AUSTRALIAN PRODUCT INFORMATION – CONTRAVE® 8/90 (NALTREXONE HYDROCHLORIDE AND BUPROPION HYDROCHLORIDE) EXTENDED-RELEASE TABLETS

1 NAME OF THE MEDICINE

Naltrexone hydrochloride and Bupropion hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CONTRAVE is a blue film-coated round biconvex tablet formulated as a fixed combination tri-layer tablet for extended-release oral delivery. 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.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

Excipient with known effect:

Contains sugars as lactose.

3 PHARMACEUTICAL FORM

Modified release tablet

CONTRAVE 8/90 (naltrexone HCl 8 mg and bupropion HCl 90 mg) is a blue film-coated, biconvex, round tablet of 12.0-12.2 mm diameter debossed with “NB-890” on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CONTRAVE is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m^2 (obese), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)

Treatment with CONTRAVE should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

4.2 DOSE AND METHOD OF ADMINISTRATION

CONTRAVE tablets should be swallowed whole with some water. The tablets should preferably be taken with food (see section 5 PHARMACOLOGICAL PROPERTIES). The tablets should not be cut, chewed, or crushed.

Upon initiating treatment, the dose should be escalated over a 4-week period as follows:

	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

The maximum recommended daily dose of CONTRAVE is two tablets taken twice daily (32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride), which is reached at the start of week 4.

If a dose is missed, patients should not take an additional dose, but take the prescribed next dose at the usual time.

Patients may develop elevated blood pressure or heart rate during CONTRAVE treatment. 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The need for continued treatment should be evaluated after 16 weeks (see section 4.1 THERAPEUTIC INDICATIONS) and re-evaluated annually.

Special Populations:

Elderly

CONTRAVE should be used with caution in patients over 65 years of age and is not recommended in patients over 75 years of age (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal Impairment

CONTRAVE is contraindicated in patients with end-stage renal failure. In patients with moderate or severe renal impairment, the maximum recommended daily dose for CONTRAVE is two tablets (one tablet in the morning and one tablet in the evening). Dose reduction is not necessary in patients with mild renal impairment. For individuals who are at elevated risk for renal impairment, in particular patients with diabetes or elderly individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with CONTRAVE (see section 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES - SPECIAL POPULATIONS).

Hepatic Impairment

CONTRAVE is contraindicated in patients with severe hepatic impairment (see section 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES - SPECIAL POPULATIONS). CONTRAVE is not recommended in patients with mild or moderate hepatic impairment.

Paediatrics

CONTRAVE is not recommended in children and adolescents below 18 years of age (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3 CONTRAINDICATIONS

CONTRAVE is contraindicated in:

- Hypersensitivity to bupropion, naltrexone or any of the excipients
- Uncontrolled hypertension
- Seizure disorder or a history of seizures
- Patients with a known central nervous system tumour
- Patients undergoing acute alcohol or benzodiazepine withdrawal
- Patients with a history of bipolar disorder
- Use of concomitant treatment containing bupropion or naltrexone
- Current or previous diagnosis of bulimia or anorexia nervosa
- Patients currently dependent on chronic opioids or opiate agonists (e.g., methadone), or patients in acute opiate withdrawal
- Concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with CONTRAVE. Starting CONTRAVE in a patient treated with reversible MAOIs is also contraindicated
- Pregnancy
- Patients with severe hepatic impairment
- Patients with end-stage renal failure

Refer to section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further details.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The safety and tolerability of CONTRAVE should be assessed at regular intervals.

The treatment should be discontinued if there are concerns with the safety or tolerability of ongoing treatment; including concerns about increased blood pressure (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

The safety and efficacy of CONTRAVE for long term use (>1 year) has not yet been established.

Identified precautions

Suicide and Suicidal Behaviour

CONTRAVE contains bupropion. Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressants in adult subjects with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in subjects less than 25 years old.

Although in placebo controlled clinical trials with CONTRAVE for the treatment of obesity in adult subjects, no suicides or suicide attempts were reported in studies up to 56 weeks duration with CONTRAVE, suicidality events (including suicidal ideation) have been reported in subjects of all ages treated with CONTRAVE post-marketing.

Close supervision of patients, particularly those at high risk, should accompany therapy with CONTRAVE especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal

behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Seizures

Bupropion is associated with a dose-related risk of seizures. Bupropion sustained release (SR) 300 mg yields an estimated seizure incidence of 0.1%. The incidence of seizure in subjects receiving CONTRAVE in clinical trials was approximately 0.06% (2/3239 subjects) vs. 0.0% (0/1515 subjects) on placebo. This incidence of seizure, along with incidence of seizure in subjects who received Contrave in a large cardiovascular outcomes trial (CVOT), was no higher than the seizure rate with bupropion as a single agent at approved doses.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold (see section 4.3 CONTRAINDICATIONS). Consider these risks before initiating treatment with CONTRAVE. CONTRAVE should be discontinued and not restarted in patients who experience a seizure while being treated with the medicinal product.

Caution should be used when prescribing CONTRAVE to patients with predisposing factors that may increase the risk of seizure including:

- history of head trauma
- excessive use of alcohol or addiction to cocaine or stimulants
- as treatment with CONTRAVE may result in lowered glucose in patients with diabetes, the dose of insulin and/or oral diabetic medicinal products should be assessed to minimise the risk of hypoglycaemia, which could predispose patients to seizure
- concomitant administration of medicinal products that may lower the seizure threshold, including antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines.

Also see section 4.3 CONTRAINDICATIONS.

