during clinical trials is very limited. In clinical studies, 21 (0.7%) of 3,024 women became pregnant while taking CONTRAVE: 11 carried to term and gave birth to a healthy infant, three had elective abortions, four had spontaneous abortions, and the outcomes of three pregnancies were unknown.

Nursing Women
The constituents and metabolites of CONTRAVE have been shown to be secreted in human milk. Transfer of naltrexone and 6-beta-naltrexol into human milk has been reported with oral naltrexone. Bupropion and its metabolites are also secreted in human milk. CONTRAVE should not be used by nursing mothers.

Pediatrics (< 18 years of age)
The safety and effectiveness of CONTRAVE in pediatric patients below the age of 18 have not been established. **CONTRAVE is not indicated for use in pediatric patients** (see **WARNINGS AND PRECAUTIONS**, **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF HARM**).

Geriatrics (≥ *65* years of age)
Of the 3,239 subjects who participated in clinical trials with CONTRAVE, 62 (2%) were 65 years and older and none were 75 years and older. Clinical studies of CONTRAVE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Older individuals may be more sensitive to the central nervous system adverse effects of CONTRAVE. Naltrexone and bupropion are known to be substantially excreted by the kidney, and the risk of adverse reactions to CONTRAVE may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. CONTRAVE should be used with caution in patients over 65 years of age (see **WARNINGS AND PRECAUTIONS**)

Hepatic Impairment

CONTRAVE has not been evaluated in subjects with hepatic impairment. Based on information available for the individual constituents, systemic exposure is significantly higher for bupropion and metabolites (two- to three-fold), and naltrexone and metabolites (up to 10-fold higher) in subjects with moderate-to-severe hepatic impairment. Therefore, the maximum recommended daily dose of CONTRAVE is one tablet in the morning in patients with mild to moderate hepatic impairment (see **WARNINGS AND PRECAUTIONS**, **Hepatic** and **DOSAGE AND ADMINISTRATION** sections). All patients with hepatic impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels. CONTRAVE is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

Renal Impairment

A dedicated pharmacokinetic study has not been conducted for CONTRAVE in subjects with renal impairment. Based on information available for the individual constituents, systemic exposure is significantly higher for bupropion and metabolites (two- to three-fold), and naltrexone and metabolites in subjects with moderate-to-severe renal impairment. Therefore, the maximum recommended daily maintenance dose for CONTRAVE is two tablets (one tablet each morning and evening) in patients with moderate or severe renal impairment. CONTRAVE is contraindicated in patients with end-stage renal disease. There is a lack of adequate information to guide CONTRAVE dosing in patients with mild renal impairment. All patients with renal impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels (see **DOSAGE AND ADMINISTRATION** and see also **CLINICAL PHARMACOLOGY**).

Lactose

CONTRAVE tablets contain lactose. This should be considered when prescribing to patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

Monitoring and Laboratory Tests

Patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be monitored for the emergence of anxiety, agitation, irritability, unusual changes in behavior, as well as the emergence of suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such monitoring should include daily observation by families and caregivers (see **WARNINGS AND PRECAUTIONS**, **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Blood pressure and pulse should be measured prior to starting therapy with CONTRAVE and should be monitored at regular intervals during CONTRAVE treatment (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, Increase in Blood Pressure and Heart Rate).

The impact on glycemic levels of CONTRAVE when used concomitantly with antidiabetic pharmacologic treatment regimens should be monitored by periodic measurements of blood glucose and HbA1c levels (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Antidiabetic Therapy).

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). Measurement of blood glucose levels prior to starting CONTRAVE and during CONTRAVE treatment is recommended in patients with type 2 diabetes (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions for CONTRAVE (incidence ≥5% and twice the incidence in placebo) are nausea, constipation, vomiting, dizziness, and dry mouth. In addition, headache was more commonly observed in CONTRAVE patients than in placebo (17.6% vs. 10.4%).

In clinical studies, 24% of subjects receiving CONTRAVE and 12% of subjects receiving placebo discontinued treatment due to an adverse event. The most frequent adverse reactions leading to discontinuation with CONTRAVE were nausea (6%), headache (2%), dizziness (1%) and vomiting (1%).

Other adverse reactions are discussed in the **WARNINGS AND PRECAUTIONS** section of this monograph.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Naltrexone / bupropion was evaluated for safety in five double-blind placebo controlled studies in 4,754 overweight or obese subjects (3,239 subjects treated with naltrexone / bupropion and 1,515 subjects treated with placebo) for a treatment period up to 56 weeks. All subjects received study drug in addition to diet and exercise counseling. One trial (N=793) evaluated patients participating in an intensive behavioral modification program and another trial (N= 505) evaluated patients with type 2 diabetes. In the 5 randomized, placebo-controlled trials, 2,482 patients received CONTRAVE 32 mg/360 mg daily in four 56-week Phase 3 trials, and n=63 received a combination of naltrexone 32 mg and bupropion SR 400 mg/day in one 24-week Phase 2 study, for a total of n=2545 subjects. The mean treatment duration was 36 weeks (median, 56 weeks). Dosing was initiated and increased weekly to reach the maintenance dose within 4 weeks. Baseline patient characteristics included a mean age of 46 years, 82% women, 78% white, 25% with hypertension, 13% with type 2 diabetes, 56% with dyslipidemia, 25% with BMI greater than 40 kg/m^2, and less than 2% with coronary artery disease.

Table 2: Treatment-emergent adverse events with incidence ≥1% and higher than in placebo in overweight or obese subjects in Phase 2/Phase 3 trials with CONTRAVE*.

System Organ Class	Adverse Reaction	CONTRAVE* N=2545 %	Placebo n=1515 %
Gastrointestinal Disorders	Nausea	32.5	6.7
	Constipation	19.2	7.2
	Vomiting	10.7	2.9
	Dry mouth	8.1	2.3
	Diarrhea	7.1	5.2
	Abdominal pain upper	3.5	1.3
	Abdominal pain	2.8	1.4
	Dyspepsia	1.7	1.1
Nervous system disorders	Headache	17.6	10.4
	Dizziness	9.9	3.4
	Tremor	4.0	0.7
	Dysgeusia	2.4	0.7
	Migraine	1.7	1.4
	Disturbance in attention	1.5	0.3
	Lethargy	1.0	0.3
Psychiatric disorders	Insomnia	9.2	5.9
	Anxiety	4.2	2.8
	Abnormal dreams	1.0	0.4
General disorders and administration site conditions	Fatigue	4.0	3.4
	Irritability	2.6	1.8
	Feeling jittery	1.4	0.3
Infections and Infestations	Influenza	3.4	3.2
	Gastroenteritis viral	3.5	2.6
	Urinary tract infection	3.3	2.8
Skin and subcutaneous tissue disorders	Hyperhidrosis	2.6	0.6
	Rash	2.4	2.0
	Alopecia	1.8	0.7
	Pruritus	1.9	0.9
Injury, poisoning and procedural complications	Muscle strain	2.2	1.7
Investigations	Blood pressure increased	2.4	1.5
	Heart rate increased	1.7	1.1
Ear and Labyrinth Disorders:	Tinnitus	3.3	0.6
	Vertigo	1.2	0.3
Vascular Disorders	Hot flush	4.2	1.2
	Hypertension	3.2	2.2
Cardiac Disorders	Palpitations	2.1	0.9
Eye Disorders	Vision blurred	1.8	1.0

*CONTRAVE 32 mg/360 mg (n=2482) for up to 52 weeks or a combination of naltrexone 32 mg and bupropion SR 400 mg/day (n=63) for up to 24 weeks

Gastrointestinal adverse reactions

The vast majority of subjects treated with naltrexone / bupropion who experienced nausea reported the event within 4 weeks of starting treatment. Events were generally self-limited; the majority of events resolved within 4 weeks and almost all resolved by Week 24. Similarly, the

majority of events of constipation in subjects treated with naltrexone/bupropion were reported during the dose escalation phase. The time to resolution of constipation was similar between subjects treated with naltrexone / bupropion and subjects treated with placebo.

Approximately half of the subjects treated with naltrexone / bupropion who experienced vomiting first reported the event during the dose escalation phase. Time to resolution for vomiting was typically rapid (within one week) and almost all events resolved within 4 weeks. The incidence of these common gastrointestinal adverse reactions in naltrexone / bupropion versus placebo was as follows: nausea (31.8% vs. 6.7%), constipation (18.1% vs. 7.2%), and vomiting (9.9% vs. 2.9%). The incidence of severe nausea, severe constipation, and severe vomiting was low, but was higher in subjects treated with naltrexone / bupropion compared to subjects treated with placebo (severe nausea: naltrexone / bupropion 1.9%, placebo <0.1%; severe constipation: naltrexone / bupropion 0.6%, placebo 0.1%; severe vomiting: naltrexone / bupropion 0.7%, placebo 0.3%). No events of nausea, constipation, or vomiting were considered serious.

Elderly patients
Elderly patients may be more sensitive to some of the central nervous system-related adverse reactions of naltrexone / bupropion (primarily dizziness and tremor). There is an increased incidence of gastrointestinal disorders with higher age categories. Common events leading to withdrawal among elderly were nausea, vomiting, dizziness, constipation.

Type 2 diabetes
Patients with type 2 diabetes treated with naltrexone / bupropion demonstrated a higher incidence of gastrointestinal adverse events, primarily nausea, vomiting, and diarrhea, than subjects without diabetes. Patients with type 2 diabetes may be more prone to these events due to concomitant medicinal product use (e.g., metformin) or may be more likely to have underlying gastrointestinal disorders (e.g., gastroparesis) predisposing to gastrointestinal symptoms.

Renal impairment
Patients with moderate renal impairment had a higher incidence of gastrointestinal and central nervous system-related adverse events, thus these patients generally had lower tolerability of naltrexone / bupropion.

