NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Naltrexone–bupropion (prolonged-release) for overweight and obesity

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using naltrexone–bupropion in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using naltrexone–bupropion in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 30 May 2017

Second appraisal committee meeting: 8 June 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Naltrexone–bupropion is not recommended, within its marketing authorisation, for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults with a BMI of:

- 30 or more, or
- 27 to 30 with 1 or more weight-related co-morbidities.

1.2 This recommendation is not intended to affect treatment with naltrexone–bupropion that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Naltrexone–bupropion could not be recommended as an option for managing overweight and obesity because the committee could not reliably make a decision on the most likely estimate of cost effectiveness.

Naltrexone–bupropion provides an innovative option after lifestyle measures have failed, and where orlistat is the only pharmaceutical alternative. The comparative analysis showed that naltrexone–bupropion has similar efficacy to orlistat.

However, the committee had concerns about the validity of the economic analysis and the robustness of the results. It concluded that the economic model had important limitations in its structure, implementation, key assumptions, and clinical data used. Whilst some of the issues the ERG was able to explore, the issues around the model structure and its implementation were outside the scope of the ERG's additional analyses.

2 The technology

Naltrexone–bupropion (Mysimba)	
Marketing authorisation	Adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (aged 18 and over) with an initial body mass index (BMI) of • 30 or more (obese) or • from 27 to 30 (overweight) in the presence of one or more weight-related co-morbidities (such as type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment should be stopped after 16 weeks if the patient has not lost at least 5% of their initial body weight.
Recommended dose and schedule	Administered orally in a prolonged-release tablet. Dose is escalated over a 4-week period to a total dose of 32 mg naltrexone and 360 mg bupropion: week 1, 1 tablet in the morning; week 2, 1 tablet morning and evening; week 3, 2 tablets in the morning and 1 in the evening; from week 4, 2 tablets morning and evening.
Price	Acquisition cost (excluding VAT) £73.00 per pack of 112 tablets (source: company's submission). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Orexigen Therapeutics and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Current management and comparators

Weight management services are tiered

3.1 The clinical expert explained that weight management should follow current guidelines such as NICE's clinical guideline on obesity: identification, assessment and management. Weight management services are tiered: tier 1 (healthy lifestyle promotions), tier 2 (lifestyle weight management programmes), tier 3 (specialist weight management services including adjunct drug treatment) and tier 4 (bariatric surgery).

The type and quality of care varies greatly across England. The committee heard that there is a disproportionately low number of bariatric surgeries currently being undertaken in the NHS. Only around 0.1% of people eligible for bariatric surgery actually have it. The patient expert stressed that limited access to services can be demoralising for patients, and there is a need for more comprehensive and equitable services across the country.

Orlistat is the only relevant pharmacologically active comparator

3.2 The clinical expert explained that orlistat is the only drug treatment currently available, after lifestyle measures alone have failed. Its use is limited by undesirable side effects, leading to poor compliance and outcomes. The patient expert explained that orlistat causes unpleasant and socially unacceptable gastrointestinal side-effects. The committee heard from the clinical expert that naltrexone–bupropion does not have the same side-effects as orlistat and may be better tolerated. The clinical expert explained that naltrexone–bupropion provides a new treatment option with a novel mechanism of action. The committee concluded that there is a need for new treatment options and that orlistat is the only relevant active comparator for this appraisal.

Duration of treatment

Treatment for obesity is likely to be recurrent and ongoing

3.3 The patient expert explained that people who are overweight or obese can be caught in a cycle of weight loss and regain, which can be psychologically distressing. The clinical expert noted that when people stop treatment they do not continue to lose weight and many will regain weight. The committee noted that this will most likely lead to further courses of naltrexone–bupropion for many patients. The committee recognised that obesity is a chronic condition and that treatment with naltrexone–bupropion could be recurrent or long-term for many people.

Analysis

A full intention-to-treat analysis would have been more appropriate

3.4 The committee had concerns over the use of a modified intention-to-treat (ITT) analysis and noted this included people who had at least one post-baseline measurement of weight while on the study drug. This removed around 20% of people from the analyses, whereas the full-ITT population included as many people as possible from the point of randomisation into the trial (including all people who dropped out, whether a post-baseline weight measurement was taken or not). The ERG explained that a modified ITT analysis could bias results in favour of naltrexone–bupropion, because drop-out before the first assessment point could have been because people stopped treatment due to intolerance or adverse events related to the study drug. The committee agreed that the full-ITT analysis was more appropriate for decision-making.

Trial results

Trials showed that naltrexone–bupropion is more effective than placebo

3.5 The committee considered the clinical evidence presented by the company, which came from 4 contrave obesity research (COR) trials done in the US. All were double-blind randomised trials with either placebo or naltrexone–bupropion given as an adjunct to standard care (lifestyle measures):

- COR-I included people who were obese or overweight. At week 56, the modified ITT results showed a mean percentage reduction in weight with naltrexone–bupropion of 6.1% compared with 1.3% with placebo.