The consumption of alcohol during CONTRAVE treatment should be minimised or avoided.

Patients receiving Opioid Analgesics

CONTRAVE must not be administered to patients receiving chronic opiate therapy due to the naltrexone component (see section 4.3 CONTRAINDICATIONS). If chronic opiate therapy is required, CONTRAVE treatment must be stopped. In patients requiring intermittent opiate treatment, CONTRAVE should be temporarily discontinued and lower doses of opioids may be needed.

Attempt to overcome blockade: An attempt by a patient to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is very dangerous and may lead to a fatal overdose or life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be advised that they may be more sensitive to opioids, even at lower doses, after CONTRAVE treatment is discontinued.

Allergic Reactions

Anaphylactoid/anaphylactic reactions characterised by symptoms such as pruritus, urticaria, angioedema, and dyspnoea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous post-marketing reports of erythema multiforme, and anaphylactic shock associated with bupropion. A patient should stop taking CONTRAVE and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, oedema, and shortness of breath) during treatment. If a patient experiences anaphylactic reactions during treatment, medical attention should be sought immediately.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness. Patients should be advised to notify their prescribing physician if they experience these symptoms. If serum sickness is suspected, CONTRAVE should be discontinued.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with CONTRAVE treatment.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, CONTRAVE should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or AGEP with the use of CONTRAVE, the treatment must not be restarted in this patient at any time.

Elevation of 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. Early, transient mean increases from baseline in systolic and diastolic blood pressure of up to 1 mmHg were observed in CONTRAVE Phase 3 clinical trials. In clinical practice with other bupropion-containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. Furthermore, post-marketing cases of hypertensive crisis have been reported during the initial titration phase with CONTRAVE.

Blood pressure and pulse should be measured prior to initiation of therapy with CONTRAVE and should be assessed at regular intervals consistent with usual clinical practice. 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 be given with caution to those patients with controlled hypertension and must not be given to patients with uncontrolled hypertension (see section 4.3 CONTRAINDICATIONS).

Cardiovascular Disease

There is no clinical experience establishing the safety of CONTRAVE in patients with a recent history of myocardial infarction, unstable heart disease or NYHA class III or IV congestive heart failure. It is recommended that CONTRAVE should not be used in this population.

Brugada syndrome

Bupropion may unmask Brugada syndrome, a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads), which may lead to cardiac arrest or sudden death. Caution is advised in patients with Brugada syndrome or a family history of cardiac arrest or sudden death.

Hepatotoxicity

Naltrexone hydrochloride can cause hepatocellular injury in high doses; although this was not seen in CONTRAVE with lower doses of naltrexone, care should be used when prescribing in patients in whom clearance may be reduced, or in whom underlying liver disease may be present.

In CONTRAVE completed clinical studies, where naltrexone hydrochloride daily doses ranged from 16 mg to 48 mg, drug-induced liver injury (DILI) was reported. There have also been cases of elevated liver enzymes from post-marketing reporting. A patient with suspected DILI should stop taking CONTRAVE and notify their prescribing physician.

Patients should be 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.

Serotonin Syndrome

Serotonin syndrome has been reported when bupropion is co-administered with drugs known to be associated with serotonin syndrome, including selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see Section 4.5 INTERACTIOINS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Serotonin syndrome has also been reported with overdosage (see Section 4.9 OVERDOSE)

Neuropsychiatric Symptoms and Activation of Mania

Activation of mania and hypomania have been reported in patients with mood disorders who were treated with other similar medicinal products for major depressive disorder. No activation of mania or hypomania was reported in the clinical trials evaluating effects of CONTRAVE in obese subjects, which excluded subjects receiving antidepressants. CONTRAVE should be used cautiously in patients with a history of mania.

Panic attacks, particularly in patients with a history of psychiatric disorders, have been reported with CONTRAVE. The cases occurred mostly during the initial titration phase and following dose changes. CONTRAVE should be used with caution in patients with a history of psychiatric disorders.

Drug Abuse and Dependence

CONTRAVE 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-week 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, randomised treatment.

However there have been reports of the inhalation of crushed tablets or injection of dissolved bupropion from use with single-ingredient products containing bupropion. This may lead to a rapid release, faster absorption and potential overdose. Seizures and/or cases of death have been reported when single-ingredient products containing bupropion have been administered intra-nasally or by parenteral injection.

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take CONTRAVE.

Use in 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 their metabolites (up to 10-fold higher) in subjects with moderate-to-severe hepatic impairment. Therefore, CONTRAVE should not be used in this population (see section 4.3 CONTRAINDICATIONS, 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES).

Use in renal impairment

CONTRAVE has not been extensively evaluated in subjects with renal insufficiency. CONTRAVE is contraindicated in patients with end-stage renal failure. In patients with moderate or severe renal impairment, the maximum recommended daily dose for CONTRAVE should be reduced, as these patients may have higher drug concentrations which could result in an increase in adverse drug reactions. For individuals who are at elevated risk for renal impairment, in particular, individuals with diabetes or elderly individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with CONTRAVE (see section 4.3 CONTRAINDICATIONS, 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly

Clinical studies of CONTRAVE did not include sufficient numbers of subjects aged 65 and over, and none over 75 years, to determine whether they respond differently than 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 effects 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 and is not recommended in patients over 75 years of age.

Paediatric use

The safety and efficacy of CONTRAVE in children and adolescents below 18 years have not yet been established. Therefore, CONTRAVE is not recommended in children and adolescents below 18 years of age.