<u>Less Common Clinical Trial Adverse Drug Reactions</u>

Adverse events observed in clinical trials at an incidence of < 1% of patients treated with CONTRAVE and with incidence twice that of placebo are provided below:

Cardiac Disorders:	Tachycardia, myocardial infarction
Ear and Labyrinth Disorders:	Motion sickness
Gastrointestinal Disorders:	Lower abdominal pain, eructation, lip swelling, haematochezia, hernia, and infrequent bowel movements

General Disorders and Administration Site Conditions: Feeling abnormal, asthenia, energy increased, thirst, feeling hot, and malaise

Hepatobiliary disorders: Cholecystitis

Infections and Infestations: Pneumonia, laryngitis, pharyngitis, respiratory tract infection, staphylococcal infection, kidney infection

Investigations: Increased blood creatinine, increased aspartate aminotransferase, increased blood calcium, increased hepatic enzymes, and decreased haematocrit

Metabolism and Nutrition Disorders: Decreased appetite, dehydration

Musculoskeletal and Connective Tissue Disorders: Muscle tightness, intervertebral disc protrusion, and jaw pain

Nervous System Disorders: Intention tremor, balance disorder, memory impairment, amnesia, mental impairment, poor quality sleep, presyncope, burning sensation, psychomotor hyperactivity

Psychiatric Disorders: Nervousness, middle insomnia, libido decreased, disorientation, dissociation, tension, agitation, mood altered mood swings, nightmare, euphoric mood

Renal and Urinary Disorders: Micturation urgency

Reproduction System and Breast Disorders: Menstruation irregular, dysmenorrhoea, vaginal hemorrhage, erectile dysfunction, and vulvovaginal dryness

Skin and Subcutaneous Tissue Disorders: Dry skin, rash erythematous, hypoesthesia facial, skin lesion, cold sweats

Post-Market Adverse Drug Reactions

Additional adverse reactions have been identified during post approval use of CONTRAVE. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Loss of consciousness

DRUG INTERACTIONS

Overview

Monoamine Oxidase Inhibitors (MAOI)
Concomitant use of MAOIs and bupropion is contraindicated. Bupropion inhibits the re-uptake of dopamine and norepinephrine and can increase the risk for hypertensive reactions when used concomitantly with drugs that also inhibit the re-uptake of dopamine or norepinephrine, including MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAOI phenelzine. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with CONTRAVE. Conversely, at least 14 days should be allowed after stopping CONTRAVE before starting an MAOI (see **CONTRAINDICATIONS**).

Opioid Analgesics
Because of the naltrexone hydrochloride component, patients taking CONTRAVE may not fully benefit from treatment with opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations, and opioid analgesics. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and opiate dose should not be increased above the standard dose. CONTRAVE may be used with caution after chronic opioid use has been stopped for 7 to 10 days in order to prevent precipitation of withdrawal (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, **Interference with the Action of Opioid Containing Drug Product**).

During CONTRAVE clinical studies, the use of concomitant opioid or opioid-like medications, including analgesics or antitussives, were excluded.

Drugs That Lower Seizure Threshold
Use extreme caution when co-administering CONTRAVE with other drugs that lower seizure threshold (e.g., antipsychotics, antidepressants, theophylline, lithium or systemic corticosteroids). Use low initial doses and increase the dose gradually. Concomitant use of other bupropion-containing products is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Dopaminergic Drugs (Levodopa and Amantadine)
Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included confusion, restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution and monitor for such adverse reactions when administering CONTRAVE concomitantly with these drugs.

CYP isozymes
Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between CONTRAVE and drugs that are inhibitors or inducers of CYP2B6 (see below, ***Effects of Other Drugs on the Pharmacokinetics of CONTRAVE)***

Bupropion and its metabolites inhibit CYP2D6 (see below, ***Potential for CONTRAVE to affect Other Drugs)***. Concomitant administration of the antipsychotic thioridazine is contraindicated, since bupropion may inhibit thioridazine metabolism, thus causing an increase in thioridazine levels and a potential increased risk of thioridazine-related serious ventricular arrhythmias and sudden death. The use of CONTRAVE together with tamoxifen may result in reduced efficacy of tamoxifen.

Drug-Drug Interactions

Potential for CONTRAVE to affect Other Drugs

Drug interaction between CONTRAVE and CYP2D6 substrates (metoprolol) or other drugs (atorvastatin, glyburide, lisinopril, nifedipine, valsartan) has been evaluated. In addition, drug interaction between bupropion, a component of CONTRAVE, and CYP2D6 substrates (desipramine) or other drugs (citalopram, lamotrigine) has also been evaluated (Table 3).

Table 3. Effect of Naltrexone / Bupropion Co-administration on Systemic Exposure of Other Drugs

	Co-administered Drug	
Naltrexone / Bupropion Dosage	**Name and Dose Regimens**	**Change in Systemic Exposure**
Initiate the following drugs at the lower end of the dose range during concomitant use with CONTRAVE		
Bupropion 150 mg twice daily for 10 days	Desipramine 50 mg single dose	↑5-fold AUC, ↑2-fold C_{max}
Bupropion 300 mg (as XL) once daily for 14 days	Citalopram 40 mg once daily for 14 days	↑40% AUC, ↑30% C_{max}
Naltrexone / Bupropion 16 mg/180 mg twice daily for 7 days	Metoprolol 50 mg single dose	↑4-fold AUC, ↑2-fold C_{max}
No dose adjustment needed for the following drugs during concomitant use with CONTRAVE:		
Naltrexone / Bupropion 16 mg/180 mg single dose	Atorvastatin 80 mg single dose	No Effect
Naltrexone / Bupropion 16 mg/180 mg single dose	Glyburide 6 mg single dose	No Effect
Naltrexone / Bupropion 16 mg/180 mg single dose	Lisinopril 40 mg single dose	No Effect
Naltrexone / Bupropion 16 mg/180 mg single dose	Nifedipine 90 mg single dose	No Effect
Naltrexone / Bupropion 16 mg/180 mg single dose	Valsartan 320 mg single dose	No Effect
Bupropion 150 mg twice daily for 12 days	Lamotrigine 100 mg single dose	No Effect
Caution is advised with the following drugs during concomitant use with CONTRAVE		
Bupropion 150 mg extended-release tablets	Digoxin	↓1.6 fold AUC, ↑1.8 fold Cl_{-renal}

Drugs Metabolized by CYP2D6

In a clinical study, CONTRAVE (32 mg naltrexone/360 mg bupropion) daily was co-administered with a 50 mg dose of metoprolol (a CYP2D6 substrate). CONTRAVE increased

metoprolol AUC and C_{max} by approximately 4- and 2-fold, respectively, relative to metoprolol alone. Similar clinical drug interactions resulting in increased pharmacokinetic exposure of CYP2D6 substrates have also been observed with bupropion as a single agent with desipramine or venlafaxine.

Concomitant administration of the antipsychotic thioridazine is contraindicated (see **CONTRAINDICATIONS**).

Co-administration of CONTRAVE with other drugs that are metabolized by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclics), antipsychotics (e.g., haloperidol, risperidone), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone and flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If CONTRAVE is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index (see **CLINICAL PHARMACOLOGY**)

Tamoxifen
Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Co-administration of this drug with strong CYP2D6 inhibitors such as bupropion can lead to reduced plasma concentrations of a primary active metabolite (endoxifen). Therefore, since chronic use of CYP2D6 inhibitors together with tamoxifen may result in reduced efficacy of tamoxifen, bupropion should not be used in combination with tamoxifen and other treatment options should be considered (see **WARNINGS AND PRECAUTIONS**).

Effects of Other Drugs on the Pharmacokinetics of CONTRAVE

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between CONTRAVE and drugs that are inhibitors or inducers of CYP2B6.

Drug interactions between CYP2B6 inhibitors (ticlopidine, clopidogrel, prasugrel), CYP2B6 inducers (ritonavir, lopinavir) and bupropion (one of the CONTRAVE components), or between other drugs (atorvastatin, glyburide, metoprolol, lisinopril, nifedipine, valsartan) and CONTRAVE have been evaluated (Table 4). While not systematically studied, carbamazepine, phenobarbital, or phenytoin may induce the metabolism of bupropion.

Table 4. Effect of Co-Administered Drugs on Systemic Exposure of Naltrexone / Bupropion

	Co-administered Drug	
Name and Dose Regimens	**CONTRAVE Components**	**Change in Systemic Exposure**
Do not exceed one tablet twice daily dose of CONTRAVE with the following drugs:		
Ticlopidine 250 mg twice daily for 4 days	Bupropion Hydroxybupropion	↑85% AUC, ↑38% C_{max} ↓84% AUC, ↓78% C_{max}
Clopidogrel 75 mg once daily for 4 days	Bupropion Hydroxybupropion	↑60% AUC, ↑40% C_{max} ↓52% AUC, ↓50% C_{max}
No dose adjustment needed for CONTRAVE with the following drugs:		

Atorvastatin 80 mg single dose	Naltrexone 6-beta naltrexol Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	No Effect No Effect No Effect No Effect No Effect No Effect
Lisinopril 40 mg single dose	Naltrexone 6-beta naltrexol Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	No Effect No Effect No Effect No Effect No Effect No Effect
Valsartan 320 mg single dose	Naltrexone 6-beta naltrexol Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	No Effect No Effect No Effect ↓14% AUC, No Effect on C_{max} No Effect No Effect
Cimetidine 800 mg single dose	Bupropion Hydroxybupropion Threo/Erythrohydrobupropion	No Effect No Effect ↑16% AUC, ↑32% C_{max}
Citalopram 40 mg once daily for 14 days	Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	No Effect No Effect No Effect No Effect
Metoprolol 50 mg single dose	Naltrexone 6-beta naltrexol Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	↓25% AUC, ↓29% C_{max} No Effect No Effect No Effect No Effect No Effect
Nifedipine 90 mg single dose	Naltrexone 6-beta naltrexol Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	↑24% AUC, ↑58% C_{max} No Effect No Effect on AUC, ↑22% C_{max} No Effect No Effect No Effect
Prasugrel 10 mg once daily for 6 days	Bupropion Hydroxybupropion	↑18% AUC, ↑14% C_{max} ↓24%AUC, ↓32% C_{max}
Use CONTRAVE with caution with the following drugs:		
Glyburide 6 mg single dose*	Naltrexone 6-beta naltrexol Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	↑2-fold AUC, ↑2-fold C_{max} No Effect ↑36% AUC, ↑18% C_{max} ↑22% AUC, ↑21% C_{max} No Effect on AUC, ↑15% C_{max} No Effect
Avoid concomitant use of CONTRAVE with following drugs:		

Ritonavir 100 mg twice daily for 17 days	Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	↓22% AUC, ↓21 % C_{max} ↓23% AUC, No Effect on C_{max} ↓38% AUC, ↓39 % C_{max} ↓48% AUC, ↓28 % C_{max}
600 mg twice daily for 8 days	Bupropion Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	↓66% AUC, ↓62% C_{max} ↓78% AUC, ↓42 % C_{max} ↓50% AUC, ↓58% C_{max} ↓68% AUC, ↓48 % C_{max}
Lopinavir / Ritonavir 400 mg/100 mg twice daily for 14 days	Bupropion Hydroxybupropion	↓57% AUC, ↓57% C_{max} ↓50% AUC, ↓31% C_{max}
Efavirenz 600 mg once daily for 2 weeks	Bupropion Hydroxybupropion	↓55% AUC, ↓34% C_{max} No Effect on AUC, ↑50% C_{max}

*Results were confounded by the food-effect due to oral glucose co-administered with the treatment.

