PROFESSIONAL INFOMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

CONTRAVE 8 mg/90 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

8 mg naltrexone hydrochloride and 90 mg bupropion hydrochloride.

Contains sugar:

lactose anhydrous 30 mg/tablet and lactose monohydrate 45,5 mg/tablet.

For the full list of excipients, refer to section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Blue film coated round biconvex tablet, plain on one side and debossed on the other side with “NB-890”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

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/m2 (obese), or
- ≥ 27 kg/m2 to < 30 kg/m2 (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).

4.2 Posology and method of administration

Posology

Adults

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

- Week 1: One tablet in the morning.
- Week 2: One tablet in the morning and one tablet in the evening.
- Week 3: Two tablets in the morning and one tablet in the evening.
- Week 4 and onwards: Two tablets in the morning and two tablets in the evening.

The maximum recommended daily dose of CONTRAVE is two tablets taken twice daily for a total dose of 32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride.

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

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

Special populations

Elderly patients (over 65 years)

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 sections 4.4, 4.8 and 5.2).

Patients with renal impairment

CONTRAVE is contraindicated in patients with end-stage renal failure (see section 4.3). 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) (see sections 4.4, 4.8 and 5.2). 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**.

Patients with hepatic impairment

CONTRAVE is contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2). **CONTRAVE** is not recommended in patients with mild or moderate hepatic impairment.

Paediatric population

The safety and efficacy of CONTRAVE in children and adolescents below 18 have not yet been established. Therefore, CONTRAVE should not be used in children and adolescents below 18 (see section 4.3).

Method of administration

Oral use. The tablets should be swallowed whole with some water. The tablets should preferably be taken with food (see section 5.2). The tablets should not be cut, chewed, or crushed.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1;
- Patients with uncontrolled hypertension (see section 4.4);
- Patients with a current seizure disorder or a history of seizures (see section 4.4);
- Patients with a known central nervous system tumour
- Patients undergoing acute alcohol or benzodiazepine withdrawal;
- Patients with a history of bipolar disorder;
- Patients receiving any concomitant treatment containing bupropion or naltrexone;
- Patients with a current or previous diagnosis of bulimia or anorexia nervosa;
- Patients currently dependent on chronic opioids (see sections 4.4 and 4.5) or opiate agonists (e.g., methadone), or patients in acute opiate withdrawal;

- Patients receiving concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with CONTRAVE (see section 4.5);
- Patients with severe hepatic impairment (see sections 4.2 and 5.2);
- Patients with end-stage renal failure (see sections 4.2 and 5.2).;
- Children under 18 years of age.

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).

Suicide and suicidal behaviour

CONTRAVE contains bupropion. 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 naltrexone or bupropion 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, with bupropion sustained release (SR) 300 mg yielding an estimated seizure incidence of 0,1 %. Plasma

concentrations of bupropion and metabolites of bupropion following single dose administration of 180 mg of bupropion as CONTRAVE tablets are comparable to concentrations observed after single dose administration of bupropion SR 150 mg; however, no study has been conducted that determined the concentrations of bupropion and metabolites of bupropion after repeated dosing of CONTRAVE tablets compared to bupropion SR tablets. As it is unknown whether the risk for seizure with bupropion is related to bupropion or a metabolite of bupropion, and there are no data demonstrating comparability of plasma concentrations with repeated dosing, there is uncertainty whether repeated dose administration CONTRAVE may be associated with a similar rate of seizures as bupropion SR 300 mg. 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 outcome 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 medicinal products, which must be considered in the selection of patients treated 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.

CONTRAVE is contraindicated in patients with central nervous system tumour, severe hepatic impairment, current or previous diagnosis of bulimia or anorexia nervosa, or withdrawal from sedatives (see section 4.3).

