MTRAC
Midlands Therapeutics Review and Advisory Committee

Considerations for Commissioners Naltrexone/bupropion *(Mysimba®▼)*

For the treatment of overweight and obesity

Commissioning considerations:
When making a decision about the use of naltrexone/bupropion, commissioners may wish to consider the following:

This guidance has been superseded.

According to the NICE technology appraisal on Naltrexone–bupropion for managing overweight and obesity (TA494):
Naltrexone–bupropion is not recommended within its marketing authorisation for managing overweight and obesity in adults alongside a reduced-calorie diet and increased physical activity.

This recommendation is due to the need for more certainty that naltrexone–bupropion will provide value for the NHS.

Strength of the evidence for efficacy
The evidence for naltrexone/bupropion was considered to be relatively strong. Four fully published randomised controlled trials (RCTs) evaluated naltrexone/bupropion as a weight loss treatment using patient-oriented outcomes for up to 56 weeks; but there was no comparison with another active pharmacological treatment i.e. orlistat. The trials were well reported, with a low risk of bias. Limitations of the trials included the low completion rates across the trials (50 to 58% completed.) The European public assessment report for Mysimba concluded that it had a moderate effect in weight management, which was considered to be clinically significant.

Description of technology

Naltrexone/bupropion is a fixed-dose combination tablet licensed as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients 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)

The Summary of Product Characteristics[1] (SPC) states that naltrexone/bupropion is a prolonged-release tablet containing 8 mg naltrexone hydrochloride and 90 mg bupropion hydrochloride (7.2 mg naltrexone+78 mg bupropion). The recommended starting daily dose is one tablet daily, escalated over a four-week period by one additional tablet per day each week. The recommended maintenance dose is four tablets daily, two in the morning and two in the evening. Treatment with naltrexone/bupropion should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

Background

In the UK, the prevalence of obesity increased from 13% of men in 1993 to 26% of men in 2013 and from 16% of women in 1993 to 24% of women in 2013.[2] NHS costs attributable to overweight and obesity are projected to reach £9.7 billion by 2050, with wider costs to society estimated to reach £49.9 billion per year.[2]

National guidance on the treatment of obesity focusses on weight loss due to diet and lifestyle interventions. Technology appraisal guidance on naltrexone bupropion advises that it was not recommended for use due to uncertainty that naltrexone–bupropion will provide value for the NHS. The alternative treatment options available include lifestyle measures alone, lifestyle measures with orlistat or bariatric surgery. The NICE clinical guideline 189[3] advises that orlistat should only be available as part of an overall plan for managing obesity in adults who meet one of the following BMI criteria:

- ≥ 28 kg/m^2 with associated risk factors
- ≥ 30 kg/m^2.

Orlistat should only be continued beyond 3 months if the person has lost at least 5% of their initial pre-treatment body weight. It is also available as a lower 60 mg over the counter medicine, and can be supplied within the terms of the marketing authorisation to adults over the age of 18 with a BMI ≥ 28 kg/m^2.

Clinical evidence for efficacy and safety

Four published, phase 3 RCTs (*COR-I*[4] and *COR-II*[5], *COR-BMOD*[6] and *COR-Diabetes*[7]) evaluated naltrexone/bupropion as an obesity treatment. *COR-I* and *COR-II* evaluated naltrexone/bupropion for weight loss in participants who were overweight (BMI ≥ 27 kg/m^2 and comorbidities [e.g. hypertension and/or dyslipidaemia]) or obese (BMI ≥ 30 kg/m^2). In the *COR-I*

trial[4] there were two active treatment groups taking naltrexone 16 mg/bupropion 360 mg *[unlicensed dose]* or naltrexone 32 mg/bupropion 360 mg daily, compared with placebo. In the *COR-II trial*,[5] the active treatment group received naltrexone 32 mg/bupropion 360 mg daily compared with placebo, but those participants who had not lost at least 5% of their baseline weight after at least 28 weeks of treatment were re-randomised to naltrexone 32 mg/bupropion 360 mg or naltrexone 48 mg/bupropion 360 mg daily *[unlicensed dose]*. The *COR-BMOD trial*[6] evaluated naltrexone 32 mg/bupropion 360 mg or placebo in addition to intensive behavioural modification to encourage weight loss in participants who were overweight or obese, and *COR-Diabetes*[7] evaluated naltrexone 32 mg/bupropion 360 mg for weight loss in patients with type 2 diabetes (HbA_{1c} between 7% [53 mmol/mol] and 10% [86 mmol/mol]) and a BMI in the range 27 to 45 kg/m^2.