Inhibitors of CYP2B6

Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. During concomitant use with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel), the CONTRAVE daily dose should not exceed two tablets (one tablet each morning and evening) (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**).

Inducers of CYP2B6

Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure and may reduce efficacy. Avoiding concomitant use with ritonavir, lopinavir, or efavirenz is recommended.

Drug Transporter Interaction

Co-administration of CONTRAVE with substrate drugs transported by OCT2 including metformin, should be approached with caution and patients should be monitored for adverse effect (see **DETAILED PHARMACOLOGY**)

In a phase 1, open–label sequential design study that evaluated the potential effect of multiple oral doses of CONTRAVE on the pharmacokinetic of a single oral dose of metformin in healthy subjects, results show that overall exposure to metformin (AUC_∞ and AUC_t) was 23% higher in the presence of CONTRAVE compared with metformin alone. The effect of CONTRAVE on metformin PK is likely due to a combination of effects on the OCT2 transporter and transient, mild effects on glomerular filtration.

Drug-Food Interactions

CONTRAVE should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure (see **WARNINGS AND PRECAUTIONS** and **CLINICAL PHARMACOLOGY**)

Drug-Laboratory Interactions

Drug-Laboratory Test Interactions
False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

Increases in Serum Creatinine
In the one-year controlled trials of CONTRAVE, larger mean increases in serum creatinine from baseline to trial endpoint were observed in the CONTRAVE group compared with the placebo group (0.07 mg/dL and 0.01 mg/dL, respectively) as well as from baseline to the maximum value during follow-up (0.15 mg/dL and 0.07 mg/dL, respectively). Increases in serum creatinine that exceeded the upper limit of normal and were also greater than or equal to 50% higher than baseline occurred in 0.6% of subjects receiving CONTRAVE compared to 0.1% receiving placebo. An in vitro drug-drug interaction study demonstrated that bupropion and its metabolites inhibit organic cation transporter 2 (OCT2), which is involved in the tubular secretion of creatinine, suggesting that the observed increase in serum creatinine may be the result of OCT2 inhibition.

Drug-Lifestyle Interactions

Use with Alcohol
Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, in post-marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. There are no known pharmacokinetic interactions between naltrexone and alcohol. The consumption of alcohol during treatment with CONTRAVE should be minimized or avoided.

Smokers
Pooled analysis of CONTRAVE data revealed no meaningful differences in the plasma concentrations of bupropion or naltrexone in smokers compared with non-smokers. The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were non-smokers. Following oral administration of a single 150 mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and non-smokers.

DOSAGE AND ADMINISTRATION

Dosing Considerations

CONTRAVE is not indicated for use in children under 18 years of age (See **WARNINGS**

AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

In order to minimize the risk of seizures (see **WARNINGS AND PRECAUTIONS, Seizures**)**, the maximum recommended daily dose should not be exceeded.**

Patients may develop elevated blood pressure or heart rate during CONTRAVE treatment; the risk may be greater during the initial three months of therapy. Blood pressure and pulse should be measured prior to starting therapy with CONTRAVE and should be monitored at regular intervals consistent with usual clinical practice. CONTRAVE should not be given to patients with uncontrolled hypertension (see **CONTRAINDICATIONS**) and should be used with caution in patients with controlled hypertension prior to treatment (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, Increase in Blood Pressure and Heart Rate).

Response to therapy should be evaluated after 12 weeks at the maintenance dosage. If a patient has not lost at least 5% of baseline body weight, discontinue CONTRAVE, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment (see **CLINICAL TRIALS**).

Dosage adjustments are required in subjects with hepatic impairment or renal impairment, and with concomitant use of CYP2B6 inhibitors (see below). All patients with hepatic or renal impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels.

Recommended Dose and Dosage Adjustment (Adults)

The recommended daily dose of CONTRAVE is two 8 mg / 90 mg tablets taken twice daily for a total dose of 32 mg / 360 mg.

CONTRAVE dosing should be escalated according to the following schedule:

	Morning Dose	**Evening Dose**
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 – Onward	2 tablets	2 tablets

A total daily dosage of two CONTRAVE 8 mg / 90 mg tablets twice daily (32 mg / 360 mg) is reached at the start of Week 4.

CONTRAVE should be taken by mouth in the morning and in the evening. **The tablets should not be cut, chewed, or crushed.** The maximum recommended dose is 32 mg / 360 mg per day (two tablets twice daily).

In clinical trials, CONTRAVE was administered with meals. However, CONTRAVE should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure (see **WARNINGS AND PRECAUTIONS** and **CLINICAL PHARMACOLOGY**)

Dose Adjustment in Patients with Renal Impairment
In patients with moderate or severe renal impairment, the maximum recommended daily dose for CONTRAVE is two tablets (one tablet each morning and evening). CONTRAVE is contraindicated in patients with end-stage renal disease. There is a lack of adequate information to guide dosing in patients with mild renal impairment (see **WARNINGS AND PRECAUTIONS**).

Dose Adjustment in Patients with Hepatic Impairment
In patients with mild or moderate hepatic impairment, the maximum recommended daily dose of CONTRAVE is one tablet in the morning (see **WARNINGS AND PRECAUTIONS**). CONTRAVE is contraindicated in severe hepatic impairment (see **CONTRAINDICATIONS**).

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant
At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with CONTRAVE. Conversely, at least 14 days should be allowed after stopping CONTRAVE before starting an MAOI antidepressant (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Concomitant Use with CYP2B6 Inhibitors
During concomitant use with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel), the maximum recommended daily dose of CONTRAVE is two tablets (one tablet each morning and evening) (see **DRUG INTERACTIONS**).

Missed Dose

CONTRAVE should be taken at the same time each day and no more than the recommended doses should be taken each day. **In order to minimize the risk of seizures,** if the normal administration time has been missed, the dose should be skipped and administration resumed at the normal administration time of the following dose.

BMI is calculated by dividing weight (in kg) by height (in meters) squared. A BMI chart for determining BMI based on height and weight is provided in Table 5.

Table 5. BMI Conversion Chart

Weight	**(lb)**	**125**	**130**	**135**	**140**	**145**	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**200**	**205**	**210**	**215**	**220**	**225**
	(kg)	**56.8**	**59.1**	**61.4**	**63.6**	**65.9**	**68.2**	**70.5**	**72.7**	**75.0**	**77.3**	**79.5**	**81.8**	**84.1**	**86.4**	**88.6**	**90.9**	**93.2**	**95.5**	**97.7**	**100.0**	**102.3**
Height																						
(in)	**(cm)**																					
58	**147.3**	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47

59	**149.9**	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	**152.4**	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	**154.9**	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	**157.5**	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	**160.0**	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	**162.6**	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	**165.1**	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	**167.6**	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	**170.2**	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	**172.7**	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	**175.3**	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	**177.8**	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	**180.3**	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	**182.9**	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	**185.4**	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	**188.0**	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	**190.5**	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	**193.0**	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

OVERDOSAGE

Human Experience

There is no clinical experience with overdosage with CONTRAVE. The maximum daily dose of CONTRAVE administered in clinical trials contained 50 mg naltrexone and 400 mg bupropion. The most serious clinical implications of CONTRAVE overdose are likely those related to overdose of bupropion.

Overdoses of up to 30 grams or more of bupropion (equivalent of up to 83 times the recommended daily dose of CONTRAVE 32 mg / 360 mg) have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

There is limited experience with overdose of naltrexone monotherapy in humans. In one study, subjects who received 800 mg naltrexone daily (equivalent to 25 times the recommended daily dose of CONTRAVE 32 mg / 360 mg) for up to one week showed no evidence of toxicity.

Animal Experience
In the mouse, rat, and guinea pig, the oral LD_{50}s for naltrexone were 1,100 to 1,550 mg/kg; 1,450 mg/kg; and 1,490 mg/kg; respectively. High doses of naltrexone (generally greater than or equal to 1,000 mg/kg) produced salivation, depression/reduced activity, tremors, and convulsions. Mortality in animals due to high-dose naltrexone administration usually was due to clonic-tonic convulsions and/or respiratory failure.

Overdosage Management

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There are no known antidotes for CONTRAVE. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdoses. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
CONTRAVE has two components: naltrexone, an opioid antagonist, and bupropion, a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine. Nonclinical studies suggest that naltrexone and bupropion have effects on two separate areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system). The exact neurochemical effects of CONTRAVE leading to

weight loss are not fully understood.

Pharmacodynamics
Combined, bupropion and naltrexone increased the firing rate of hypothalamic pro-opiomelanocortin (POMC) neurons *in vitro*, which are associated with regulation of appetite. The combination of bupropion and naltrexone also reduced food intake when injected directly into the ventral tegmental area of the mesolimbic circuit in mice, an area associated with regulation of reward pathways and cravings.