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 (see section 4.3). If chronic opiate therapy is required, CONTRAVE treatment must be stopped. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued, and opiate dose should not be increased above the standard dose. During CONTRAVE clinical studies, the use of concomitant opioid or opioid like medicinal products, including analgesics or antitussives were excluded. However, approximately 12 % of subjects took a concomitant opioid or opioid like medicinal product while enrolled in the CONTRAVE clinical studies, the majority of whom continued study treatment without interruption of CONTRAVE dose, without untoward consequences.

Attempt to overcome blockade: The attempt 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 aware that they may be more sensitive to lower doses of opioids after treatment with CONTRAVE is discontinued.

Allergic reactions

Anaphylactoid/anaphylactic reactions characterized 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, Stevens Johnson syndrome, 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.

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.

Elevation of blood pressure

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 a cardiovascular outcome trial (CVOT) of patients at increased risk of a cardiovascular event, mean increases from baseline in systolic and diastolic blood pressure of approximately 1 mmHg compared to placebo were also observed. In clinical practice with other bupropion containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. 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).

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. CONTRAVE should be used with caution in patients with active coronary artery disease (e.g., ongoing angina or recent history of myocardial infarction) or history of cerebrovascular disease.

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

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.

Elderly patients

Clinical studies of CONTRAVE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Elderly patients may be more sensitive to the central nervous system adverse reactions 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, a condition that is more common in elderly individuals. Due to these reasons, CONTRAVE should be used with caution in patients over 65 years of age and is not recommended in patients over 75 years of age.

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 (see sections 4.2, 4.8, and 5.2). 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.

Hepatic impairment

CONTRAVE has not been evaluated in subjects with hepatic impairment. CONTRAVE is contraindicated in patients with severe hepatic impairment, and not recommended in patients with mild or moderate hepatic impairment (see sections 4.2, 4.8, and 5.2).

In patients with mild hepatic 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 (see sections 4.2 and 5.2)

Serotonin Syndrome

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when naltrexone/bupropion was co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.5 and 4.8). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g nausea, vomiting, diarrhoea). If serotonin syndrome is suspected, a discontinuation of therapy should be considered.

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 naletrexone/bupropion. The cases occurred mostly during the initial titration phase and following dose changes. Naltrexone/bupropion should be used with caution in patients with a history of psychiatric disorders.

Data in animals suggest a potential for abuse of bupropion. However, studies on abuse liability in humans and extensive clinical experience show that bupropion has low abuse potential.

Influence on the ability to drive and use machines

The use of CONTRAVE has been associated with somnolence and episodes of loss of consciousness, sometimes caused by seizure. Patients must be advised to exercise caution while driving or operating machines during treatment with CONTRAVE, especially at the beginning of the treatment or during the titration phase. Patients who experience dizziness, somnolence, loss of consciousness or seizure should be advised to avoid driving or operating machines until these adverse effects have resolved. Alternatively, treatment cessation might be considered (see sections 4.7 and 4.8).

Lactose

Contains lactose. Patients with hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take CONTRAVE.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOI)

Since monoamine oxidase A and B inhibitors also enhance the catecholaminergic pathways, by a different mechanism from bupropion, CONTRAVE must not be used with MAOI (see section 4.3).

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).

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, antidiarrhoeal 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). 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.

Drugs metabolised by cytochrome P450 (CYP) enzymes

Bupropion is metabolised to its major active metabolite hydroxybupropion primarily by the cytochrome P450 CYP2B6; thus, the potential exists for interaction when administered with medicinal products that induce or inhibit CYP2B6. Although not metabolised by the CYP2D6 isoenzyme, bupropion and its main metabolite, hydroxybupropion, inhibit the CYP2D6 pathway and the potential exists to affect medicinal products metabolised by CYP2D6.

CYP2D6 substrates

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 bupropion 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., propafenone and flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medicinal product. Although citalopram is

not primarily metabolised by CYP2D6, in one study, bupropion increased the Cmax and AUC of citalopram by 30 % and 40 %, respectively.

There have been post-marketing reports of serotonin syndrome, a potentially life-threatening condition, when naltrexone/bupropion was co-administered with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) (see section 4.4 and 4.8).