- COR-II included the same population as above. At week 28, the modified ITT results showed a mean percentage reduction in weight of 6.6% with naltrexone–bupropion compared with 2.1% with placebo.

- COR-BMOD included the same population as above but had an intensive standard care regimen. At week 56, the modified ITT results showed a mean percentage reduction in weight of 9.7% with naltrexone–bupropion compared with 5.5% with placebo.

- COR-DM included people who were obese or overweight and who had type 2 diabetes. At week 56, the modified ITT results showed a mean percentage reduction in weight with naltrexone–bupropion of 5.1% compared with 1.8% with placebo.

The committee considered that the trials were all good quality. However, the company presented the results for the modified-ITT population and the committee was mindful of the limitations of this analysis (see section 3.4). The committee noted that the full-ITT analysis in the clarification response similarly showed naltrexone–bupropion to be more effective than placebo in all 4 of the COR trials. It also noted that there was a smaller effect in the trial of people with type 2 diabetes (COR-DM). The clinical expert explained that a smaller effect has been shown in obesity drug trials of patients with type 2 diabetes and the reason is not fully understood. The committee concluded that the results showed naltrexone–bupropion to be more effective than placebo in all the COR trials.

Non-intensive adjunctive care to pharmacological treatment is more likely seen in practice

3.6 The committee noted that the trials were done in the US but heard from the clinical expert that the characteristics of participants in the trials are similar to those likely to be seen in practice in England. The trials had more female than male participants, which reflects the population in England who are more likely to engage with the health service to lose weight. The committee considered the generalisability of adjunctive care regimens in the trials. The clinical expert explained that the intensive regimen in COR-BMOD was unlikely to reflect standard practice in England, because of the variation in care in some regions (see section

3.1). The regimens in the other COR trials would be more representative of practice in England, where people have general counselling on lifestyle measures. The committee concluded that standard care in the trials, other than COR-BMOD, is applicable to practice in England.

People who are overweight are not well represented in the trials

3.7 The marketing authorisation for naltrexone–bupropion is for people who are overweight (body mass index [BMI] of 27 to 30) with a co-morbidity, and for those who are obese (BMI over 30). The committee noted that only a small percentage of patients in the trials were overweight. It heard from the clinical expert that this is representative of the clinical population most likely to be seen by the health service in England, because people who are obese are more likely to seek help. Therefore, the committee concluded that the appraisal should focus on people who are obese because there is very limited data to inform a decision on those who are overweight.

Indirect treatment comparisons to orlistat

There is similar efficacy between naltrexone–bupropion and orlistat but orlistat may be more effective in changing mean weight in people with type 2 diabetes

3.8 The company provided indirect comparisons for naltrexone–bupropion against orlistat. The committee noted that the company had presented separate results for people with and without type 2 diabetes, but had used the modified ITT population and pooled the COR trials together. The ERG commented that it is inappropriate to pool the data because of statistical and clinical heterogeneity between the trials. The trials were done in 2 different populations (COR-DM included people with type 2 diabetes whereas the other studies did not), COR-II had an earlier assessment point than the other trials (28 weeks rather than 56 weeks) and COR-BMOD had a more intensive standard care regimen. The committee agreed with the ERG's view that COR-BMOD should be considered separately to the other regimens because this is unlikely to be seen in

practice (see section 3.6) and that separate analyses for people with and without type 2 diabetes are appropriate. The committee noted that the ERG had presented an exploratory analysis for people with or without type 2 diabetes excluding COR-BMOD using the committee's preferred full-ITT population. The committee considered that these analyses were most appropriate. It was aware that the results favoured orlistat for one outcome in people with type 2 diabetes (mean percentage weight change) but that there were no other statistically significant differences between the 2 drugs. The committee concluded that the results from the ERG's analyses suggest similar efficacy between naltrexone–bupropion and orlistat but that orlistat may be more effective in changing mean weight in people with type 2 diabetes.

Company's economic model

The model did not capture the full treatment pathway

3.9 The company presented a discrete event simulation (DES) model that compared naltrexone–bupropion with orlistat as an adjunct to standard care and standard care alone. The committee agreed with the ERG that a DES approach was reasonable but was concerned that the model does not reflect the full treatment pathway for people with obesity. The model did not capture episodes of retreatment with naltrexone–bupropion, which the committee had concluded is a likely scenario for many people (see section 3.3). The committee also considered that bariatric surgery may be a subsequent treatment option for some people (see section 3.1). The committee concluded that the structure of the model was appropriate but that episodes of retreatment and a transition to bariatric surgery should be included in the model.