Cardiac Electrophysiology
In a randomized, double-blind, placebo- and positive-controlled, 3-way crossover study, 78 healthy subjects were treated with 8 mg naltrexone and 90 mg bupropion twice daily on Days 1 to 3, 16 mg naltrexone and 180 mg bupropion twice daily on Days 4 to 10, and 16 mg naltrexone and 180 mg bupropion on the morning of Day 11. Naltrexone / bupropion was associated with an elevation in heart rate, with statistically significant differences from placebo in mean change from baseline heart rate from pre-dose to 23.5 h post-dose, inclusive, on Day 11. The maximum difference from placebo was 7.5 bpm (90% CI 6.2, 8.8) at the 3 h time point. No noteworthy effects on the QTc, QRS, or PR intervals were evident. In this study, in which naltrexone/bupropion was not administered with food, the mean C_{max} values were 1.2 ng/mL for naltrexone and 103.9 ng/mL for bupropion.

Pharmacokinetics

Absorption

Naltrexone
Following single oral administration of CONTRAVE (two 8 mg naltrexone / 90 mg bupropion tablets) to healthy subjects, mean peak naltrexone concentration (C_{max}) was 1.4 ng/mL, time to peak concentration (T_{max}) was 2 hours, and extent of exposure ($AUC_{0\text{-}inf}$) was 8.4 ng·hr/mL.

Bupropion
Following single oral administration of CONTRAVE (two 8 mg naltrexone / 90 mg bupropion tablets) to healthy subjects, mean peak bupropion concentration (C_{max}) was 168 ng/mL, time to peak concentration (T_{max}) was three hours, and extent of exposure ($AUC_{0\text{-}inf}$) was 1,607 ng·hr/mL.

Food Effect on Absorption
When CONTRAVE was administered with a high-fat meal, the AUC and C_{max} for naltrexone increased 2.1-fold and 3.7-fold, respectively, and the AUC and C_{max} for bupropion increased 1.4-fold and 1.8-fold, respectively. Thus, CONTRAVE should not be taken with high-fat meals because of the resulting significant increases in bupropion and naltrexone systemic exposure.

Distribution

Naltrexone
Naltrexone is 21% plasma protein bound. The mean apparent volume of distribution at steady

state for naltrexone (Vss/F) is 5,697 liters.

Bupropion
Bupropion is 84% plasma protein bound. The mean apparent volume of distribution at steady state for bupropion (Vss/F) is 880 liters.

Metabolism

Naltrexone
The major metabolite of naltrexone is 6-beta-naltrexol. The activity of naltrexone is believed to be the result of both the parent and the 6-beta-naltrexol metabolite. Though less potent, 6-beta-naltrexol is eliminated more slowly and thus circulates at much higher concentrations than naltrexone. Naltrexone and 6-beta-naltrexol are not metabolized by cytochrome P450 enzymes and *in vitro* studies indicate that there is no potential for inhibition or induction of important isozymes.

Bupropion
Bupropion is extensively metabolized with three active metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion. The metabolites have longer elimination half-lives than bupropion and accumulate to a greater extent. Following bupropion administration, more than 90% of the exposure is a result of metabolites. In vitro findings suggest that CYP2B6 is the principal isozyme involved in the formation of hydroxybupropion whereas cytochrome P450 isozymes are not involved in the formation of the other active metabolites. Bupropion and its metabolites inhibit CYP2D6. Plasma protein binding of hydroxybupropion is similar to that of bupropion (84%) whereas the other two metabolites have approximately half the binding.

Excretion

Naltrexone
Naltrexone and its metabolites are excreted primarily by the kidney (53% to 79% of the dose). Urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose. Urinary excretion of unchanged and conjugated 6-beta-naltrexol accounts for 43% of an oral dose. The renal clearance for naltrexone ranges from 30 to 127 mL/min, suggesting that renal elimination is primarily by glomerular filtration. The renal clearance for 6-beta-naltrexol ranges from 230 to 369 mL/min suggesting an additional renal tubular secretory mechanism. Fecal excretion is a minor elimination pathway.

Following single oral administration of CONTRAVE tablets to healthy subjects, mean elimination half-life ($T_{1/2}$) was approximately 5 hours for naltrexone. Following twice daily administration of CONTRAVE, naltrexone did not accumulate and its kinetics appeared linear. However, in comparison to naltrexone, 6-beta-naltrexol accumulates to a larger extent (accumulation ratio ~3).

Bupropion
Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose

of bupropion excreted unchanged was 0.5%, a finding consistent with the extensive metabolism of bupropion.

Following single oral administration of CONTRAVE tablets to healthy subjects, mean elimination half-life ($T_{½}$) was approximately 21 hours for bupropion. Following twice daily administration of CONTRAVE, metabolites of bupropion, and to a lesser extent unchanged bupropion, accumulate and reach steady-state concentrations in approximately one week.

Special Populations and Conditions

Pediatrics
The pharmacokinetics of CONTRAVE in individuals under 18 years old has not been evaluated.

Geriatrics
The pharmacokinetics of CONTRAVE have not been evaluated in the geriatric population. The effects of age on the pharmacokinetics of naltrexone or bupropion and their metabolites have not been fully characterized. An exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple doses, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

Gender
Pooled analysis of CONTRAVE data suggested no clinically meaningful differences in the pharmacokinetic parameters of bupropion or naltrexone based on gender.

Race
Pooled analysis of CONTRAVE data suggested no clinically meaningful differences in the pharmacokinetic parameters of bupropion or naltrexone based on race.

Hepatic Insufficiency
Pharmacokinetic data are not available with CONTRAVE in patients with hepatic impairment. Subjects with hepatic insufficiency were excluded from CONTRAVE Phase 3 trials. The following information is available for individual constituents:

<u>Naltrexone</u>
An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function, has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Bupropion

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in two single-dose trials, one trial in patients with alcoholic liver disease and a second trial in patients with mild-to-severe cirrhosis.

The first trial showed that the half-life of hydroxybupropion was significantly longer in eight patients with alcoholic liver disease than in eight healthy volunteers (32±14 hours vs 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the two patient groups were minimal.

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in nine subjects with mild-to-moderate hepatic cirrhosis compared with eight healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in subjects with mild-to-moderate hepatic cirrhosis. In subjects with severe hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites were seen (Table 6).

Table 6. Pharmacokinetics of Bupropion and Metabolites in Patients With Severe Hepatic Cirrhosis: Ratio Relative to Healthy Matched Controls

	C_{max}	**AUC**	**$t_{½}$**	**T_{max}***
Bupropion	1.69	3.12	1.43	0.5 h
Hydroxybupropion	0.31	1.28	3.88	19 h
Threo / erythrohydrobupropion amino alcohol	0.69	2.48	1.96	20 h

* = Difference

The dose of CONTRAVE should be reduced in patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION, Dose Adjustment in Patients with Hepatic Impairment**). CONTRAVE is contraindicated in severe hepatic impairment (see **CONTRAINDICATIONS**).

Renal Insufficiency

A dedicated pharmacokinetic study has not been conducted for CONTRAVE in subjects with renal impairment. Subjects with renal insufficiency were excluded from CONTRAVE Phase 3 trials. The following information is available for the individual constituents:

Naltrexone

Limited information is available for naltrexone in patients with moderate to severe renal impairment. In a study of seven patients with end-stage renal disease requiring dialysis, peak plasma concentrations of naltrexone were elevated at least 6-fold compared to healthy subjects.

Bupropion

Limited information is available for bupropion in patients with moderate to severe renal impairment. An inter-trial comparison between normal subjects and patients with end-stage renal failure demonstrated that the bupropion C_{max} and AUC values were comparable in the two groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-

fold increase, respectively, in AUC for patients with end-stage renal failure. A second trial, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that exposure after a single 150 mg dose of sustained-release bupropion was approximately 2-fold higher in patients with impaired renal function while levels of the hydroxybupropion and threo / erythrohydrobupropion (combined) metabolites were similar in the two groups. The elimination of bupropion and/or the major metabolites of bupropion may be reduced by impaired renal function.

The dose of CONTRAVE should be reduced in patients with moderate or severe renal impairment. CONTRAVE is contraindicated for use in patients with end-stage renal disease.

STORAGE AND STABILITY

Store at room temperature (15° to 25°C).

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

CONTRAVE 8 mg / 90 mg (naltrexone HCl 8 mg and bupropion HCl 90 mg) extended-release, tri-layer tablets are blue, round, bi-convex, film-coated tablets debossed with “NB-890” on one side. CONTRAVE tablets are available as follows:

- CONTRAVE extended-release tablets are available in bottles of 120 tablets.

CONTRAVE is available for oral administration as a round, bi-convex, film-coated, extended-release tablet. Each tablet has a trilayer core composed of two drug layers, containing the drug and excipients, separated by a more rapidly dissolving inert layer. Each tablet contains 8 mg of naltrexone hydrochloride and 90 mg of bupropion hydrochloride. Tablets are blue and are debossed with NB-890 on one side. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, edetate disodium, FD&C Blue No. 2 indigo carmine aluminum lake, hydroxypropyl cellulose, hypromellose, lactose anhydrous, lactose monohydrate, L-cysteine hydrochloride, macrogol/peg, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

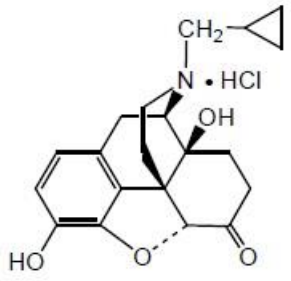
Proper name: Naltrexone Hydrochloride

Chemical name: morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, hydrochloride, (5α)

Molecular formula: $C_{20}H_{23}NO_4 \bullet HCl$

Molecular mass: 377.86 g/mol

Structural formula:



Physicochemical properties:

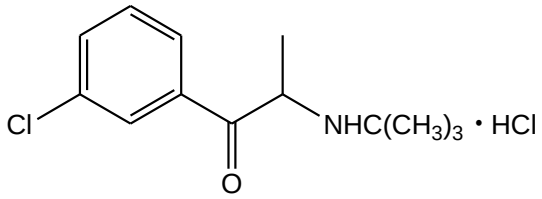
Description: Naltrexone hydrochloride is a white to yellowish, crystalline compound.

Solubility: It is soluble in water to the extent of about 100 mg/mL.