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. 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 medicinal product should be considered, particularly for those concomitant medicinal products with a narrow therapeutic index. When feasible, the option of therapeutic drug monitoring should be considered for medicinal products with a narrow therapeutic index, such as tricyclic antidepressants.

<u>CYP2B6 inducers, inhibitors and substrates</u>

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

Since bupropion is extensively metabolised, caution is advised when CONTRAVE is co administered with medicinal products known to induce CYP2B6 (e.g., carbamazepine, phenytoin, ritonavir, efavirenz) as these may affect the clinical efficacy of CONTRAVE. 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.

Co administration of medicinal products that may inhibit the metabolism of bupropion via CYP2B6 isoenzyme (e.g., CYP2B6 substrates: cyclophosphamide, ifosfamide, and CYP2B6

inhibitors: orphenadrine, ticlopidine, clopidogrel), may result in increased bupropion plasma levels and lower levels of active metabolite hydroxybupropion. The clinical consequences of the inhibition of the metabolism of bupropion via CYP2B6 enzyme and the consequent changes in the bupropion hydroxybupropion ratio are currently unknown, but could potentially lead to reduced efficacy of naltrexone / bupropion.

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 CONTRAVE are likely due to inhibition of OCT2 and not indicative of changes in creatinine clearance. Use of CONTRAVE with other OCT2 substrates (e.g., metformin) in clinical trials did not indicate the need for dose adjustment or other precautions.

Other interactions

Although clinical data do not identify a pharmacokinetic interaction between bupropion and alcohol, 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.

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

- 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

CONTRAVE is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors, bupropion or naltrexone, patients undergoing acute alcohol or benzodiazepine withdrawal, patients currently dependent on chronic opioids, or opiate agonists (see Section 4.3).

Administration of CONTRAVE to patients receiving either levodopa or amantadine concurrently should be undertaken with caution. Limited clinical data suggest a higher incidence of adverse reactions (e.g., nausea, vomiting, and neuropsychiatric adverse reactions – see section 4.8) in patients receiving bupropion concurrently with either levodopa or amantadine.

Administration of CONTRAVE with inhibitors or inducers of UGT 1A2 and 2B7 should be undertaken with caution as these may alter the exposure of naltrexone.

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

CONTRAVE has not been studied in conjunction with alpha adrenergic blockers or clonidine.

Since bupropion is extensively metabolised, caution is advised when CONTRAVE is co administered with medicinal products known to inhibit metabolism (e.g. valproate), as these may affect its clinical efficacy and safety.

CONTRAVE should preferably be taken with food, as it is known that both naltrexone and bupropion plasma concentrations are increased with food and the safety and efficacy data from clinical trials is based on dosing with food.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amounts of data from the use CONTRAVE in pregnant women. The combination has not been tested in reproductive toxicity studies. Studies with naltrexone in animals have shown reproductive toxicity (see section 5.3); animal studies with bupropion show no clear evidence of reproductive harm. The potential risk for humans is unknown.

CONTRAVE should not be used during pregnancy or in women currently attempting to become pregnant.

Breast feeding

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 should not be used during breast feeding.

Fertility

There are no data on fertility from the combined use of naltrexone and bupropion. No effect on fertility in reproductive toxicity studies have been observed with bupropion. Naltrexone administered orally to rats caused a significant increase in pseudopregnancy and a decrease in pregnancy rates at approximately 30 times the naltrexone dose provided by CONTRAVE. The relevance of these observations to human fertility is not known (see section 5.3).

4.7 Effects on ability to drive and use machines

CONTRAVE has an influence on the ability to drive and use machines. When driving vehicles or using machines, it should be taken into account that dizziness, somnolence, loss of consciousness and seizure may occur during treatment.