Effects on laboratory tests

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 with medicines that also inhibit the re-uptake of dopamine or norepinephrine. At least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with CONTRAVE. Conversely, at least 14 days should be allowed after stopping CONTRAVE before starting an MAOI (see section 4.3 CONTRAINDICATIONS).

Opioid Analgesics

CONTRAVE is contraindicated in patients currently dependent on chronic opioid or opiate agonist therapy (e.g., methadone), or patients in acute opiate withdrawal (see section 4.3 CONTRAINDICATIONS). Due to the antagonistic effect of naltrexone at the opioid receptor, patients taking CONTRAVE may not fully benefit from treatment with opioid-containing medicinal products, such as cough and cold remedies, anti-diarrhoeal 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 (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If chronic opiate therapy is required, CONTRAVE treatment must be stopped. 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.

Potential for CONTRAVE to Affect Other Medicines

Metabolised by CYP2D6 substrates

In vitro human P450 studies have shown that bupropion and hydroxybupropion are inhibitors of CYP2D6. In a clinical study, CONTRAVE (32 mg naltrexone hydrochloride/360 mg bupropion hydrochloride daily) was co-administered with a 50 mg dose of metoprolol (a CYP2D6 substrate). CONTRAVE increased metoprolol AUC and Cmax 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 medicinal product with desipramine and venlafaxine.

Co-administration of CONTRAVE with drugs that are metabolised by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclic antidepressants, e.g. desipramine, imipramine, paroxetine), antipsychotics (e.g., haloperidol, risperidone and thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., 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 metabolised 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. When feasible, the option of therapeutic drug monitoring should be considered for medications with a narrow therapeutic index, such as tricyclic antidepressants.

Post-marketing data show a possible pharmacodynamics interaction between bupropion and SSRIs and SNRIs resulting in an increased risk of serotonin syndrome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Serotonin syndrome).

Potential for Other Drugs to Affect CONTRAVE

Bupropion is primarily metabolised to its major active metabolite hydroxybupropion by the CYP2B6 isozyme. The potential exists for a drug interaction between CONTRAVE and drugs that induce or are substrates of the CYP2B6 isozyme.

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, the CONTRAVE dose should not exceed two tablets (one in the morning and evening) (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Inducers of CYP2B6

Ritonavir, Lopinavir and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure and may reduce efficacy. In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by 20 to 80%. Similarly, efavirenz 600 mg once daily for two weeks reduced the exposure of bupropion by approximately 55% in healthy volunteers. Concomitant use with these drugs is not recommended.

OCT2 substrates

Bupropion and its metabolites competitively inhibit the OCT2 in the basolateral membrane of the renal tubule responsible for creatinine secretion, in a manner similar to the OCT2 substrate cimetidine. Therefore, mild increases in creatinine observed after long-term treatment with naltrexone/bupropion are likely due to inhibition of OCT2 and not indicative of changes in creatinine clearance. Use of naltrexone/bupropion with other OCT2 substrates (e.g., metformin) in clinical trials did not indicate the need for dose adjustment or other precautions.

Drugs that Lower the Seizure Threshold

Use extreme caution when coadministering CONTRAVE with other drugs that lower the seizure threshold (e.g. antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually. Concomitant use of other bupropion-containing products is contraindicated (see section 4.3 CONTRAINDICATIONS).

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 effects have included 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 effects when administering CONTRAVE concomitantly with these drugs.

Use with Alcohol

In post marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. There are no known pharmacokinetic interactions between naltrexone and alcohol. The consumption of alcohol during CONTRAVE treatment should be minimised or avoided.

Other Interactions

Coadministration of CONTRAVE with digoxin may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with CONTRAVE and digoxin. Clinicians should be aware that digoxin levels may rise on discontinuation of CONTRAVE and the patient should be monitored for possible digoxin toxicity.

Table 1: Summary Table for Potential Drug Interactions:

Category	**Interaction**
MAOI	Increased risk of hypertensive reactions can occur when used concomitantly
Opioid Analgesics (e.g. Methadone, and other opioid containing analgesics or antitussives)	Contraindicated. Interference with the action of opioid containing drug products
Drugs Metabolised by CYP2D6 Substrates: **- Antiarrhythmics** (e.g. Flecainide) **- Antidepressants** (e.g. Desipramine, venlafaxine, imipramine, paroxetine, other tricyclic antidepressants and SSRIs) **- Antipsychotics** (e.g. Haloperidol, risperidone, thioridazine) **- Beta-blocker** (e.g. Metoprolol)	Bupropion inhibits CYP2D6 and can increase concentrations of these drugs
CYP2B6 Inhibitors (e.g. Ticlopidine and Clopidogrel)	Concomitant treatment with these drugs can increase bupropion exposure
CYP2B6 Inducers (e.g. Ritonavir, Lopinavir and Efavirenz)	May reduce efficacy by reducing bupropion exposure, avoid concomitant use
OCT2 substrates (e.g. Metformin)	Bupropion and its metabolites could inhibit OCT2; exercise caution
Drugs that Lower Seizure Threshold (e.g. antipsychotics, antidepressants, theophylline, or systemic corticosteroids	Exercise extreme caution when coadministering with these drugs
Dopaminergic Drugs (e.g. Levodopa and Amantadine)	CNS toxicity can occur when used concomitantly with Contrave

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on fertility from the combined use of naltrexone and bupropion. No effect on fertility was observed with bupropion in rats at oral doses up to 300 mg/kg/day (approximately 8 times the maximum recommended human dose of bupropion provided by CONTRAVE, based on body surface area). Naltrexone administered orally to rats caused a significant increase in pseudopregnancy and a decrease in pregnancy rates at 100 mg/kg/day, approximately 30 times the naltrexone dose provided by CONTRAVE. The relevance of these observations to human fertility is not known.