Drug Substance

Proper name:	Bupropion Hydrochloride
Chemical name:	(±)-1-(3 chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propranone hydrochloride
Molecular formula:	$C_{13}H_{18}ClNO•HCl$
Molecular mass:	276.2 g/mol

Structural formula:



Physicochemical properties

Description:	Bupropion hydrochloride powder is white, crystalline.
Solubility:	Highly soluble in water

CLINICAL TRIALS

Study demographics and trial design

The effects of CONTRAVE on weight loss in conjunction with reduced caloric intake and increased physical activity was studied in Phase 2 and Phase 3 double-blind, placebo-controlled obesity trials (BMI range 27 to 45 kg/m2) with study durations of 16 to 56 weeks in which patients were randomized to naltrexone (16 to 50 mg/day) and/or bupropion (300 to 400 mg/day) or placebo.

Effect on Weight Loss and Weight Maintenance

Four Phase 3 56-week multicenter, double-blind, placebo-controlled obesity trials (CONTRAVE Obesity Research, or COR-I, COR-II, COR-BMOD, and COR-Diabetes) were conducted to evaluate the effect of CONTRAVE in conjunction with lifestyle modification in 4,536 patients randomized to CONTRAVE or placebo. The COR-I, COR-II, and COR-BMOD trials enrolled patients with obesity (BMI 30 kg/m^2 or greater) or overweight (BMI 27 kg/m^2 or greater) and at least one comorbidity (hypertension or dyslipidemia). The COR-Diabetes trial enrolled patients with BMI greater than 27 kg/m^2 with type 2 diabetes with or without hypertension and/or dyslipidemia and not achieving glycemic goal of a HbA1c less than 7% either with or without oral antidiabetic agents.

Treatment was initiated with a three-week dose-escalation period followed by approximately 1 year of continued therapy. Patients were instructed to take CONTRAVE with food. COR-I, COR-II and COR-Diabetes included a program consisting of instruction to follow a reduced-calorie diet resulting in an approximate 500 kcal/day decrease in caloric intake, behavioral counseling, and increased physical activity. COR-BMOD included an intensive behavioral modification program consisting of 28 group counseling sessions over 56 weeks as well as a prescribed diet and exercise regimen.

In the Phase 3 COR-I, COR-II and COR-BMOD combined, the mean age was 46 years, 83% were female, 77% were Caucasian, 18% were Black, and 5% were other races. At baseline, mean BMI was 36 kg/m^2 and mean waist circumference was 110 cm. Of the overall population from these three trials, 25% had hypertension, 33% had fasting glucose levels ≥100 mg/dL (5.6 mmol/L) at baseline, 54% had dyslipidemia at study entry, and 11% had type 2 diabetes. In the Phase 3 COR-Diabetes trial, the mean age was 54 years, 54% were female, 80% were Caucasian, 16% were Black, and 4% were other races. At baseline, mean BMI was 37 kg/m^2, mean waist circumference was 115 cm and mean HbA1c was 8%. At study entry, 62% had hypertension and 84% had dyslipidemia.

A substantial percentage of randomized patients withdrew from the trials prior to Week 56: 45% for the placebo group and 46% for the CONTRAVE group. The majority of these patients discontinued within the first 12 weeks of treatment. Approximately 24% of patients treated with CONTRAVE and 12% of patients treated with placebo discontinued treatment because of an adverse reaction.

The two co-primary endpoints were percent change from baseline body weight and the proportion of subjects achieving ≥5% total decreased body weight. The primary endpoint was at

Week 56 for Studies COR-I, COR-BMOD and COR-Diabetes. In Study COR-II, the primary endpoint was Week 28, since non-responders were re-randomized to a higher naltrexone dose starting at Week 28. For this reason, efficacy results for COR-II are not fully described; however, results were generally consistent with those of Study COR-I.

Results from COR-I, COR-BMOD and COR-Diabetes are shown below.

In the 56-week COR-I trial, the mean change in body weight was -5.4% among patients assigned to CONTRAVE 32 mg / 360 mg compared with -1.3% among patients assigned to placebo (Intent-To-Treat [ITT] population), as shown in Table 7 and Figure 1. In this trial, the achievement of at least a 5% reduction in body weight from baseline occurred more frequently for patients treated with CONTRAVE 32 mg / 360 mg compared with placebo (42% vs 17%).

As seen in Table 7, in the COR-I study subjects had a mean percent body weight loss of -5.4% while receiving CONTRAVE compared to -1.3% in placebo-treated subjects. Weight loss of at least 5% baseline body weight was observed more frequently for subjects treated with CONTRAVE (31%) compared to placebo (12%) (Table 7). More pronounced weight loss was observed in the cohort of subjects who completed 56 weeks of treatment with CONTRAVE (-8.1%) compared to placebo (-1.8%). Comparable results were seen in the COR-II study, which was of similar design, with significant weight loss observed in CONTRAVE–treated subjects compared to placebo at the Week 28 primary endpoint, and sustained through 56 weeks from baseline (Table 7).

CONTRAVE was also evaluated in combination with intensive behavioural modification counseling in the COR-BMOD study. Correspondingly, there was greater mean weight loss from baseline for CONTRAVE treatment (-8.1%) compared to study COR-I (-5.4%) at Week 56, and for placebo (-4.9%) compared to study COR-I (-1.3%).

The treatment effects observed in obese and overweight subjects with type 2 diabetes mellitus (Study COR-Diabetes) were somewhat less pronounced than those observed in the other Phase 3 studies, but CONTRAVE (-3.7%) was significantly ($p<0.001$) more efficacious than placebo (-1.7%) treatment in this population.

Table 7 - Mean Weight Loss (% Change) from Baseline to Week 56 (ITT/LOCF) in CONTRAVE Phase 3 Studies COR-I, COR-BMOD, and COR-Diabetes

	COR-I		**COR-BMOD**		**COR-Diabetes**	
	CONTRAVE 32 mg/360 mg	**Placebo**	**CONTRAVE 32 mg/360 mg**	**Placebo**	**CONTRAVE 32 mg/360 mg**	**Placebo**
N	**538**	**536**	**565**	**196**	**321**	**166**
Intent-to-Treat Analysis Set†						
Baseline (kg)	99.8	99.5	100.3	101.8	104.2	105.3
LS Mean % Change from Baseline (95% CI)	-5.4* (-6.0, -4.8)	-1.3 (-1.9, -.07)	-8.1* (-8.8, -7.4)	-4.9 (-6.1, -3.7)	-3.7 (-4.3, -3.1)	-1.7 (-2.5, -0.9)
Difference from placebo (LS Mean) (95% CI)	-4.0* (-4.8, -3.3)		-3.2* (-4.5, -1.8)		-2.0* (-3.0, -1.0)	

CI, Confidence Interval; LS, Least Squares.

95% confidence intervals calculated as LS Mean ±1.96 x Standard Error.
† Subjects who were randomized, had a baseline body weight measurement, and had at least one postbaseline body weight measurement during the defined treatment phase. All available body weight data during the double-blind treatment phase are included in the analysis, including data collected from subjects who discontinued study drug. Results are based on last-observation carried- forward (LOCF).
* Difference from placebo, p<0.001.
Studies COR-I, COR-BMOD, and COR-Diabetes were conducted in subjects who were obese, or overweight or obese with comorbidities. Study COR-BMOD had a more intensive behavioural modification program. Study COR-Diabetes was conducted in subjects who were overweight or obese and had type 2 diabetes mellitus.

The percentages of patients who achieved at least 5% or at least 10% body weight loss from baseline were greater among those assigned to CONTRAVE, compared with placebo (Table 8), in all four obesity trials.

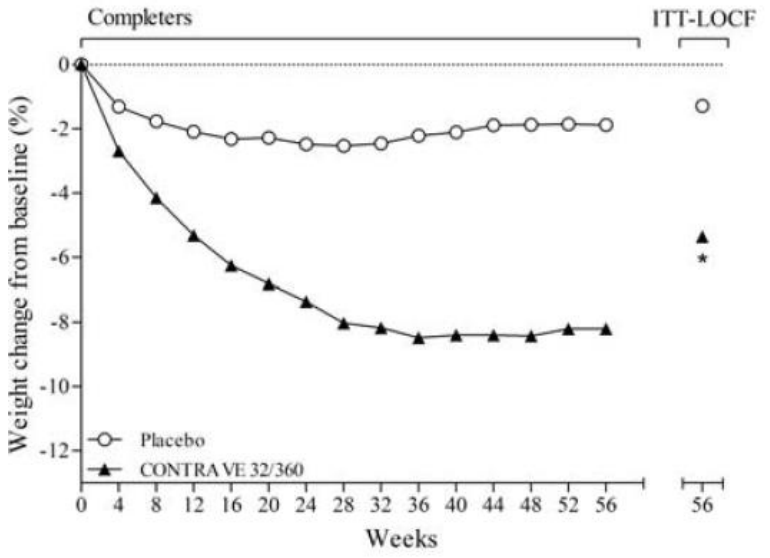
Table 8 - Percentage (%) of Subjects Losing ≥5% and ≥10% of Body Weight from Baseline to Week 56 (ITT/LOCF and All Randomized/BOCF) in Phase 3 Studies COR-I, COR-BMOD, and COR-Diabetes

	COR-I		COR-BMOD		COR-Diabetes	
	CONTRAVE 32 mg/ 360 mg	**Placebo**	**CONTRAVE 32 mg/ 360 mg**	**Placebo**	**CONTRAVE 32 mg/ 360 mg**	**Placebo**
Intent-to-Treat Analysis Set†						
N	538	536	565	196	321	166
≥5% Weight Loss	42*	17	57*	43	36*	18
≥10% Weight Loss	21*	7	35*	21	15**	5
Randomized Population†‡						
N	583	581	591	202	335	170
≥5% Weight Loss	31*	12	46**	34	28*	14
≥10% Weight Loss	17*	5	30*	17	13**	5

† Subjects who were randomized, had a baseline body weight measurement, and had at least one postbaseline body weight measurement during the defined treatment phase. All available body weight data during the double-blind treatment phase are included in the analysis, including data collected from subjects who discontinued study drug. Results are based on last-observation carried- forward (LOCF).
‡With baseline observation carried forward (BOCF), i.e. subjects who discontinued before Week 56 were considered as non-responders
* Difference from placebo, p<0.001
** Difference from placebo, p<0.01
Studies COR-I, COR-BMOD, and COR-Diabetes were conducted in subjects who were obese, or overweight or obese with comorbidities. Study COR-BMOD had a more intensive behavioural modification program. Study COR-Diabetes was conducted in subjects who were overweight or obese and had type 2 diabetes mellitus.

