# Naltrexone and bupropion for weight management in adults June 2015

## Summary

### Background and licensed indication

Naltrexone and bupropion prolonged-release tablets (Mysimba™ Orexigen Therapeutics Ireland Limited), is a new treatment option for weight management as an adjunct to a reduced calorie diet and increased physical activity. It was approved in the EU in March 2015 (1) and is indicated for use in adults with a body mass index (BMI) ≥ 30 (obesity), or adults with a BMI of ≥ 27 (overweight) who have at least one weight related condition such as controlled hypertension, type 2 diabetes or dyslipidaemia. (1) Treatment should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. In the USA it is launched as Contrave™.

### Dosing

TWO prolonged release tablets containing naltrexone 8mg / bupropion 90 mg TWICE daily. (2) The dose should be increased slowly over four weeks starting with ONE tablet daily: doses should be reduced in renal and hepatic impairment. (2)

### Alternatives

- Weight management programmes
- Pharmacological therapy with orlistat
- Weight loss surgery

### NICE

There is no timeline for a NICE TA (3)

### Clinical studies

- The EMA approval was based the results of four phase 3, multicentre, double-blind, placebo-controlled clinical trials which included a total of 4,536 obese and overweight adults, with and without weight related clinical conditions, treated for one year. (4-7)
- These studies were conducted to evaluate the effect of naltrexone / bupropion in conjunction with lifestyle modification. COR-I, COR-II and COR-BMOD enrolled patients without diabetes, and COR-Diabetes included patients with type 2 diabetes with or without hypertension and or dyslipidaemia.
- Exclusion criteria included existing or previous severe cardiovascular events. Seizure risks, and a clinically diagnosed eating disorder or other serious psychiatric disorder.
- The co-primary end points of % change from baseline body weight and % of patients achieving at least 5% reduction in body weight were achieved across all trials with a mean placebo subtracted weight loss of around 4%.

### Safety

Naltrexone and bupropion are already approved for use in the EU for other indications and so there is some additional safety information to accompany the safety findings from the clinical trials programme for this indication. In the clinical trials for weight management in obese and overweight adults, the most frequently reported adverse effects were nausea, headache, constipation, dizziness, vomiting and dry mouth. (8) Increases in resting heart rate and blood pressure were also reported. When used for other indications, bupropion caused agitation, anxiety, insomnia and (rarely) seizures. Naltrexone has been reported to cause elevations in aminotransferases and hepatotoxicity. The use of antidepressants, including bupropion, has also been associated with suicidal thoughts and behaviour and serious neuropsychiatric reactions. (8)

### Convenience

Mysimba™ is an oral treatment option for obese and certain overweight adults. The alternatives; weight management programmes including psychosocial support are not always effective. Pharmacological therapy with orlistat is limited by the gastrointestinal side effects. Mysimba™ may also offer an alternative to surgery in certain patients.

### Risk assessment

Naltrexone and bupropion are already in clinical use, however there are still unknown risks associated with the use of this combination in overweight and obese adults, with cardiovascular and other comorbidities. Further analysis of ongoing clinical trials, will provide fuller understanding of the risks.

### Budget impact

In 2011, 24% of men and 26% of women (>16 years) were classed obese in England. The UK price not available.

### Funding

CCG commissioned.

### Suggested place in therapy

Naltrexone / bupropion may be considered as a treatment option for obese adults, or for overweight adults who have at least one weight related condition. (1) It should be used alongside diet and exercise and treatment should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

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1. Background and introduction

Naltrexone hydrochloride and bupropion hydrochloride 8mg / 90mg, prolonged release tablets (Mysimba™ Orexigen Therapeutics Ireland Limited), is a new treatment option for weight management, in adults, as an adjunct to a reduced calorie diet and increased physical activity. Naltrexone is an opioid antagonist, and bupropion, a relatively weak inhibitor of the neuronal reuptake of dopamine and noradrenaline. (4) Nonclinical studies suggest that naltrexone and bupropion have effects on two separate areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory centre) and the mesolimbic dopamine circuit (reward system). The exact neurochemical effects of Mysimba™ leading to weight loss are not fully understood. (4) It was approved in the EU in March 2015. (1) In the USA, the FDA licensed this drug under the trade name Contrave™ in September 2014. (1,9)

Mysimba™ is indicated for use in adults:
- with a body mass index (BMI) or 30 kg/m² or greater (obese) or
- with a BMI of 27 kg/m² or greater (overweight) who have at least one weight related condition such as controlled hypertension, type 2 diabetes or dyslipidaemia. (1)