Use in pregnancy – Pregnancy Category B3

CONTRAVE is contraindicated in pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. CONTRAVE should not be used during pregnancy or in women currently attempting to become pregnant. If CONTRAVE is used during pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

There are no or limited amounts of data from the use of naltrexone/bupropion in pregnant women. The combination has not been tested in reproductive toxicity studies.

Naltrexone increased the incidence of early fetal loss when administered to rats at oral doses ≥ 30 mg/kg/day (9 times the maximum recommended therapeutic dose, based on body surface area) and to rabbits at oral doses ≥ 60 mg/kg/day (36 times the maximum recommended therapeutic dose, based on body surface area). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of organogenesis at doses up to 200 mg/kg/day (approximately 60 and 120 times the maximum recommended therapeutic dose, based on body surface area, in the respective species).

Studies in pregnant mice, rats and rabbits showed no evidence of adverse effects on embryofetal development at oral doses up to 100, 450 and 150 mg/kg/day, respectively. In mice and rats, administration of bupropion in late gestation had no effects on parturition. The predictive value of these studies is limited by low exposure. In mice and rabbits, systemic exposure (based on AUC) to bupropion and its metabolites achieved at these dose levels is expected to be less than in humans at the maximum recommended therapeutic dose. In rats, exposure to bupropion was up to approximately twice, and to its metabolites was less than, human exposure.

Use in lactation

Naltrexone and bupropion and their metabolites are excreted in human milk.

Since there is limited information on the systemic exposure to naltrexone and bupropion in infants/newborns being breast-fed, a risk to the newborns/infants cannot be excluded.

CONTRAVE is not recommended for nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

CONTRAVE may affect the ability to perform tasks that require judgment or motor and cognitive skills. When driving vehicles or using machines, it should be taken into account that dizziness, somnolence, loss of consciousness and seizure may occur during treatment (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)). Patients should therefore exercise caution before driving or use of machinery until they are reasonably certain CONTRAVE does not adversely affect their performance.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

CONTRAVE was evaluated for safety in five double-blind placebo-controlled studies in 4,754 overweight or obese subjects (3,239 subjects treated with CONTRAVE and 1,515 subjects treated with placebo) for a treatment period up to 56 weeks.

In clinical studies, 23.8% of subjects receiving CONTRAVE and 11.9% of subjects receiving placebo discontinued treatment due to an adverse event. The most frequent adverse reactions leading to discontinuation with CONTRAVE were nausea, headache, dizziness and vomiting.

Tabulated Summary of Adverse Reactions

The safety profile of CONTRAVE presented below is based on clinical studies performed with the fixed-dose combination (adverse reactions at an incidence of at least 0.1% and twice that of placebo) and/or post marketing data sources.

The frequencies of adverse reactions are ranked according to the following: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2: Adverse reactions reported in subjects who received CONTRAVE

System Organ Class	Frequency	Adverse Reaction
Blood and Lymphatic System Disorders	Common	Lymphocyte count decreased
Cardiac Disorders	Common	Palpitations
	Uncommon	Tachycardia
Ear and Labyrinth Disorders	Common	Tinnitus, Vertigo
	Uncommon	Motion sickness
Gastrointestinal Disorders	Very Common	Nausea, Constipation, Vomiting
	Common	Dry mouth, Toothache[a], Abdominal pain upper
	Uncommon	Lower abdominal pain, Eructation, Lip swelling, Dental caries[a], Haematochezia, Hernia
	Not Known	Abdominal discomfort, Dyspepsia
General Disorders and Administration Site Conditions	Common	Feeling jittery
	Uncommon	Feeling abnormal, Asthenia, Thirst, Feeling hot
	Not known	Fatigue
Hepatobiliary Disorders	Uncommon	Cholecystitis, Hepatic enzymes increased
Metabolism and Nutrition Disorders	Uncommon	Dehydration
Immune System Disorders	Uncommon	Urticaria (NB)
	Very rare	Angioedema
Psychiatric Disorders	Uncommon	Abnormal dreams, Nervousness, Dissociation (feeling spacey), Tension, Agitation, Mood swing.
	Not Known	Anxiety, Hallucination, Insomnia, Irritability, Panic attack
Nervous System Disorders	Common	Dizziness, Tremor, Dysgeusia, Disturbance in attention, Lethargy
	Uncommon	Intention tremor, Balance disorder, Amnesia, Mental impairment, Presyncope
	Not Known	Headache Serotonin syndrome*

System Organ Class	Frequency	Adverse Reaction
Vascular Disorders	Common	Hot flush Hypertension**
Investigations	Uncommon	Increased blood creatinine, Decreased haematocrit
Musculoskeletal and Connective Tissue Disorders	Uncommon	Intervertebral disc protrusion, Jaw pain
Renal and Urinary Disorders	Uncommon	Micturition urgency
Reproductive System and Breast Disorders	Uncommon	Irregular menstruation, Vaginal haemorrhage, Erectile dysfunction, Vulvovaginal dryness
Skin and Subcutaneous Tissue Disorders	Common	Hyperhidrosis, Pruritus, Alopecia
	Not known	Rash, Erythema multiforme and Stevens Johnson syndrome, Acute generalised exanthematous pustulosis (AGEP)

a - Toothache and dental caries, while not meeting the criteria for inclusion in this table, are listed based on the subset of patients with dry mouth, in which a higher incidence of toothache and dental caries was observed in subjects treated with CONTRAVE versus placebo.