Patients should be cautioned about driving or operating hazardous machinery in case CONTRAVE may affect their ability to engage in such activities (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

CONTRAVE was evaluated for safety in five double blind placebo controlled studies in 4754 overweight or obese subjects (3239 subjects treated with CONTRAVE and 1515 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 for CONTRAVE are nausea, constipation, vomiting, dizziness, and dry

mouth. The most frequent adverse reactions leading to discontinuation with CONTRAVE were nausea, headache, dizziness and vomiting.

Tabulated summary of adverse reactions

Adverse reactions reported with the fixed dose combination

The safety profile of CONTRAVE (NB) 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.

Certain expected side effects

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).

System Organ Class	Frequency	Adverse Reaction (Medicinal Product*)
Infections and Infestations	Uncommon	Oral herpes (N), Tinea pedis (N)
Blood and Lymphatic System Disorders	Common	Lymphocyte count decreased (NB)
	Uncommon	Lymphadenopathy (N)
	Rare	Idiopathic thrombocytopenic purpura (N)
Immune System Disorders**	Common	Hypersensitivity reactions such as urticaria (B)
	Uncommon	Urticaria (NB)
	Very rare	Angioedema (NB), More severe hypersensitivity reactions including angioedema, dyspnoea/ bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness. (B)
Metabolism and Nutrition Disorders	Common	Decreased appetite (N)
	Uncommon	Dehydration (NB), Anorexia (B)
	Rare	Blood glucose disturbances (B)

Psychiatric Disorders	Very common	Anxiety (N), Insomnia (N,B)
	Common	Irritability (N), Affective disorders (N), Depression (B), Anxiety (B)
	Uncommon	Abnormal dreams (NB,N)[a], Nervousness (NB,N)[a], Dissociation (feeling spacey) (NB), Tension (NB), Agitation (NB,N,B)[a], Mood swings (NB), Confusional state (N), Depression (N), Hallucination (N), Paranoia (N), Disorientation (N), Nightmare (N), Libido disorder (N), Confusion (B)
	Rare	Irritability (B), Suicidal ideation (N), Attempted suicide (N), Hostility (B), Hallucinations (B), Depersonalisation (B), abnormal dreams including nightmares (B)
	Very Rare	Delusions (B), Paranoid ideation (B), Restlessness (B), Aggression (B)
	Not known	Suicidal ideation and suicidal behaviour (B)****, Psychosis (B), Anxiety (NB), Hallucination (NB), Insomnia (NB), Irritability (NB), Panic attack (NB)
Nervous System Disorders	Very common	Headache (N), Restlessness (N)
	Common	Dizziness (NB,N,B)[a], Tremor (NB,N,B)[a], Dysgeusia (NB), Disturbance in attention (NB), Lethargy (NB), Concentration disturbance (B), Headache (B), Somnolence (NB), Taste disorders (B)

	Uncommon	Intention tremor (NB), Balance disorder (NB), Amnesia (NB), Mental impairment (NB), Presyncope (NB), Somnolence (N)
	Rare	Dystonia (B), Ataxia (B), Parkinsonism (B), Incoordination (B), Loss of consciousness (NB), Memory impairment (B), Paraesthesia (B), Syncope (B), Seizures(B)***
	Not known	Headache (NB) Serotonin syndrome (NB)******
Eye Disorders	Common	Lacrimation increased (N)
	Uncommon	Vision blurred (N), Eye irritation (N), Eye swelling (N), Eye pain or asthenopia (N), Photophobia (N), Visual disturbance (B)
Ear and Labyrinth Disorders	Common	Tinnitus (NB,N,B)[a], Vertigo (NB,N)[a]
	Uncommon	Motion sickness (NB), Ear pain (N), Ear discomfort (N)
Cardiac Disorders	Common	Palpitations (NB,N,B)[a], Electrocardiogram change (N)
	Uncommon	Tachycardia (NB,N,B)[a]
Vascular Disorders	Common	Hot flush (NB)
	Uncommon	Blood pressure fluctuation (N), Increased blood pressure (sometimes severe) (B), Flushing (N,B)
	Rare	Vasodilation (B), Postural hypotension (B)
	Not known	Hypertension (NB)