Treatment with Mysimba™ should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

Mysimba™ is a combination of two approved medicines; naltrexone and bupropion in a prolonged release formulation. Naltrexone is already used to treat alcohol and opioid dependence and bupropion is already used to treat depression and seasonal affective disorder and as an aid to smoking cessation treatment. The exact licensed indications of both bupropion and naltrexone may differ in the UK and the US. (9,10)

Obesity is a global problem and a major risk factor for several chronic diseases including cardiovascular disease, type 2 diabetes, fatty liver disease, gallstones, gastro-oesophageal reflux disease, and reduced quality of life with cancer. (11, 12) In England obesity rates have nearly doubled between 1993 and 2011, from 12% to 24% in men and from 16% to 26% in women. (12)

Alternative therapies include:
- Weight management programs; dietary advice, weight loss targets, physical activity programmes, behavioural interventions and psychosocial support.
- Pharmacological therapy with orlistat, the only drug licensed and available in the UK for weight management. Drug therapy should only be considered in patients who have seriously attempted weight loss through weight management programmes. (12,13) Treatment with orlistat should be considered as an adjunct to life style interventions for people with BMI ≥ 30 kg/m², or a BMI ≥ 28 kg/m² and associated risk factors (such as type 2 diabetes, hypertension, or dyslipidaemia). In the USA, lorcaserin and phentermine/topiramate and liraglutide are also approved for weight management. (14) In March 2015 liraglutide was approved in the EU for chronic weight management in adults who have obesity or are overweight with comorbidities. Novo Nordisk plan to launch liraglutide 3mg for this indication in the EU and US in 2015. (15) There is an LMEN review of sub-cutaneous liraglutide for this indication in progress.
- Weight loss surgery may be an option if non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months in people with BMI ≥ 40 kg/m², or a BMI ≥ 35 kg/m² and other significant comorbidities (for example type 2 diabetes, hypertension, obstructive sleep apnoea and severe mobility problems) that could be improved if they lost weight. Surgery is the first line option in adults with BMI ≥ 50 kg/m² (0.8% of the obese population). (12,13)

There is guidance from NICE on the treatment of overweight and obese adults. (12) In the UK, pharmacological intervention of obesity with orlistat is recommended as a treatment option in people with a BMI of 30 kg/m² or greater or 28 kg/m² and greater with associated risk factors. (13)

2. Proposed place in therapy

Naltrexone / bupropion may be considered a treatment option for obese adults (BMI ≥ 30kg/m²), or for overweight adults (BMI ≥ 30kg/m²) who have at least one weight related condition such as controlled hypertension, type 2 diabetes or dyslipidaemia. (1)

It should be used an adjunct to a reduced calorie diet and increased physical activity and treatment should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. If licensed, this will be an alternative pharmacological intervention licensed for weight loss in the UK, the other being is orlistat. Two other pharmacological interventions for weight loss have been licensed in the UK (sibutramine and rimonabant), but they were subsequently withdrawn due to safety concerns. (16)

3. Evidence selected for inclusion

The licence application for naltrexone / bupropion prolonged release tablets for weight management, is based on four key phase 3 clinical trials: (1,4-7)

The phase 3 clinical trials programme included 4,536 overweight or obese adults treated for on year. Patients were excluded based on existing or previous severe cardiovascular events, such as congestive heart failure (Class III or IV), history of myocardial infarction, angina, acute limb ischaemia within the last six months or a history of stroke. Based on increased seizure risks associated with bupropion, patients were also excluded if they had a history of seizures, were predisposed to seizures (e.g. head trauma), had a clinically diagnosed eating disorder or had other serious psychiatric disorders (including depression and or suicidal ideation / attempts). (4-7, 14)
In 2010, Greenway et al published the COR-I study. (4) Patients (N=1,742) were randomised into one of three treatment groups: bupropion 360mg / naltrexone prolonged release (PR) 32mg / day, bupropion 360mg / naltrexone PR 16mg / day, or placebo. This 56 week trial included uncomplicated patients with a BMI of 30-45 kg/m² or patients with a BMI for 27-45 kg/m² who also had dyslipidaemia or hypertension. The primary endpoints were the percentage of weight loss and the proportion of patients achieving a weight loss of 5% or greater. The primary efficacy analysis included all patients with a post baseline weight measurement (N=1,453).