Of the subjects with observed data at Week 16 in the four Phase 3 clinical trials, 50.8% of those randomized to receive CONTRAVE had lost ≥5% of their baseline body weight, compared to 19.3% of placebo-treated subjects (Week 16 Responders). Additionally, Week 16 Responders who received CONTRAVE had a high retention rate with 87% completing 1 year of treatment. The ≥5% weight loss threshold at Week 16 had 86.4% positive predictive value and 84.8% negative predictive value for determining whether a subject treated with CONTRAVE would achieve at least 5% weight loss at Week 56. Patients who did not meet the early response criterion were not found to have increased tolerability or safety issues relative to patients who did have a favorable early response.

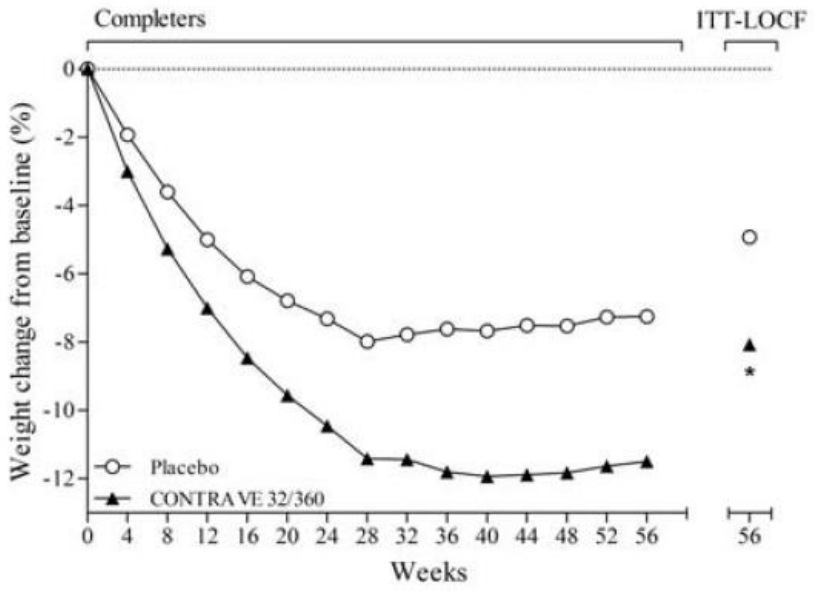
The time course of weight loss up to Week 56 is shown by study in Figures 1, 2 and 3 below, for the patients who completed 56 weeks of double-blind treatment; the results for the ITT/LOCF are indicated for the Week 56 endpoint.



* p<0.001 vs placebo

Figure 1 – Weight Loss Over Time in Completer Population: COR-I Trial

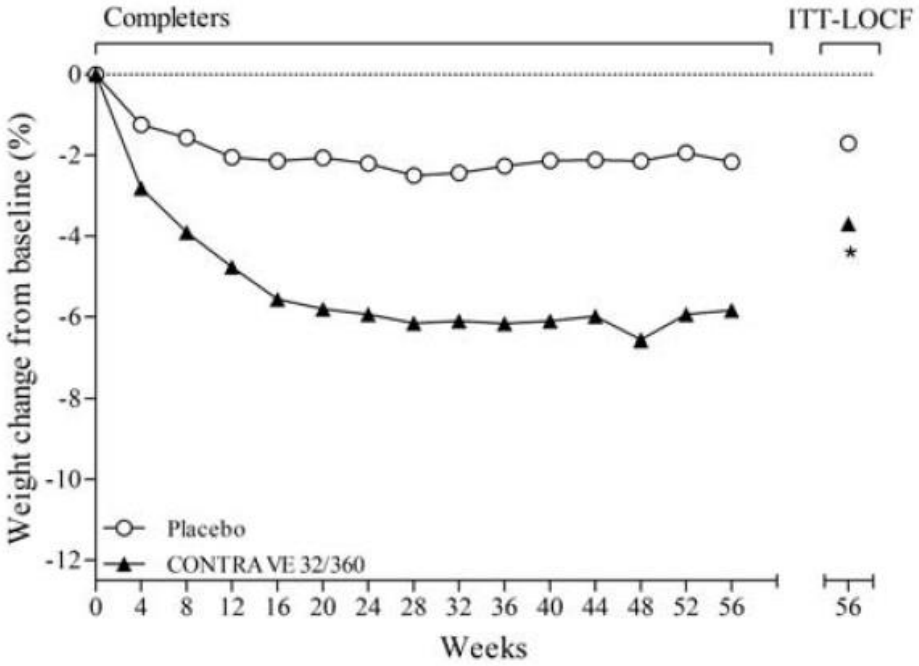
COR-I trial: 50.1% in the placebo group and 49.2% in the CONTRAVE group discontinued the drug.



* p<0.001 vs placebo

Figure 2 – Weight Loss Over Time in Completer Population: COR-BMOD Trial

COR-BMOD trial: 41.6% in the placebo group and 42.1% in the CONTRAVE group discontinued the drug.



* p<0.001 vs placebo

Figure 3 – Weight Loss Over Time in Completer Population: COR-Diabetes Trial

COR-Diabetes trial: 41.2% in the placebo group and 47.8% in the CONTRAVE group discontinued the drug.

Effect on Cardiovascular and Metabolic Parameters

Changes in cardiovascular and metabolic parameters associated with obesity are presented for studies COR-I and COR-BMOD (patients without diabetes) in Table 9 and for Study COR-Diabetes in Table 10. Changes in mean blood pressure and heart rate are also further described elsewhere (**WARNINGS AND PRECAUTIONS**, **Cardiovascular**, Increase in Blood Pressure and Heart Rate).

Table 9 - Change in Cardiovascular and Metabolic Parameters from Baseline to Week 56 in Phase 3 Studies COR-I and COR-BMOD (overweight or obese patients without Diabetes)

Parameters	**COR-I**				
	CONTRAVE 32 mg/360 mg N=471		**Placebo N=511**		
	Baseline mean	Change from baseline†	Baseline mean	Change from baseline†	CONTRAVE minus placebo (LS Mean)
Waist circumference, cm	108.8	-6.2	110.0	-2.5	-3.8
Systolic blood pressure, mmHg	118.9	-0.1	119.0	-1.9	1.8
Diastolic blood pressure, mmHg	77.1	0.00	77.3	-0.9	0.9
Heart rate, bpm	72.1	1.0	71.8	-0.2	1.2
		% Change from baseline†		% Change from baseline†	
Triglycerides, mmol/L*	1.3	-11.6	1.3	1.7	-10.7
HDL-C, mmol/L	1.3	8.0	1.3	0.8	7.2
LDL-C, mmol/L	3.1	-2.0	3.1	-0.5	-1.5
Parameters	**COR-BMOD**				
	CONTRAVE 32 mg/360 mg N=482		**Placebo N=193**		
	Baseline mean	Change from baseline†	Baseline mean	Change from baseline†	CONTRAVE minus placebo (LS Mean)
Waist circumference, cm	109.3	-10.0	109.0	-6.8	-3.2
Systolic blood pressure, mmHg	116.9	-1.3	116.7	-3.9	2.6
Diastolic blood pressure, mmHg	78.2	-1.4	77.2	-2.8	1.4
Heart rate, bpm	70.7	1.1	70.4	0.2	0.9
		% Change from baseline†		% Change from baseline†	
Triglycerides, mmol/L*	1.24	-17.8	1.16	-7.4	-9.9
HDL-C, mmol/L	1.6	9.4	1.4	2.8	6.6
LDL-C, mmol/L	2.8	7.1	2.8	10.0	-2.9

*Values are baseline median, median % change, and the Hodges-Lehmann estimate of the median treatment difference

† Least square means, from all randomised subjects who had a baseline measurement and had at least one post-baseline body weight measurement while on study drug. Based on LOCF with the last on-drug observation carried forward.
Studies COR-I and COR-BMOD were conducted in subjects who were obese, or overweight or obese with comorbidities. Study COR-BMOD had a more intensive behavioural modification program.

Table 10 - Change in Cardiovascular and Metabolic Parameters from Baseline to Week 56 in the Phase 3 Study COR-Diabetes (overweight or obese patients with Type 2 Diabetes Mellitus)

	CONTRAVE 32 mg/360 mg N=265		**Placebo N=159**		
Parameters	Baseline mean	Change from baseline†	Baseline mean	Change from baseline†	CONTRAVE minus placebo (LS Mean)
HbA1c, %	8.0	-0.6	8.0	-0.1	-0.5
Fasting glucose, mmol/L	8.9	-0.7	9.1	-0.2	-0.4
Waist circumference, cm	115.6	-5.0	114.3	-2.9	-2.1
Systolic blood pressure, mmHg	125.0	0.0	124.5	-1.1	1.2
Diastolic blood pressure, mmHg	77.5	-1.1	77.4	-1.5	0.4
Heart rate, bpm	72.9	0.7	73.1	-0.2	0.9
	Baseline mean	% Change from baseline†	Baseline mean	% Change from baseline†	CONTRAVE minus placebo (LS Mean)
Triglycerides, mmol/L*	1.7	-7.7	1.9	-8.6	-3.3
HDL-C, mmol/L	1.2	7.4	1.2	-0.2	7.6
LDL-C, mmol/L	2.6	2.4	2.6	4.2	-1.9

† Least square means, from all randomised subjects who had a baseline measurement and had at least one post-baseline body weight measurement while on study drug. Based on LOCF with the last on-drug observation carried forward.
*Values are baseline median, median % change, and the Hodges-Lehmann estimate of the median treatment difference

Effect on Body Composition

In a subset of subjects, body composition was measured using dual energy X-ray absorptiometry (DEXA) (CONTRAVE = 79 subjects and placebo = 45 subjects). The DEXA assessment showed that treatment with CONTRAVE was associated with greater reductions from baseline in total body fat than placebo. The results in this small sample of subjects indicated that most of the change in body mass in CONTRAVE and placebo (-6.97 kg CONTRAVE and -2.01 kg placebo) was attributable to a decrease in fat mass (-4.72 kg CONTRAVE and -1.44 kg placebo) as opposed to lean mass (-1.94 CONTRAVE vs. -0.60 placebo), as measured by DEXA. In terms of body composition, the decreases in percent fat mass in both CONTRAVE and placebo were -2.44% vs. -0.77%, respectively as measured by DEXA.