* - Serotonin syndrome may occur as a consequence of an interaction between bupropion and a serotonergic medicinal product such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (see section 4.4 and 4.5).

** - Post-marketing cases of hypertensive crisis have been reported during the initial titration phase.

Description of selected adverse reactions

Seizures: The incidence of seizure in CONTRAVE over the course of the clinical program was 0.06% (2/3239 subjects). Among the group of subjects treated with CONTRAVE, both cases of seizures were considered as serious and led to treatment discontinuation (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). There were no cases of seizures in the placebo group.

Gastrointestinal adverse reactions: The incidence of the most common gastrointestinal adverse reactions for CONTRAVE 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 constipation, or vomiting was low, but was higher in subjects treated with CONTRAVE compared to subjects treated with placebo (severe nausea: CONTRAVE 1.9%, placebo <0.1%; severe constipation: CONTRAVE 0.6%, placebo 0.1%; severe vomiting: CONTRAVE 0.7%, placebo 0.3%). No events of nausea, constipation, or vomiting were considered serious.

Most subjects treated with CONTRAVE 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, most constipation events were reported during the dose escalation phase. The time to resolution of constipation was similar between subjects treated with CONTRAVE and subjects treated with placebo. Approximately half of the subjects treated with CONTRAVE 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.

Other frequent adverse reactions: The majority of subjects treated with CONTRAVE who reported dizziness, headache, insomnia, or dry mouth, first reported these events during the dose escalation phase. Dry mouth may be associated with toothache and dental caries; in the subset of patients with dry mouth, a higher incidence of toothache and dental caries were observed in subjects treated with CONTRAVE compared to subjects treated with placebo. The incidence of

severe headache, severe dizziness, and severe insomnia was low, but was higher in subjects treated with CONTRAVE compared to subjects treated with placebo (severe headache: CONTRAVE 1.1%, placebo 0.3%; severe dizziness: CONTRAVE 0.6%, placebo 0.2%; severe insomnia: CONTRAVE 0.4%, placebo <0.1%). No events of dizziness, dry mouth, headache, or insomnia in subjects treated with CONTRAVE were considered serious.

Elderly patients

Elderly patients may be more sensitive to some of the central nervous system-related adverse reactions of CONTRAVE (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 CONTRAVE demonstrated a higher incidence of gastrointestinal adverse events, primarily nausea, vomiting, and diarrhoea, 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 CONTRAVE at a total daily dose of 32 mg naltrexone / 360 mg bupropion, which is thought to be due to higher plasma concentrations of active metabolites. The types of tolerability events were similar to the events observed in patients with normal renal function (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 5 PHARMACOLOGICAL PROPERTIES).

Post-marketing data:

Nervous system disorders

Rare frequency: loss of consciousness, syncope

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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

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 these overdose 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 subjects recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in subjects ingesting large doses of the drug.

Serotonin syndrome has also been reported.

Naltrexone

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

Overdose Management

In case of an overdose, provide supportive care, including close medical supervision and monitoring. An adequate airway, oxygenation, and ventilation should be ensured. Cardiac rhythm and vital signs should be monitored. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended.

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

No antidotes are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: A08AA Centrally acting anti-obesity products,

ATC code: A08AA62 bupropion and naltrexone.

Mechanism of action

The exact neurochemical appetite suppressant effects of naltrexone/bupropion (NB) are not fully understood. The medicinal product has two components: naltrexone, a mu-opioid antagonist, and bupropion, a moderately weak inhibitor of neuronal reuptake of dopamine and norepinephrine. These components affect two principal areas of the brain, specifically the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic reward system. 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, the area associated with regulation of reward pathways.

In the arcuate nucleus of the hypothalamus, bupropion stimulates pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH), which in turn binds to and stimulates melanocortin 4 receptors (MC4-R). When α-MSH is released, POMC neurons

simultaneously release β-endorphin, an endogenous agonist of the mu-opioid receptors. Binding of β-endorphin to mu-opioid receptors on POMC neurons mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH. Blocking this inhibitory feedback loop with naltrexone is proposed to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying the effects of bupropion on energy balance. *In vitro* and *in vivo* data in mice suggest that naltrexone and bupropion may have greater than additive effects in this region to reduce food intake when administered together.

Clinical trials

The effects of CONTRAVE on weight loss in conjunction with reduced caloric intake and increased physical activity, were examined in double-blind, placebo-controlled trials (BMI range 27 to 45 kg/m^2) with study durations of 16 to 56 weeks randomised to naltrexone hydrochloride (16 to 50 mg/day) and/or bupropion hydrochloride (300 to 400 mg/day) or placebo.

Effect on weight loss and weight maintenance

Four 56-week Phase 3 multicentre, double-blind, placebo-controlled obesity trials (NB-301, NB-302, NB-303 and NB-304) were conducted to evaluate the effect of CONTRAVE in conjunction with lifestyle modification in 4,536 subjects randomised to CONTRAVE or placebo. The NB-301, NB-302 and NB-303 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 dyslipidaemia). The NB-304 trial enrolled patients with BMI greater than 27 kg/m^2 with type 2 diabetes with or without hypertension and/or dyslipidaemia.