Respiratory, Thoracic, and Mediastinal Disorders	Common	Chest pain (N)
	Uncommon	Nasal congestion (N), Nasal discomfort (N), Rhinorrhea (N), Sneezing (N), Oropharyngeal pain (N), Sputum increased (N), Sinus disorder (N), Dyspnoea (N), Dysphonia (N), Cough (N), Yawning (N)
Gastrointestinal Disorders	Very Common	Abdominal pain (N), Nausea (NB,N)[a], Constipation (NB,N,B)[a], Vomiting (NB,N)[a]
	Common	Dry mouth (NB,N,B)[a], Toothache (NB)[b], Abdominal pain upper (NB), Diarrhoea (N), Gastrointestinal disturbance including nausea and vomiting (B), Abdominal pain (B)
	Uncommon	Lower abdominal pain (NB), Eructation (NB) Lip swelling (NB), Dental caries (NB)[b], Haematochezia (NB), Hernia (NB), Flatulence (N), Haemorrhoids (N), Ulcer (N)
	Not known	Abdominal discomfort (NB), Dyspepsia (NB)
Hepatobiliary Disorders	Uncommon	Cholecystitis (NB), Liver disorder (N), Blood bilirubin increased (N), Hepatitis (N), Hepatic enzymes increased (NB)
	Rare	Jaundice (B), Hepatitis (B)
Skin and Subcutaneous Tissue Disorders	Common	Hyperhidrosis (NB), Pruritus (NB,N,B)[a], Alopecia (NB,N)[a], Rash (N,B), Sweating (B)
	Uncommon	Acne (N), Seborrhoea (N)
	Rare	Erythema multiforme and Stevens Johnson syndrome (B), Exacerbation of psoriasis (B)

	Not known	Rash (NB) Cutaneous lupus erythematosus (NB) Systemic lupus erythematosus syndrome aggravated (NB)
Musculoskeletal and Connective Tissue Disorders	Very common	Arthralgia (N), Myalgia (N)
	Uncommon	Intervertebral disc protrusion (NB), Jaw pain (NB), Groin pain (N)
	Rare	Twitching (B)
	Very rare	Rhabdomiolysis (N)
Renal and Urinary Disorders	Uncommon	Micturition urgency (NB), Pollakiuria (N), Dysuria (N)
	Rare	Urinary frequency and/or retention (B)
Reproductive System and Breast Disorders	Common	Ejaculation delayed (N)
	Uncommon	Irregular menstruation (NB), Vaginal haemorrhage (NB), Erectile dysfunction (NB,N)[a], Vulvovaginal dryness (NB)
General Disorders and Administration Site Conditions	Common	Feeling jittery (NB), Energy increased (N), Chills (N), Fever (B), Hyperhidrosis (N)
	Uncommon	Feeling abnormal (NB), Asthenia (NB,N,B)[a], Thirst (NB,N)[a], Feeling hot (NB,N)[a], Increased appetite (N), Weight gain (N), Pyrexia (N), Peripheral coldness (N), Pain (N), Chest Pain (B)
	Not known	Fatigue (NB)
Investigations	Uncommon	Increased blood creatinine (NB), Decreased haematocrit (NB)

* N = Naltrexone; B = Bupropion; NB = Naltrexone/Bupropion

** Hypersensitivity may manifest as skin reactions. See “Immune system disorders” and “Skin and subcutaneous tissue disorders”.

*** The incidence of seizures is approximately 0,1 % (1/1000). The most common type of seizures is generalised tonic clonic seizures, a seizure type which can result in some cases in post ictal confusion or memory impairment (see section 4.4).

**** Cases of suicidal ideation and suicidal behaviour have been reported during bupropion therapy (see section 4.4).

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

****** 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 Re-uptake Inhibitors (SNRIs) (see section 4.4 and 4.5).

[a] Adverse reactions were listed in the NB frequency category if observed in NB and in one or both of the individual components.