The percentage of weight loss was −1.3% in the placebo group, −5.0% in the 16mg group and −6.1% in the 32mg (p<0.001) and 50% of all patients completed the study.

In 2011 the COR-BMOD study was published. (5) In this trial, naltrexone / bupropion was combined with an intensive behaviour modification program (BMOD). Patients (N=793) were randomised at a 1:3 ratio into BMOD plus placebo or BMOD plus bupropion 360mg / naltrexone PR 32mg / day. This 56 week trial had the same inclusion criteria as COR-I. The co-primary endpoints were percentage of change in weight and the proportion of patients who lost ≥5% of the baseline weight at week 56. A modified population was used, which included patients with ≥1 post baseline weight measurement whilst taking the study drug (placebo plus BMOD N=193, naltrexone / bupropion plus BMOD N=482). At week 56, weight loss was 5.12% with placebo plus BMOD and 9.3% with bupropion 360mg / naltrexone PR 32mg / day plus BMOD (p<0.001). Of the patients completing the study, the weight loss was 7.3% (N=106) and 11.5% (N=301) respectively (p<0.001).

In 2013 Hollander et al (6) published. This trial was similar in design to COR-I and also incorporated a behaviour modification programme, but this had only two treatment arms: placebo versus placebo plus bupropion 360mg / naltrexone PR 32mg. At baseline, 12, 24, 36 and 48 weeks, patients received instructions to follow a hypocaloric diet (500 kcal/day deficit) and increase physical activity, and behavioural modification advice. Weight and vital signs were measured at each visit. Treatments were allocated in a 1:2 proportion (N=1,496). The co-primary endpoints were percentage of change in weight and the proportion of patients who lost ≥5% of the baseline weight at week 28. A greater weight loss was observed in the intervention group at week 28 (-6.5% vs – 1.9% p<0.001). As a secondary outcome there was an extension to 56 weeks and patients who had not achieved weight loss greater than 5% by week 28. Around 50% of patients were randomised to this extension and there was no significant difference in weight loss outcomes between these groups.

In 2013 Hollander et al (7) studied the effects of naltrexone / bupropion prolonged-release combination therapy on body weight and glycaemic parameters in overweight and obese patients with type 2 diabetes. The efficacy and safety of 32 mg naltrexone / 360 mg bupropion prolonged release tablets in overweight or obese patients with type 2 diabetes with or without background oral diabetic drugs were investigated in a 56-week, double-blind, placebo controlled study. Five hundred and five patients received standardised lifestyle intervention and were randomised 2:1 to naltrexone / bupropion or placebo. Co-primary end points were weight change and achievement of ≥5% weight loss. In the modified intent-to-treat population naltrexone / bupropion resulted in significantly greater weight reduction (-5.0 vs. -1.8%; p < 0.001) and proportion of patients achieving ≥5% weight loss (44.5 vs. 18.9%, p < 0.001) compared with placebo. Naltrexone / bupropion also resulted in significantly greater HbA1c reduction (-0.6 +/-0.1% [6.6 vs. 1.1 mmol/mol]; p < 0.001), percent of patients achieving HbA1c <7% (53 mmol/mol) (44.1 vs. 26.3%; p < 0.001), and improvement in triglycerides and HDL cholesterol compared with placebo. The authors of this study concluded that naltrexone / bupropion therapy in overweight / obese patients with type 2 diabetes induced weight loss, which was associated with improvements in glycaemic control and select cardiovascular risk factors and was generally well tolerated with a safety profile similar to that in patients without diabetes.