DETAILED PHARMACOLOGY

The effects of combined bupropion and naltrexone use have not been studied in animals. Non-clinical pharmacokinetic and pharmacodynamic information is available from studies performed individually with naltrexone and bupropion.

MICROBIOLOGY

None

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to evaluate carcinogenesis, mutagenesis, or impairment of fertility with the combined products in CONTRAVE have not been conducted. The following findings are from studies performed individually with naltrexone and bupropion. The potential carcinogenic, mutagenic and fertility effects of the metabolite 6-beta-naltrexol are unknown. Safety margins were estimated using body surface area exposure (mg/m^2) based on a body weight of 100 kg.
In a two-year carcinogenicity study in rats with naltrexone, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (approximately 50 times the recommended therapeutic dose on a mg/m^2 basis for the naltrexone maintenance dose for CONTRAVE) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day was 4%, but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a two-year dietary study with naltrexone in male and female mice.

Lifetime carcinogenicity studies of bupropion were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 15 and 3 times the maximum recommended human dose (MRHD) of the bupropion component in CONTRAVE, respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 5 to 15 times the MRHD of the bupropion component in CONTRAVE on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the Drosophila recessive lethal assay, and in non-specific DNA repair tests with E. coli. However, no evidence of genotoxic potential was observed in a range of other in vitro tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Bupropion produced a positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenetic studies.

Naltrexone administered orally to rats caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day (approximately 50 times the MRHD of the

naltrexone component in CONTRAVE on a mg/m^2 basis). There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.
A fertility study of bupropion in rats at doses up to 300 mg/kg/day (approximately 15 times the MRHD of the bupropion component in CONTRAVE on a mg/m^2 basis) revealed no evidence of impaired fertility.

Reproduction

Animal Data

Reproduction and developmental studies have not been conducted for the combined products naltrexone and bupropion in CONTRAVE. Safety margins were estimated using body surface area exposure (mg/m^2) based on a body weight of 100 kg.

Separate studies with bupropion and naltrexone have been conducted in pregnant rats and rabbits.

Naltrexone administered orally has been shown to increase the incidence of early fetal loss in rats administered ≥30 mg/kg/day (180 mg/m^2/day) and rabbits administered ≥60 mg/kg/day (720 mg/m^2/day), doses at least 15 and 60 times, respectively, the maximum recommended human dose [MRHD] of the naltrexone component in CONTRAVE on a mg/m^2 basis. There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (approximately 100 and 200 times the recommended therapeutic dose, respectively, on a mg/m^2 basis). Rats do not form appreciable quantities of the major human metabolite, 6-beta-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known.

Bupropion was administered orally in studies conducted in rats and rabbits at doses up to 450 and 150 mg/kg/day, respectively (approximately 20 and 15 times the MRHD, respectively, of the bupropion component in CONTRAVE on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately 2 times the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater (approximately 5 times the MRHD of the bupropion component in CONTRAVE on a mg/m^2 basis). When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 15 times the MRHD of the bupropion component in CONTRAVE on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrCONTRAVE®
Naltrexone hydrochloride 8mg and Bupropion hydrochloride 90 mg
Extended-release Tablets

Read this carefully before you start taking **CONTRAVE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CONTRAVE**.

What is CONTRAVE used for?
CONTRAVE should be taken with a reduced-calorie diet and increased physical activity. It is for weight management in:

- obese patients.
- overweight patients who have at least one weight-related condition, such as:
  - high blood pressure that is controlled by medicine
  - Type 2 diabetes
  - a high amount of lipids (cholesterol or other types of fat) in the blood.

It is not known if it is safe to take CONTRAVE with other weight loss products. Other products include prescription drugs, over the counter drugs, and natural health products.

It is not known if CONTRAVE changes your risk of heart problems or stroke or of death due to heart problems or stroke.

CONTRAVE is not for use in patients 18 years of age and younger.

How does CONTRAVE work?
CONTRAVE contains two medicines, naltrexone hydrochloride and bupropion hydrochloride. These medicines work on two separate areas of the brain that are involved in controlling eating (hunger and cravings).

What are the ingredients in CONTRAVE?
Medicinal ingredients: naltrexone hydrochloride and bupropion hydrochloride

Non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Edetate Disodium, FD&C Blue No. 2 Indigo Carmine Aluminum Lake, Hydroxypropyl Cellulose, Hypromellose, Lactose Anhydrous, Lactose Monohydrate, L-Cysteine Hydrochloride, Macrogol/Peg, Magnesium Stearate, Microcrystalline Cellulose, Polyvinyl Alcohol-Part Hydrolyzed, Talc, and Titanium Dioxide.

CONTRAVE comes in the following dosage form:
Extended release tablets. Each tablet contains 8 mg naltrexone hydrochloride and 90 mg

bupropion hydrochloride. The tablets are blue, round, and have "NB-890" on one side.

Do not use CONTRAVE if you:

- are allergic (hypersensitive) to naltrexone, bupropion or any of the other ingredients in CONTRAVE
- have uncontrolled high blood pressure
- have severe liver problems
- have end-stage kidney failure
- have or had seizures
- are taking thioridazine, an antipsychotic medicine. An ingredient in CONTRAVE may cause the level of thioridazine in your blood to increase
- use other medicines that contain bupropion such as WELLBUTRIN® SR, WELLBUTRIN® XL and ZYBAN®
- have or had an eating disorder such as:
  - anorexia (eating very little)
  - bulimia (eating too much and throwing up so you don't gain weight)
- are dependent on opioid pain medicines or use medicines to help stop taking opioids such as methadone or buprenorphine or are in opioid withdrawal.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines and you stop using them all of a sudden
- are taking medicines called monoamine oxidase inhibitors (MAOIs).
  - Ask your healthcare provider or pharmacist professional if you are not sure if you take an MAOI.
  - **Do not** start CONTRAVE until you have stopped taking your MAOI for at least 14 days.
- are pregnant or planning to become pregnant. Tell your healthcare professional right away if you become pregnant while taking CONTRAVE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CONTRAVE. Talk about any health conditions or problems you may have, including if you:

- have or had depression or other mental illnesses (such as bipolar disorder)
- have attempted suicide in the past
- have or had liver problems
- have high blood pressure
- have or had a heart attack
- have kidney problems
- are over the age of 65
- are lactose intolerant because CONTRAVE contains lactose. Lactose is an ingredient in milk.
- are breastfeeding or plan to breastfeed. CONTRAVE can pass into your breast milk and may harm your baby. You and your healthcare professional should decide if you should take CONTRAVE or breastfeed. You should not do both.

Other warnings you should know about:

New or Worsened Emotional or Behavioral Problems, Including Self-Harm

- One of the ingredients in CONTRAVE is bupropion. Bupropion has caused some people to experience unusual feelings of agitation, mania (feeling very high, talking fast, taking more risks, and needing less sleep), hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm, or harm to others.
- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when you start taking CONTRAVE and when your dose changes.
- Keep all follow-up visits with your healthcare professional as scheduled. Call your healthcare professional between visits as needed, especially if you have concerns about symptoms.
- Your healthcare professional will monitor you for any signs of suicidal thoughts or behavior.
- If you are depressed and taking CONTRAVE, you may experience a worsening of your symptoms, including having suicidal thoughts or behaviors.
- If you, your family, or friends notice mental health changes that are unusual for you while on CONTRAVE, stop taking the drug and talk to your doctor. If the symptoms are severe, seek immediate emergency help.

Risk of seizures

- Bupropion, one of the ingredients in CONTRAVE, can cause seizures. The risk of having a seizure while taking CONTRAVE is related to the dose. It is important that you take CONTRAVE exactly as your healthcare professional tells you to.
- If you have a seizure while taking CONTRAVE, stop taking CONTRAVE and call your healthcare provider right away.
- The risk of having a seizure while taking CONTRAVE is higher if you have certain **medical conditions**. Tell your healthcare professional if you have or had any of the following, as they might increase your risk of seizures:
  - Seizures
  - Head injury
  - Eating disorder
  - Severe stroke
  - Heart problems
  - Tumor or infection in your brain or spine
  - Low blood sugar (hypoglycemia)
  - Low levels of salt (sodium) in your blood (hyponatremia)
  - Liver problems
  - Abuse of alcohol, sedatives (drugs that make you sleepy), street drugs or are in withdrawal from sedatives
  - Have diabetes and are taking insulin or other medicines to control your blood sugar
- The risk of having a seizure while taking CONTRAVE is higher if you take **other medicines** that increase the risk of seizures, which include:
  - Other drugs that contain bupropion
  - Antipsychotics

- Other antidepressants (tricyclic antidepressants)
- Theophylline (used to treat asthma)
- Steroids (used to treat inflammation)

Risk of opioid overdose
Naltrexone, one of the ingredients in CONTRAVE, can increase your chance of having an opioid overdose if you take opioid medicines while taking CONTRAVE. Examples of opioids or opioid-containing medicines include heroin, prescription pain medicines, and methadone.

You can accidentally overdose in 2 ways:

- Naltrexone blocks the effects of opioids. Because of this, do not take large amounts of opioids to try to overcome the opioid-blocking effects of naltrexone. It can lead to serious injury, coma, or death.
- After you take naltrexone, its blocking effect slowly decreases and goes away over time.
  - If you have used opioid street drugs or opioid-containing medicines in the past, using opioids in amounts that you used before treatment with CONTRAVE can lead to overdose and death.
  - You may also be more sensitive to the effects of lower amounts of opioids:
    - after you have gone through detoxification
    - when your next dose of CONTRAVE is due
    - if you miss a dose of CONTRAVE
    - after you stop CONTRAVE treatment

It is important that you tell your family and the people closest to you of this increased sensitivity to opioids and the risk of overdose.