The model was not implemented properly

3.10 The ERG had concerns about how the economic model was implemented using Discrete Integrated Condition Event (DICE) methodology in Excel, which caused extremely slow run times. The company recognised the

limitations of executing the model in Excel and using DICE. The committee concluded that an alternative approach to implementing the DES model would be more practical for decision-making.

There were too few patient simulations to produce reliable deterministic results

3.11 The committee considered the deterministic results presented by the company. It noted the company's estimate that 1,000 simulations would be needed to attain stable results. In contrast, the committee noted that the model from Ara et al. (2012), which had a larger cohort, used 1,000,000 simulations. The ERG estimated that a minimum of 1,500 runs would be needed, and probably many more, to attain stable results. The ERG explained that it ran 1,000 simulations on 2 occasions and these resulted in very different incremental cost-effectiveness ratios (ICERs), differing by almost £7,000 per QALY gained. The committee concluded that far too few simulations had been run by the company and the deterministic results were not sufficiently reliable for decision-making.

The probabilistic sensitivity analysis did not produce reliable results

3.12 The ERG explained that the company did not run enough iterations to produce stable results for the probabilistic sensitivity analysis (PSA). The committee was aware that past PSAs run over 1,000 iterations to produce results, but the company ran only 500. The committee also noted that the company had not included important parameters in the PSA, which are subject to great uncertainty (time to treatment discontinuation [TTD], natural history of BMI model, and obesity-related events). The committee concluded that the PSA results were not sufficiently reliable for decision-making.

Model assumptions

The baseline characteristics may not reflect the population under consideration

3.13 The company's model used sources other than the trials to estimate some of the baseline characteristics, such as proportions of current smokers and people with type 2 diabetes. The ERG expressed a preference for using the COR trials as its source for the baseline characteristics. The committee recalled its earlier conclusion that the trial population was generalisable (see section 3.6) and concluded that it preferred the ERG's estimates for the baseline characteristics in the model.

Using a modified intention-to-treat analysis to inform time to treatment discontinuation is inappropriate

3.14 The company's estimates for TTD were based on the results from the pooled COR trials and the indirect treatment comparison to orlistat. The committee reiterated its views about the inappropriateness of using a modified ITT population and of pooling the trial results (see sections 3.4 and 3.8). The committee also noted that to derive TTD for orlistat, the estimates for naltrexone–bupropion TTD were scaled to orlistat treatment at an earlier assessment point. It heard from the ERG that scaling could lead to bias in favour of naltrexone–bupropion and it preferred to remove the scaling and use the full-ITT. The committee concluded that it preferred the ERG's assumptions on treatment effectiveness and TTD.

Weight regain towards baseline BMI is more appropriate than a predicted return to BMI

3.15 The company's model was based on a previous one by Ara et al. (2012). But the ERG explained that the company had deviated from the assumptions used in Ara et al. (2012). The company assumed that people regained weight to a predicted BMI rather than returning to their baseline weight after all treatment, including standard management, had stopped.

The committee concluded that return towards baseline weight is a more likely scenario.

Cost-effectiveness results

The ICERs are unreliable

3.16 The committee agreed with the company's overall approach to the decision problem for the eligible overall population for treatment with naltrexone–bupropion and with the subgroups for people with and without type 2 diabetes. The committee noted that the incremental results for the comparison with orlistat suggested naltrexone–bupropion is not a cost effective use of NHS resources, but the results were not robust because of model limitations (see sections 3.10 and 3.11). Although the structure of the model using DES was appropriate, implementation using DICE (see section 3.10) had caused slow run times and limited the number of simulations. The committee agreed that the same model implemented in a different way may have produced more stable results. It concluded that it was unable to assess the cost effectiveness of naltrexone–bupropion and could not therefore recommend it as an option for use in the NHS.

Other factors

Naltrexone–bupropion is considered an innovative technology

3.17 The committee recalled that naltrexone–bupropion offers a different mechanism of action to current treatment (orlistat) and may be better tolerated that orlistat (see section 3.2). The committee accepted that naltrexone–bupropion could be considered innovative. However it could not assess cost effectiveness (see section 3.16) and therefore was unable to recommend naltrexone–bupropion for use in the NHS.

Conclusion

3.18 The committee recognised there is a need for new pharmacological treatments, where orlistat is the only one currently available, but it had

concerns about the validity of the economic analysis and the robustness of the results. The committee concluded that the economic model had limitations in its structure, implementation, key assumptions, and in the clinical data used. Whilst the ERG was able to explore some of these issues, it could not resolve all of the committee's concerns on the model structure and its implementation.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Iain B. Squire
Vice Chair, appraisal committee A
April 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Hamish Lunagaria
Technical Lead

Zoe Charles
Technical Adviser

Liv Gualda
Project Manager

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