Treatment was initiated with a 3-week dose escalation period followed by approximately 1 year of continued therapy. Patients were instructed to take CONTRAVE with food. NB-301 and NB-303 included a program consisting of a reduced-calorie diet, behavioural counselling, and increased physical activity. NB-302 included an intensive behavioural modification program as well as a prescribed diet and exercise regimen. NB-304 evaluated patients with type 2 diabetes not achieving glycaemic goal of HbA1c less than 7% either with oral antidiabetic agents or with diet and exercise alone. Of the overall population of 4,536 subjects in these trials, 25% had hypertension, 33% had fasting glucose levels ≥5.6 mmol/L at baseline, 54% had dyslipidaemia at study entry, and 11% had type 2 diabetes. The mean age was 46 years, 83% were female and 77% Caucasian. At baseline, mean BMI was 36 mg/kg^2 and mean waist circumference was 110 cm. The two co-primary endpoints were percent change from baseline body weight and the proportion of subjects achieving ≥5% total decreased body weight.

NB-301 study subjects had a mean percent body weight loss of -5.4% while receiving CONTRAVE compared to -1.3% in placebo-treated subjects (Table 3). Weight loss of at least 5% baseline body weight was observed more frequently for subjects treated with CONTRAVE (31%) compared to placebo (12%) (Table 4). 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 NB-303, 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 4).

CONTRAVE was also evaluated in combination with intensive behavioural modification counselling in NB-302. There was greater mean weight loss from baseline for CONTRAVE

treatment (-8.1%) compared to NB-301 (-5.4%) at Week 56, and for placebo (-4.9%) compared to NB-301 (-1.3%).

The treatment effects observed in obese and overweight subjects with type 2 diabetes mellitus (Study NB-304) were less pronounced than those observed in the other Phase 3 studies. However, CONTRAVE (-3.7%) was significantly ($p<0.001$) more efficacious than placebo (-1.7%) treatment in this population.

Table 3: Mean Weight Loss (% Change) from Baseline to Week 56 in CONTRAVE Studies NB-301, NB-302, and NB-304 and from Baseline to Week 28 in Study NB-303

	56-Week Data						**28-Week Data**	
	NB-301		**NB-302**		**NB-304**		**NB-303**	
	NB	**PBO**	**NB**	**PBO**	**NB**	**PBO**	**NB**	**PBO**
Intent-to-Treat Analysis Set[+]								
N	538	536	565	196	321	166	943	474
Baseline (kg)	99.8	99.5	100.3	101.8	104.2	105.3	100.4	99.4
LS Mean (95% CI) % Change From Baseline	-5.4* (-6.0, -4.8)	-1.3 (-1.9, -0.7)	-8.1* (-8.8, -7.4)	-4.9 (-6.1, -3.7)	-3.7* (-4.3, -3.1)	-1.7 (-2.5, -0.9)	-5.7* (-6.1, -5.3)	-1.9 (-2.4, -1.4)
Completers Analysis Set[++]								
N	296	290	301	106	175	100	619	319
Baseline (kg)	99.8	99.2	101.2	100.4	107.0	105.1	101.2	99.0
LS Mean (95% CI) % Change From Baseline	-8.1 (-9.0, -7.2)	-1.8 (-2.7, -0.9)	-11.5 (-12.6, -10.4)	-7.3 (-9.0, -5.6)	-5.9 (-6.8, -5.0)	-2.2 (-3.4, -1.0)	-7.8 (-8.3, -7.3)	-2.4 (-3.0, -1.8)

CI, Confidence Interval; LS, Least Squares.
95% confidence intervals calculated as LS Mean ± 1.96 × Standard Error.

[+] Subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement during the defined treatment phase. Results are based on last-observation-carried-forward (LOCF).

[++] Subjects who have a baseline and a post-baseline body weight measurement and completed 56 weeks (Studies NB-301, NB-302, and NB-304) or 28 weeks (NB-303) of treatment.

* Difference from placebo, $p<0.001$.

The percentages of subjects with ≥5% or ≥10% body weight loss from baseline were greater with CONTRAVE compared to placebo in all four Phase 3 obesity trials (Table 4).

Table 4: Percentage (%) of Subjects losing ≥5% and ≥10% of Body Weight from Baseline to Week 56 in studies NB-301, NB-302, and NB-304 and from Baseline to Week 28 in Study NB-303

	56-Week Data						**28-Week Data**	
	NB-301		**NB-302**		**NB-304**		**NB-303**	
	NB	**PBO**	**NB**	**PBO**	**NB**	**PBO**	**NB**	**PBO**
Randomized Population[+]								
N	583	581	591	202	335	170	1001	495
≥5% Weight	31*	12	46**	34	28*	14	42*	14
≥10% Weight Loss	17*	5	30*	17	13**	5	22*	6
Completers[++]								
N	296	290	301	106	175	100	619	319
≥5% Weight Loss	62	23	80	60	53	24	69	22
≥10% Weight Loss	34	11	55	30	26	8	36	9

\+ With baseline observation carried forward (BOCF)

++ Subjects who have a baseline and a post-baseline body weight measurement and completed 56 weeks (Studies NB-301, NB-302, and NB-304) or 28 weeks (NB-303) of treatment.

* Difference from placebo, $p<0.001$

** Difference from placebo, $p<0.01$

Of the subjects with observed data at Week 16 in the four Phase 3 clinical trials, 50.8% of those randomised to receive CONTRAVE had lost ≥5% of their baseline body weight, compared to 19.3% of placebo-treated subjects (Week 16 Responders). At one year, the average weight loss (using LOCF methodology) among these Week 16 Responders who received CONTRAVE was 11.3%, with 55% losing ≥10% bodyweight. Additionally, Week 16 Responders who received CONTRAVE had a high retention rate with 87% completing 1 year of treatment.