[b] 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 NB versus placebo.

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). There were no cases of seizures in the placebo group.

Gastrointestinal adverse reactions: The vast majority of 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, the majority of events of constipation in subjects treated with

CONTRAVE 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. The incidence of these common gastrointestinal adverse reactions in 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, severe constipation, and severe 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.

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, 4.4, and 5.2).

4.9 Overdose

Human overdose experience

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

Bupropion

Acute ingestion of doses in excess of 10 times the maximum therapeutic dose of bupropion (equivalent to approximately in excess of 8 times the recommended daily dose of naltrexone / bupropion) has 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 CONTRAVE) for up to one week showing no evidence of toxicity.

Overdose management

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 should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of combined use of bupropion and naltrexone overdoses. No specific antidotes for combined use of bupropion and naltrexone are known.

Due to the dose related risk of seizures with bupropion, hospitalisation following suspected overdose with CONTRAVE should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological class: A 11.3 Anorexigenics

Mechanism of action and pharmacodynamic effects

The exact neurochemical appetite suppressant effects CONTRAVE are not fully understood. The medicinal product has two components: naltrexone, a mu opioid antagonist, and bupropion, a weak inhibitor of neuronal dopamine and norepinephrine reuptake. These components affect two principal areas of the brain, specifically the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic reward system.

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. Preclinical data suggests that naltrexone and bupropion may have greater than additive effects in this region to reduce food intake when administered together.

<u>Clinical efficacy and safety</u>

The effects of CONTRAVE on weight loss, weight maintenance, waist circumference, body composition, obesity related markers for cardiovascular and metabolic parameters and patient reported assessments were examined in double blind, placebo controlled obesity Phase 2 and Phase 3 trials (BMI range 27 45 kg/m2) 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 multicentre, double blind, placebo controlled obesity Phase 3 studies (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. Treatment was initiated with a dose escalation period. Three of these studies (NB 301, NB 302 and NB 304) designated the primary endpoint at 56 weeks, and 1 study (NB 303)

designated the primary endpoint at week 28, but continued for 56 weeks. Studies NB 301, NB 303, and NB 304 included periodic instruction from the study sites to reduce caloric intake and increase physical activity, while NB 302 included an intensive behavioural modification program consisting of 28 group counselling sessions over 56 weeks, as well as a prescribed rigorous diet and exercise regimen. NB 304 evaluated subjects with type 2 diabetes not achieving glycaemic goal of HbA1c <7% (53 mmol/mol) with oral anti diabetes agents or on diet and exercise alone. NB 303 included a re-randomization in a blinded manner and the addition of a higher dose of naltrexone (naltrexone hydrochloride 48 mg/bupropion hydrochloride 360 mg) at week 28 to half of the cohort of subjects in the active treatment arm who did not adequately respond to treatment, and as such the primary endpoint comparing weight change with 32 mg naltrexone hydrochloride /360 mg bupropion hydrochloride vs. placebo was evaluated at week 28.

Of the overall population of 4,536 subjects in the CONTRAVE Phase 3 studies, 25 % had hypertension, 33 % had fasting glucose levels ≥ 100 mg/dL (5.6 mmol/L) at baseline, 54 % had dyslipidaemia at study entry, and 11 % had type 2 diabetes.

In the combined Phase 3 studies, the mean age was 46 years, 83 % were female, and 77 % were White, 18 % were Black and 5 % were other races. Baseline mean BMI was 36 kg/m2 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. Data summaries for mean change in body weight reflect the Intent to Treat (ITT) population, defined as subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement during the defined treatment phase, using a last observation carried forward (LOCF) analysis, as well as a completers analysis. Summaries of the proportion of subjects achieving ≥ 5 % or ≥ 10 % reduction in body weight utilize a baseline observation carried forward (BOCF) analysis of all randomized subjects. Overall adherence was similar between trials, and similar between treatment groups. Treatment adherence rates for the integrated Phase 3 studies

were: 67% NB vs. 74 % Placebo at 16 weeks, 63 % NB vs. 65 % Placebo at 26 Weeks, 55 % NB vs. 55 % Placebo at 52 Weeks.