Table 1: Summary efficacy data from the four published phase 3 clinical studies are shown below:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Length of study</th>
<th>N</th>
<th>Objective</th>
<th>Placebo-subtracted weight loss (ITT analysis)</th>
<th>% achieving ≥5% weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR-I (4)</td>
<td>56 weeks</td>
<td>1,742</td>
<td>Compare safety and efficacy of two doses of naltrexone/bupropion prolonged release (PR) in overweight and obese adults</td>
<td>-4.8% at week 56 with bupropion 360mg plus naltrexone 32mg per day</td>
<td>48% vs. 16% with placebo</td>
</tr>
<tr>
<td>COR-BMOD (5)</td>
<td>56 weeks</td>
<td>793</td>
<td>Assess the safety and efficacy of naltrexone/bupropion PR in overweight and obese adults with controlled hypertension and / or dyslipidaemia with or without behaviour modification</td>
<td>-4.2% at week 56 with bupropion 360mg plus naltrexone 32mg per day and BMOD</td>
<td>54.3% vs 41.6% with BMOD only</td>
</tr>
<tr>
<td>COR-II (6)</td>
<td>28 weeks (with extension to 56 weeks)</td>
<td>1,496</td>
<td>Assess the safety and efficacy of naltrexone/bupropion PR in overweight and obese adults with controlled hypertension and/or dyslipidaemia with or without diet and exercise</td>
<td>-4.6% at week 28 with bupropion 360mg plus naltrexone 32mg per day</td>
<td>50.5% vs 17.1% with placebo</td>
</tr>
<tr>
<td>COR-diabetes (7)</td>
<td>56 weeks</td>
<td>505</td>
<td>Assess the safety and efficacy of naltrexone/bupropion PR in overweight and obese adults with diabetes.</td>
<td>3.2% with bupropion 360mg plus naltrexone 32mg per day</td>
<td>44.5% vs. 18.9% with placebo</td>
</tr>
</tbody>
</table>

In addition the LIGHT study, a phase 3 clinical trial, recruited 8,909 patients. It had been intended to run for four years and was designed to assess the cardiovascular health outcomes of the combination of bupropion and naltrexone in overweight and obese adults.
4. Critical evaluation

4.1. Clinical application

Patients included in the published phase 3 studies were aged 18-65 years (or 18-70 in COR-Diabetes) so the findings may not apply to older overweight or obese adults. Similarly, the breadth of the exclusion criteria limits the usefulness of the data in clinical practice in the wider population. Whilst the cardiovascular risks are being addressed in an ongoing study (the LIGHT study), the safety of naltrexone / bupropion in patients at risk of seizures or psychiatric complications has not been studied. The COR-I and COR-II studies comprised a generally healthy population of white middle aged women (who made up 80-85% of the population studied) and, due to adverse effects such as nausea and loss to follow up, the study completion rates were low; 50% in COR-I and 54% in COR-II - all groups. Women are more likely to seek pharmacotherapy for weight loss than are men, so these are common limitations of weight loss studies. Active cardiovascular disease and diabetes were excluded and so the safety findings may not be generalisable to patients with high cardiovascular risk. Data on adherence to diet and exercise regimens were not obtained; therefore the contribution of these interventions to the study outcome cannot be fully understood.

COR-BMOD was again a large study which included very few men, and very few patients with significant co-morbidities. The BMOD programme, consisted of an intensive programme which included having groups of patients meet on a regular basis with dieticians, behavioural psychologists and / or exercise specialists over the 56 weeks. This resulted in the BMOD only group achieving substantial weight loss compared to the ‘placebo-only’ groups of other studies. In addition, the results of the pre-specified modified ITT analysis excluded the 18.4% of naltrexone / bupropion plus BMOD patients who did not have a post baseline measurement of bodyweight on study drug. If the full ITT population had been used, i.e. for the entire randomised population, the results would have been more conservative.

Taken together, the data from the completed phase 3 clinical trials, meets the primary objectives. The mean placebo subtracted weight loss was around 4%. Putting this onto context, in COR-I and COR-II patients lost 5-6 kg corrected with respect to placebo and all patients weighed around 100 kg at the beginning of the study. Although modest, this weight loss is greater than with orlistat which in trials has demonstrated a mean efficacy placebo adjusted weight loss of 2.9% at one year with 54% of patients achieving ≥5% weight loss compared with 33% of placebo. (14) With no head to head studies of naltrexone / bupropion and orlistat, it is difficult to compare the results as the trials differed in design.

Safety

4.2.1. Key adverse events

The main safety and tolerability concerns identified with the naltrexone / bupropion combination relate to central nervous system and gastrointestinal adverse effects, adverse events, and uncertainties with regard to cardiovascular outcomes in the longer term. (1) Nausea is the most common adverse effect of the naltrexone / bupropion combination and this occurred in 30% of patients in the clinical trials (8). Intolerable nausea was a common cause of withdrawal from the study. Headache, constipation, dizziness, vomiting, dry mouth also occurred frequently and more often with the active drug than with placebo. Increases in resting heart (HR) rate and in blood pressure (BP) were reported in the clinical trials. (4,8)

Bupropion and naltrexone are both already being used (separately) in clinical practice so there are data available on adverse effects and events of both these agents. Used in about the same dosage for the treatment of depression, bupropion has caused agitation, anxiety, insomnia and (rarely) seizures. One seizure was reported in COR-II. (6)

The clinical significance of the increases in BP and HR are unclear, especially for patients with cardiac and cerebrovascular disease, since patients with a history of heart attack or stroke in the previous six months, life threatening arrhythmias, or congestive heart failure were excluded from the clinical trials. BP and pulse should be measured prior to starting the drug and at regular intervals, particularly among patients with controlled high blood pressure prior to treatment.