The trials were all 56 weeks long, including a dose escalation period of 3-4 weeks during which the dose of naltrexone/bupropion was gradually increased to the maintenance dose. Other requirements were to follow a 500 kcal deficit diet and increase physical activity levels. The *COR-BMOD* trial included an intensive programme of behaviour modification including attendance at group sessions with a regular 'weigh in'.[6]

The co-primary outcomes were mean percentage change in weight from baseline, and the proportion of participants achieving ≥ 5% decrease from baseline weight after 56 weeks' treatment *(data from COR-II were reported for the first 28-week double-blind period only)*. Additional endpoints included the change in cardiometabolic risk factors (e.g. waist circumference, blood pressure), and the Impact of Weight on Quality of Life-Lite questionnaire (IWQoL-Lite).

Results

Weight loss: In the *COR-I* and *COR-II* trials treatment with naltrexone/bupropion 32 mg/360 mg resulted in a mean percentage weight loss from baseline of ~6% *vs.* 1 to 2% in placebo-treated participants ($p < 0.001$).[4,5] In the *COR-BMOD* trial, the percentage weight loss was 9.3% in naltrexone/bupropion 32 mg/360 mg treated participants *vs.* 5.1% in placebo-treated participants ($p < 0.001$).[6] With intensive behaviour modification the placebo group showed results approaching the levels of active treatment in the other trials. Participants in the *COR-Diabetes* trial showed -5% weight change from baseline, compared with -1.8% for placebo-treated participants ($p < 0.001$).[7] The proportions of participants treated with naltrexone/bupropion achieving ≥ 5% weight loss was 48% and 56% in the *COR-I* and *COR-II* trials respectively, *versus* about 17% of placebo-treated participants ($p < 0.001$).[4,5] In the *COR-BMOD* trial, 66% of participants achieved ≥5% weight loss *vs.* 42.5% of placebo participants; whilst in the *COR diabetes* trial 45% of participants achieved the 5% threshold *vs.* 19% with placebo treatment ($p < 0.001$, all comparisons).

Cardiometabolic factors: significantly greater improvements in waist circumference were reported with naltrexone/bupropion treatment *vs*. placebo ($p < 0.05$). Changes in systolic and diastolic blood pressure were small.

Weight-related quality of life: three trials reported this outcome[4-6] and found significantly greater improvements for all naltrexone/bupropion-treated groups compared with placebo.

Adverse events

Across the trials, discontinuation rates were high at 42-50% of participants. Withdrawals due to adverse events were significantly greater with active treatment (40-60%) than with placebo (20-30%; $p < 0.0001$).[4-6] Withdrawals due to insufficient weight loss and loss of consent were greater with placebo treatment ($p < 0.05$).[4-6] The most frequent treatment-emergent adverse events were nausea, headache, and constipation. Nausea and constipation were more common with active treatment than placebo ($p < 0.0001$) in two trials[5,6]. Headache was significantly more frequent with naltrexone/bupropion treatment than placebo in one trial ($p < 0.05$).[5]

There were no significant differences in the incidence of cardiac disorders or psychiatric disorders in naltrexone/bupropion-treated participants compared with placebo.[4-7]

Considerations for cost impact

- According to 2009 mid-year population estimates for the West Midlands,[8] there are approximately 1.1 million obese adults and 1.6 million overweight adults.
- Our estimate of the potential cost impact is based on the current US price of naltrexone/bupropion (as Contrave®) and your CCGs current use of prescribed orlistat 120 mg (DDDs). Use of naltrexone/bupropion in place of orlistat in 10% of patients would result in increased drug acquisition costs of £6.60-£15.70 per 1000 head of registered population.

References

1. Consilient Health Ltd. Mysimba 8 mg/90 mg prolonged-release tablets. EMC 2018
2. About Obesity. Public Health England 2015
3. Clinical Guideline 189 Obesity: identification, assessment and management of overweight and obesity in children, young people and adults. NICE 2014 http://www.nice.org.uk/guidance/cg189/resources/guidance-obesity-identification-assessment-and-management-of-overweight-and-obesity-in-children-young-people-and-adults-pdf
4. Greenway FL et al. COR-I. *Lancet* 2010; 376(9741):595-605.
5. Apovian CM et al. (COR-II. *Obesity (Silver Spring)* 2013; 21(5):935-943.
6. Wadden TA et al. COR-BMOD trial. *Obesity (Silver Spring)* 2011; 19(1):110-120.
7. Hollander P C et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 2013; 36(12):4022-4029.
8. Quality, Innovation, Productivity & Prevention: Obesity. Department of Health West Midlands 2011 http://nhfshare.heartforum.org.uk/RMAssets/OLC_Resources/West_Midlands/ObesityQIPP/2473_WM.pdf