In the 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. Weight loss of at least 5% baseline body weight was observed more frequently for subjects treated with CONTRAVE (31 %) compared to placebo (12 %). 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 NB 303 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.

CONTRAVE was also evaluated in combination with intensive behavioural modification counselling in the NB 302 study. Correspondingly, there was greater mean weight loss from baseline for CONTRAVE treatment (- 8,1 %) compared to study NB 301 (5,4 %) at Week 56, and for placebo (- 4,9 %) compared to study NB 301 (- 1,3 %).

The treatment effects observed in obese and overweight subjects with type 2 diabetes mellitus (Study NB 304) were somewhat less pronounced than those observed in the other Phase 3 studies. CONTRAVE (- 3,7 %) was significantly ($p < 0,001$) more efficacious than placebo (1,7 %) treatment in this population.

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.

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). 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. 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 favourable early response.

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. 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 naltrexone / bupropion-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 subjects, body composition was measured using dual energy X ray absorptiometry (DEXA) (CONTRAVE = 79 subjects and placebo = 45 subjects) and multislice computed tomography (CT) scan (CONTRAVE = 34 subjects and placebo = 24

subjects). The DEXA assessment showed that treatment with CONTRAVE was associated with greater reductions from baseline in total body fat and in visceral adipose tissue than placebo. As expected, CONTRAVE treated subjects had a greater mean increase from baseline compared with placebo treated subjects in percent of total body lean mass. These results suggest that most of the total weight loss was attributable to a reduction in adipose tissue, including visceral adipose.

Paediatric population

No studies have been performed in children and adolescents under the age of 18. CONTRAVE should not be used in children and adolescents.

5.2 Pharmacokinetic properties

The results of a single dose relative bioavailability study in healthy subjects demonstrated that CONTRAVE tablets, when dose adjusted, are bioequivalent based on AUC0-∞ 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 CONTRAVE, 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 CONTRAVE (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 CONTRAVE (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 bioavailablity, with only 5 6% reaching the systemic circulation intact.

Food effect:

When CONTRAVE 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 CONTRAVE tablets with food.

Distribution:

The mean volume of distribution at steady state of oral naltrexone and bupropion given as CONTRAVE, Vss/F, was 5697 liters and 880 liters, respectively.

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

Biotransformation and elimination:

Following single oral administration of CONTRAVE tablets to healthy subjects, mean T½ elimination half life was approximately 5 hours for naltrexone and 21 hours for bupropion.

<u>Naltrexone</u>

The major metabolite of naltrexone is 6 beta naltrexol. Though less potent than naltrexone, 6 beta naltrexol is eliminated more slowly and thus circulates at much higher concentrations than naltrexone. Naltrexone and 6 beta naltrexol are not metabolised by cytochrome P450 enzymes and in vitro studies indicate that there is no potential for inhibition or induction of important isozymes. Naltrexone is primarily metabolized to 6 beta naltrexol by the dihydrodiol dehydrogenases (DD1, DD2 and DD4). 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-methyl transferases (COMT), and glucuronidation, thought to be mediated by UGT1A1 and UGT2B7.

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

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. 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.

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.

Following oral administration of 200 mg of 14C bupropion hydrochloride 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.

Accumulation:

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 unmetabolised bupropion) accumulate and reach steady state concentrations in approximately one week. No study has been performed comparing AUC or Cmax of CONTRAVE prolonged release tablets with bupropion PR or naltrexone IR

administered as single agents in the multiple dose setting (i.e., under steady state conditions).