Effect on cardiovascular and metabolic parameters

Improvements were observed for waist circumference (including subjects with type 2 diabetes), triglycerides, HDL-C and LDL-C/HDL-C ratio for subjects treated with CONTRAVE vs. placebo in all Phase 3 studies. Improvements in triglycerides, HDL-C and LDL-C/HDL-C ratio were seen in CONTRAVE-treated subjects diagnosed with baseline dyslipidaemia irrespective of dyslipidaemia treatment. Changes in mean blood pressure are described in section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE. In addition, in subjects who did not have type 2 diabetes, there were reductions in fasting insulin and HOMA-IR, a measure of insulin resistance, in CONTRAVE-treated subjects.

Effects on glycaemic control in obese subjects with type 2 diabetes

After 56 weeks of treatment in subjects with type 2 diabetes (NB-304), CONTRAVE exhibited improvements in glycaemic control parameters compared to placebo. Greater HbA1c improvement compared to placebo was observed at the first post-baseline measurement (Week 16, $p<0.001$). Mean HbA1c change from baseline at week 56 was -0.63% for subjects treated with CONTRAVE compared to subjects on placebo -0.14% ($p<0.001$). In subjects with baseline HbA1c >8% (64 mmol/mol), HbA1c changes at endpoint were -1.1% and -0.5% for CONTRAVE compared to placebo, respectively. Improvements were observed for fasting glucose, fasting

insulin, HOMA-IR and percent of subjects requiring rescue diabetes medicinal products for subjects treated with CONTRAVE vs. placebo.

Effect on body composition

In a subset of 124 subjects (79 CONTRAVE, 45 placebo), body composition was measured using dual energy X-ray absorptiometry (DEXA). The DEXA assessment showed that treatment with CONTRAVE was associated with a significantly greater decrease from baseline in total fat mass than placebo ($p<0.001$).

Long term Use

Pivotal studies evaluated the use of CONTRAVE for up to 52 weeks. Long term efficacy and safety data is limited.

5.2 PHARMACOKINETIC PROPERTIES

The results of a single dose relative bioavailability study in healthy subjects demonstrated that naltrexone/bupropion tablets, when dose adjusted, are bioequivalent based on $AUC_{0-\infty}$ mean ratio and 90% confidence intervals to naltrexone immediate release (IR) or bupropion prolonged release (PR) administered as single agents.

Absorption

Following single oral administration of naltrexone/bupropion tablets to healthy subjects, peak concentrations of naltrexone and bupropion occurred approximately 2 and 3 hours post administration of naltrexone/bupropion, respectively. There were no differences in bioavailability, as measured by AUC, of naltrexone or bupropion when administered in combination compared to each administered alone. However, given the prolonged nature of the drug release for naltrexone/bupropion, C_{max} for naltrexone was markedly reduced compared to the 50 mg naltrexone hydrochloride IR administered alone (about 2-fold difference after dose adjustment). The bupropion C_{max} from naltrexone/bupropion (180 mg bupropion hydrochloride) was equivalent to the C_{max} of bupropion PR (150 mg bupropion hydrochloride), indicating that the bupropion C_{max} achieved with naltrexone/bupropion (360 mg bupropion hydrochloride/day) is comparable to that achieved with commercially available bupropion PR (300 mg bupropion hydrochloride/day) administered alone.

Naltrexone and bupropion are well absorbed from the gastrointestinal tract (>90% absorbed), however, naltrexone has a significant first pass effect thereby limiting systemic bioavailability, with only 5-6% reaching the systemic circulation intact.

Distribution

The mean volume of distribution at steady state of oral naltrexone and bupropion given as naltrexone/bupropion, V_{SS}/F, was 5697 litres and 880 litres, respectively.

Plasma protein binding is not extensive for naltrexone (21%) or bupropion (84%) indicating low potential for drug interactions by displacement.

Metabolism

Following single oral administration of naltrexone/bupropion tablets to healthy subjects, mean $T_{½}$ elimination half-life was approximately 5 hours for naltrexone and 21 hours for bupropion.

When naltrexone/bupropion was given with a high-fat meal the AUC and C_{max} for naltrexone increased 2.1-fold and 3.7-fold and the AUC and C_{max} for bupropion increased 1.4-fold and 1.8-fold, respectively. At steady state, the food effect resulted in AUC and C_{max} increases of 1.7- and 1.9-fold for naltrexone, and 1.1- and 1.3-fold for bupropion, respectively. Clinical experience included varying prandial conditions and supports the use of naltrexone/bupropion tablets with food.

Naltrexone

The major metabolite of naltrexone is 6-beta-naltrexol. Naltrexone is primarily metabolised to 6-beta-naltrexol by the dihydrodiol dehydrogenases (DD1, DD2 and DD4). 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.

Other major metabolic routes are the formation of the metabolites 2-hydroxy-3-O-methyl naltrexone and 2-hydroxy-3-O-methyl-6-beta-naltrexol, believed to be mediated by catechol-O-ethyl transferases (COMT), and glucuronidation, thought to be mediated by UGT1A1 and UGT2B7.

Bupropion

Bupropion is extensively metabolised 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, while CYP1A2, 2A6, 2C9, 3A4 and 2E1 are less involved. In contrast, formation of threohydrobupropion has been reported in the literature to be mediated by 11-beta-hydroxysteroid dehydrogenase 1. The metabolic pathway responsible for the formation of erythrohydrobupropion is unknown.