Sudden opioid withdrawal

- People who take CONTRAVE must not use any type of opioid **for at least 7 to 10 days before starting CONTRAVE**. This includes street drugs, prescription pain medicines (including tramadol), cough, cold, or diarrhea medicines that contain opioids, or opioid dependence treatments, such as buprenorphine or methadone.
- Using opioids in the 7 to 10 days before you start taking CONTRAVE may cause you to suddenly have symptoms of opioid withdrawal when you take it. Sudden opioid withdrawal can be severe, and you may need to go to the hospital.
- Tell your healthcare professional you are taking CONTRAVE before a medical procedure or surgery.

Increase in Blood Pressure and Heart Rate

- CONTRAVE may cause an increase in blood pressure and heart rate. Your healthcare professional will monitor you before you start taking CONTRAVE and during treatment.
- You may be more at risk if you already have high blood pressure.
- If you have a significant increase in your blood pressure or heart rate while taking CONTRAVE, your treatment will be stopped.

Patients with Type 2 Diabetes Mellitus who are Taking Antidiabetic Medicines

- You may be more at risk of developing low blood sugar (hypoglycemia) if you have

Type 2 diabetes and you lose weight while taking CONTRAVE. This applies only if you take medicines to treat Type 2 diabetes such as insulin or sulphonylureas.
- Your healthcare professional will monitor your blood sugar levels before and during treatment with CONTRAVE.
- You may need a change in your antidiabetic medicine.

Angle-Closure Glaucoma
CONTRAVE may cause an acute attack of glaucoma. Get immediate medical attention if you have:
- eye pain
- changes in vision
- swelling or redness in or around the eye.

Liver Damage
CONTRAVE may cause damage to your liver. See your healthcare professional right away if you have any of the following symptoms:
- abdominal pain
- dark urine
- diarrhea
- fatigue
- fever
- headache
- loss of appetite
- yellowing of the skin and the whites of the eyes
- nausea and vomiting

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CONTRAVE:

- Medicines to treat depression or Parkinson's disease (monoamine oxidase inhibitors such as phenelzine, selegiline, or rasagiline).
- Alcohol:
  - You should only drink a very small amount of alcohol or none at all while taking CONTRAVE.
- Opioids and opioid-containing medicines, used to treat:
  - cough and cold (mixtures containing dextromethorphan or codeine)
  - opiate addiction (methadone)
  - pain (morphine, codeine, tramadol)
  - diarrhea (loperamide).
- Medicines used to prevent malaria.
- Antibiotics to treat infections (quinolones such as ciprofloxacin).
- Medicines to treat asthma (theophylline).
- Medicines to treat hay fever, itch, swelling and other allergic reactions (antihistamines

and steroids).
- Medicines to lower sugar levels in your blood (metformin, insulin, glyburide or glibenclamide, nateglinide or repaglinide).
- Medicines to help you to sleep (sedatives such as diazepam).
- Medicines to treat depression (desipramine, venlafaxine, imipramine, paroxetine, citalopram) or other mental health problems (risperidone, haloperidol, thioridazine).
- Some medicines used to treat high blood pressure (metoprolol, clonidine).
- Some medicines used to treat irregular heart rhythm (propafenone, flecainide).
- Some medicines used to treat cancer (cyclophospamide, ifosphamide, tamoxifen).
- Some medicines for Parkinson's disease (levodopa, amantadine or orphenadrine).
- Medicines mainly used in the treatment of heart disease or stroke (ticlopidine, digoxin, or clopidogrel).
- Medicines used in the treatment of HIV infection and AIDS (efavirenz, lopinavir and ritonavir).
- Medicines used to treat epilepsy (valproate, carbamazepine, phenytoin or phenobarbital).

If you take a urine drug screening test, CONTRAVE may give a positive test result for amphetamines. Tell the laboratory technician that you are taking CONTRAVE. They can do a more specific drug screening test for you.

How to take CONTRAVE:

- Use CONTRAVE with a reduced calorie-diet and increased physical activity.
- Take CONTRAVE exactly as your healthcare professional tells you to.
  - **Do not** change your CONTRAVE dose without talking with your healthcare professional.
  - Do not take more CONTRAVE than your healthcare professional tells you to, or it may increase your risk of seizures.
  - Your healthcare professional will change your dose if needed.
  - Your healthcare professional should tell you to stop taking CONTRAVE if you have not lost a certain amount of weight after 16 weeks of treatment.
- Your healthcare professional will monitor:
  - your blood pressure and heart rate before you take CONTRAVE and during your treatment.
  - you for side effects if you have kidney or liver problems.
- **Swallow CONTRAVE tablets whole. Do not cut, chew, or crush the tablets.** Tell your healthcare professional if you cannot swallow CONTRAVE tablets whole.
- Take each dose of CONTRAVE with food. Do not take CONTRAVE with high-fat meals. It may increase your risk of seizures.
- Your dose may be decreased if you:
  - have kidney or liver problems.
  - take certain medicines.
- **Do not** drink a lot of alcohol while taking CONTRAVE. Talk with your healthcare professional if you drink a lot of alcohol. If you suddenly stop drinking alcohol, you may increase your chance of having a seizure.

Usual dose:

- The table below explains how your dose of CONTRAVE will be slowly increased over the first 4 weeks. At week 4, you will be taking the usual adult dose:
  - 2 tablets in the morning and 2 tablets in the evening.
  - This is also the maximum daily dose for CONTRAVE. It is important that you not take more than the maximum daily dose:
    - **Do not** take more than 2 tablets in the morning and 2 tablets in the evening.
    - **Do not** take more than 2 tablets at the same time or more than 4 tablets in 1 day.

	Morning Dose	**Evening Dose**
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 and Onward	2 tablets	2 tablets

Overdose:

If you think you have taken too much CONTRAVE contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Risk of opioid overdose: You may be at risk of having an opioid overdose if you take opioid medicines while taking CONTRAVE.

You should get emergency medical help right away if you:

- have trouble breathing
- become very drowsy with slowed breathing
- have slow, shallow breathing (little chest movement with breathing)
- feel faint, very dizzy, confused, or have unusual symptoms

Missed Dose:

If you miss a dose of CONTRAVE, wait until your next regular time to take it. **Do not** take more than 1 dose of CONTRAVE at a time. This will help reduce your risk of having a seizure.

What are possible side effects from using CONTRAVE?

These are not all the possible side effects you may feel when taking CONTRAVE. If you experience any side effects not listed here, contact your healthcare professional. Please also see the warnings section.

In clinical trials, patients who were elderly, had Type 2 diabetes or kidney problems had more of certain side effects than other patients.

The common side effects of CONTRAVE include:

- Nausea
- Constipation
- Diarrhea
- Dizziness
- Feeling off balance or like everything is spinning (vertigo)
- Dry mouth
- Headache or migraine
- Trouble sleeping
- Vomiting
- Abdominal pain
- Indigestion
- Shaking (tremor)
- Foul, salty, rancid or metallic taste in the mouth
- Sleepiness, feeling tired, lack of energy
- Trouble paying attention
- Abnormal dreams
- Flu
- A lot more sweating than usual
- Itching
- Rash
- Hair loss
- Ringing in the ear
- Blurred vision

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<u>VERY COMMON</u> **New or worse anxiety**		✓	
<u>COMMON</u> **New or worse depression**		✓	
<u>UNCOMMON</u> **Visual problems (angle-closure glaucoma):** o eye pain; o changes in vision; o swelling or redness in or around the eye.		✓	
Unusual changes in behavior or mood: agitation, sadness, feeling		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
over-excited.			
Increases in blood pressure or heart rate: your blood pressure and heart rate should be monitored during your treatment. Symptoms may include: headaches, nosebleeds, dizziness, a flushed face, fatigue, and fast heart rate.		✓	
Liver damage or hepatitis: o pain in the stomach area lasting more than a few days; o dark urine; o yellowing of the whites of your eyes; o tiredness.		✓	
<u>RARE</u> **Seizures**			✓
New or Worsened Emotional or Behavioral Problems: o thoughts about suicide or dying; o attempts to commit suicide; o new or worse irritability.			✓
Increased risk of low blood sugar (hypoglycemia) in people with Type 2 diabetes mellitus who also take medicines to treat their diabetes: you should check your blood sugar before you start taking CONTRAVE and while you take CONTRAVE. Symptoms may include: sweating, nervousness, shaking, faintness, palpitations, and hunger.		✓	
<u>VERY RARE</u> **Severe allergic reactions:** o chest pain; o fever;			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
○ hives; ○ itching in your eyes; ○ painful sores in your mouth or around; ○ rash; ○ swelling of your lips or tongue; ○ swollen lymph glands; ○ trouble breathing.			
New or Worsened Emotional or Behavioral Problems: ○ feeling very agitated or restless; ○ acting aggressive; ○ being angry or violent; ○ acting on dangerous impulses.			✓
UNKNOWN **Manic episodes:** mania (feeling very high, talking fast, taking more risks, and needing less sleep).			✓
Panic attacks: sudden intense fear and discomfort.			✓
Hallucinations: Sensing or seeing things that are not there.			✓
If you had taken opioid medicines less than 7 – 10 days before taking CONTRAVE. **Opioid withdrawal:** nausea and vomiting, anxiety, insomnia, hot and cold flushes, perspiration, muscle cramps, diarrhea.			✓
If you take opioid medicines while taking CONTRAVE. **Opioid overdose:** having trouble breathing, becoming very drowsy with slowed			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
breathing, having slow, shallow breathing, feeling faint, very dizzy, confused, or having unusual symptoms.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Tell your healthcare professional about any side effect that does not go away.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store CONTRAVE at room temperature between 15°C to 25°C.
Keep out of reach and sight of children.

If you want more information about CONTRAVE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by calling the manufacturer at 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

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