Special populations

Gender and race: Pooled analysis of CONTRAVE data revealed no meaningful gender or race related differences in the pharmacokinetic parameters of bupropion or naltrexone. However, only Caucasian and Black subjects were investigated to a significant extent. No dosage adjustment is necessary based on gender or race.

Elderly people: The pharmacokinetics of CONTRAVE have 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. CONTRAVE is not recommended in patients over 75 years of age.

Smokers: Pooled analysis of CONTRAVE data revealed no meaningful differences in the plasma concentrations of bupropion or naltrexone in smokers compared to nonsmokers. 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 nonsmokers. Following oral administration of a single 150 mg dose of bupropion hydrochloride, there was no statistically significant difference in Cmax, half-life, Tmax, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

Hepatic impairment: Pharmacokinetic data are 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 (see section 4.2). CONTRAVE is contraindicated in end-stage renal failure (see section 4.3).

5.3 Preclinical safety data

The effects of combined bupropion and naltrexone use have not been studied in animals. Non-clinical data on individual components reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Any effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. However, there is some evidence on hepatotoxicity with increasing dose, since reversible increases of liver enzymes have been found in humans with therapeutic and higher doses (see section 4.4 and 4.8). Liver changes are seen in animal studies with bupropion but these reflect the action of a hepatic enzyme inducer. At recommended doses in humans, bupropion does not induce its own metabolism. This suggests that the hepatic findings in laboratory animals have only limited importance in the evaluation and risk assessment of bupropion.

<u>Reproduction toxicity:</u>

Naltrexone (100 mg/kg/day, approximately 30 times the dose of naltrexone in CONTRAVE on a mg/m2 basis) caused a significant increase in pseudo pregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known. Naltrexone has been shown to have an embryocidal effect in rats dosed with 100 mg/kg/day of naltrexone (30 times the CONTRAVE dose) prior to and throughout gestation, and in

rabbits treated with 60 mg/kg/day of naltrexone (36 times the CONTRAVE dose) during the period of organogenesis.

A fertility study of bupropion in rats at doses up to 300 mg/kg/day, or 8 times the bupropion dose provided by CONTRAVE revealed no evidence of impaired fertility.

Genotoxicity:

Naltrexone was negative in the following in vitro genotoxicity studies: bacterial reverse mutation assay (Ames test), the heritable translocation assay, CHO cell sister chromatid exchange assay, and the mouse lymphoma gene mutation assay. Naltrexone was also negative in an in vivo mouse micronucleus assay. In contrast, naltrexone tested positive in the following assays: Drosophila recessive lethal frequency assay, non-specific DNA damage in repair tests with E. coli and WI 38 cells, and urinalysis for methylated histidine residues. The clinical relevance of these equivocal findings is unknown.

Genotoxicity data indicate that bupropion is a weak bacterial mutagen, but not a mammalian mutagen, and therefore is of no concern as a human genotoxic agent. Mouse and rat studies confirm the absence of carcinogenicity in these species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

L-Cysteine Hydrochloride

Microcrystalline Cellulose

Hydroxypropyl Cellulose

Magnesium Stearate

Lactose Anhydrous

Lactose Monohydrate

Crospovidone type A

FD&C Blue #2 Aluminium Lake (E132)

Hypromellose

Edetate Disodium

Colloidal Silicon Dioxide

Film-coating:

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol 3350

Talc

FD&C Blue #2 Aluminium Lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store at or below 30°C

6.5 Nature and contents of container

PVC/PCTFE/PVC/Aluminium blisters. 28 tablets per blister.

Pack size: blisters are packed in a carboard box containing 112 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand,

1686

8 REGISTRATION NUMBER

52/11.3/0478

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 July 2020

10 DATE OF REVISION OF THE TEXT

25 April 2023

Registration No.:
Namibia (NS3): 20/32.2/0114

REFERENCES		
1.	Approved EU SmPC, Mysimba 8mg/90 mg	Module 1.3.1.2.1
2.	PVC (PVC 110) USRN – 20 March 2023	Module 1.0 Attachment 1