Excretion

Following twice daily administration of CONTRAVE, naltrexone does not accumulate, while 6-beta-naltrexol accumulates over time. Based on its half-life, 6-beta-naltrexol is estimated to reach steady state concentrations in approximately 3 days. Metabolites of bupropion, and to a lesser extent unchanged bupropion, accumulate and reach steady-state concentrations in approximately one week.

Naltrexone

Naltrexone and its metabolites are excreted primarily by the kidney (37 to 60% of the dose). The derived value for renal excretion of naltrexone after oral administration, adjusting for plasma protein binding, is 89 mL/min. The enzyme responsible for the main elimination pathway is not known. Faecal excretion is a minor elimination pathway.

Bupropion

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

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

Special Populations

Elderly

The pharmacokinetics of naltrexone/bupropion has not been evaluated in the elderly population. Because naltrexone and bupropion metabolic products are excreted in the urine and elderly people are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatic impairment

Pharmacokinetic data is not available with CONTRAVE in patients with hepatic impairment.

Based on information available from published literature and the existing product labels 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 cirrhosis exhibiting moderate-to-severe hepatic impairment. CONTRAVE is contraindicated in patients with severe hepatic impairment and is not recommended in patients with mild or moderate hepatic impairment.

Renal impairment

A single-dose pharmacokinetic study has been conducted for CONTRAVE in subjects with mild, moderate, and severe renal impairment, compared with subjects with normal renal function. The results from this study demonstrated that the area under the curve for plasma naltrexone and metabolites and for plasma bupropion and metabolites was increased by less than two-fold in patients with moderate and severe renal impairment, and smaller increases were observed for patients with mild renal impairment. Based on these results, there are no dose adjustments recommended for patients with mild renal impairment. For patients with moderate or severe renal impairment, the maximum recommended daily dose for CONTRAVE should be reduced. CONTRAVE is contraindicated in end-stage renal failure (see sections DOSE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line (Chinese hamster ovary), 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 (mouse lymphoma), a chromosomal aberration assay and an assay for DNA damage in human cells (WI-38; lung fibroblasts). Naltrexone did not exhibit clastogenicity *in vivo* in bone marrow micronucleus assays conducted in mice and rats, and did not induce translocations in the spermatozoa of treated mice.

Genotoxicity tests showed that bupropion did not cause gene mutations in bacterial or mammalian cells *in vitro*, chromosomal damage *in vitro* or DNA damage *in vivo*. An increase in chromosomal aberrations was observed in one of three *in vivo* rat bone marrow cytogenetic studies.

Carcinogenicity

No carcinogenicity studies have been performed with naltrexone and bupropion in combination.

In a two-year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males, and tumours of vascular origin in males and females. The incidence of mesotheliomas in males given naltrexone at a dietary dose of 100 mg/kg/day was 6%, compared with a historical incidence of 4%. The incidences of vascular tumours in males and females given dietary doses of 100 mg/kg/day (30 times the maximum recommended therapeutic dose, based on body surface area) 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 2-year dietary study with naltrexone in male and female mice involving dosing at up to 100 mg/kg/day (15 times the maximum recommended therapeutic dose, based on body surface area). It should be noted that the potential carcinogenicity of the major human metabolite, 6β-naltrexol, has not been addressed in these studies as mice and rats do not form appreciable quantities of this metabolite.

Lifetime carcinogenicity studies were performed in rats and mice at oral doses up to 300 and 150 mg/kg/day, respectively. In male rats and male and female mice, systemic exposure (based on AUC) to bupropion and its metabolites at these dose levels was less than in humans at the maximum recommended therapeutic dose. In female rats, exposure to bupropion was up to approximately 4-fold, and to its metabolites was less than, human exposure. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day and this may be secondary to hepatic enzyme induction. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumours of the liver and other organs was seen in either study.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, hyprolose, lactose, cysteine hydrochloride monohydrate, crospovidone, magnesium stearate, hypromellose, disodium edetate, lactose monohydrate, silicon dioxide, OPADRY II complete film coating system 85F90663 BLUE and indigo carmine aluminium lake.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

CONTRAVE tablets are presented in PVC/PCTFE/PVC/Aluminium blister packs.

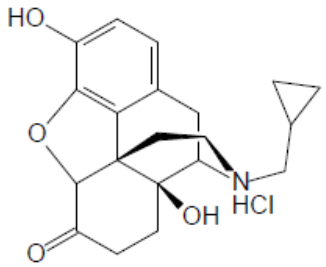
Pack size: 112 and 28 (starter pack) tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

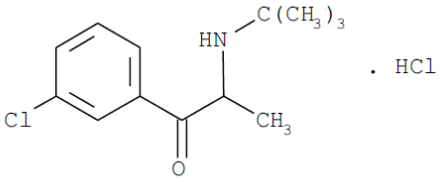
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Naltrexone HCl
Molecular formula: $C_{20}H_{23}NO_4.HCl$
Molecular weight: 377.86



Bupropion HCl
Molecular formula: $C_{13}H_{18}ClNO.HCl$
Molecular weight: 276.2

The chemical name of naltrexone hydrochloride is (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. It is a white to yellowish, crystalline compound and is soluble in water to the extent of about 100 mg/ml.

The chemical name of bupropion is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water.

CAS number

Naltrexone HCl - 16676-29-2

Bupropion HCl - 31677-93-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited
Level 10, 12 Help St,
Chatswood, NSW 2067

Toll-free Number: 1800 630 056

9 DATE OF FIRST APPROVAL

24 August 2018

10 DATE OF REVISION

19 July 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Header	Removal of the Black Triangle Scheme

® = Registered trademark