An interim analysis of an ongoing cardiovascular outcomes trial in overweight and obese adults with cardiovascular risk factors found that naltrexone / bupropion did not increase the risk of adverse cardiovascular events. (2,8)

In addition, and as a requirement of the US approval, there are two efficacy, safety, and clinical pharmacology studies in paediatric patients (one in patients 12-17 years and one in patients 7-11 years of age); a nonclinical (animal) juvenile toxicity study with a particular focus on growth and development as well as behaviour, learning, and memory; a study to evaluate the effect on cardiac conduction; clinical trials to evaluate dosing in patients with hepatic or renal impairment and a clinical trial to
A safety review of the four phase 3 clinical trials (14) made comparisons in terms of safety with other pharmacological interventions used for weight loss. Only orlistat is licensed and available for this indication in the UK, and it has a different mode of action. The usefulness of orlistat is however limited by its gastrointestinal side effects. Lorcaserin and a combination product containing phentermine/topiramate are licensed in the US but not approved for use in the UK. (14)

The presence of bupropion, a dopamine and noradrenaline reuptake inhibitor means that healthcare professionals should be alerted to the increased risk of suicidal thoughts and behaviours associated with antidepressant drugs. Serious neuropsychiatric events have also been reported in patients taking bupropion for smoking cessation. (9) The package insert for the US product Contrave™ contains a boxed warning about suicidal thoughts, behaviour and serious neuropsychiatric reactions. The clinical trial programme for naltrexone / bupropion did not find any associations with suicidality, although patients with a history of severe depression or suicidal ideation were excluded from the trials. (8) Naltrexone has been reported to cause elevations in aminotransferases and hepatotoxicity. (2)

4.2.2. Risk assessment.
Not available.

4.2. Potential advantages and disadvantages over existing technologies

4.2.1. Convenience
An oral medication taken twice a day for weight management, which may be convenient for patients.

4.2.2. Healthcare resource utilisation

4.2.3. Suitability for shared care
May be suitable for shared care, dependent of current local pathways and funding. The drug is initiated slowly over 4 weeks with doses being reduced in renal and hepatic impairment. There are also monitoring requirements in terms of compliance and adverse effects (e.g. BP monitoring). The exclusion criteria would also need to be clearly indicated (e.g. clients with history of seizures or serious psychiatric disorders. There may also need to be some monitoring of mental health state, anxiety, suicidal thoughts etc. As a result, it may be more suitable if this drug is initiated and stabilized in secondary care and then continued in primary care.

4.2.4. Drug cost and likely budgetary impact
No budget impact model or UK price available. In the USA Contrave™ is priced between $45 and $70 per month. (18)

5. Health Economics
No health economic data were identified.

6. Likely commissioning and funding pathway
Likely to be CCGs commissioned, dependent on locally agreed pathways.

7. Suggested place in therapy
Naltrexone / bupropion (Mysimba™) may be considered a treatment option for obese adults (BMI ≥30kg/m²), or for overweight adults (BMI ≥ 27kg/m²) who have at least one weight related condition such as controlled hypertension, type 2 diabetes or dyslipidaemia. (1) This license is almost identical to that for orlistat, but at a lower BMI of 27 with at least one associated risk factor as opposed to a BMI of >28 with associated risk factors (orlistat).

It should be used an adjunct to a reduced calorie diet and increased physical activity and treatment should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. Prescribers’ should be aware that data beyond one year is lacking, both in terms of efficacy and adverse effects and weight loss appears to tail off after around 30 weeks.

As there are no head to head studies with orlistat, it is unclear how this agent will be used in practice. It may be that it is considered in patients who have tried and failed with orlistat due to inefficacy or intolerable side effects. The adverse effect profile of the two drugs differs significantly, as they have a differing mechanism of action, so this may inform prescribing decisions. Until a price is known, it is difficult to speculate where naltrexone / bupropion might sit in a treatment pathway, and whether this would be at the same point as orlistat or later.

References

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Medline: *NALTREXONE/ AND *BUPROPION/
Embase: *AMFEBUTAMONE/ PLUS NALTREXONE/

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