NICE National Institute for Health and Care Excellence

NICE guidance

Naltrexone–bupropion for managing overweight and obesity

Technology appraisal guidance
Published: 12 December 2017

www.nice.org.uk/guidance/ta494

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 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.

1.2 This recommendation is not intended to affect treatment with naltrexone–bupropion that was started in the NHS before this guidance was published. Adults 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

Obesity is very common in England, affecting about 30% of the population. Current management for overweight and obesity is lifestyle measures alone, lifestyle measures with orlistat or bariatric surgery.

Clinical trial evidence shows that naltrexone–bupropion with lifestyle measures is more effective than lifestyle measures alone, but its long-term effectiveness is unknown.

The estimate of cost effectiveness for naltrexone–bupropion with lifestyle measures, compared with lifestyle measures alone, is highly uncertain because of uncertainties in the modelling assumptions. Large numbers of people could be eligible for treatment which could potentially be long-term, leading to high overall costs for naltrexone–bupropion. Therefore, in these circumstances more certainty is needed that naltrexone–bupropion will provide value for the NHS.

2 The technology

Marketing authorisation

2.1 Adjunct to a reduced-calorie diet and increased physical activity, Naltrexone–bupropion (Mysimba) is indicated for the management of weight in adult patients (aged 18 and over) with an initial BMI of

- 30 kg/m^2 or more (obese) or
- from 27 kg/m^2 to 30 kg/m^2 (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

2.2 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

2.3 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 4) 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 but access to these services varies greatly across England

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. The prevalence of the condition is high in England with about 30% of the population defined as obese. Weight management services are tiered: tier 1 (healthy lifestyle promotions), tier 2 (lifestyle weight management programmes), tier 3 (weight management services including adjunct drug treatment) and tier 4 (bariatric surgery). The committee heard from the clinical experts that the type and quality of care and access to these services varies greatly across England. In some parts of the country, the already patchy tier 3 services are being de-commissioned, with most people not having access to multi-disciplinary weight management services. A disproportionately low number of bariatric surgeries are currently being done 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 not widely used and new pharmacological treatment options to manage overweight and obesity are needed

3.2 The clinical experts 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 adherence and

outcomes and so most people do not want to take it, or stop treatment after a short time. The patient expert also highlighted that orlistat causes unpleasant and socially unacceptable gastrointestinal side-effects. The committee heard from the clinical experts that there is therefore a high unmet clinical need for novel pharmacological approaches to treatment. Naltrexone–bupropion provides a new treatment option with a novel mechanism of action that does not have the same side-effects as orlistat and may be better tolerated. The committee concluded that orlistat is not widely used in clinical practice and that there is a need for new pharmacological treatment options to manage overweight and obesity.

Pharmacological treatment is only effective when it is given with lifestyle interventions

3.3 The committee heard from the clinical expert that any pharmacological treatment for weight management should be part of an integrated care pathway that includes lifestyle management. All pharmacological interventions for obesity are much less effective without adjunct lifestyle measures. The expert commented that naltrexone–bupropion should first be available in tier 3 services where comprehensive lifestyle management and monitoring would be available, but it is highly likely that it would become available in primary care in the future. The committee recognised that adjunct lifestyle measures alongside pharmacological treatment are important for treatment success and the population that may have access to naltrexone–bupropion is likely to be large, given the high prevalence of obesity (see section 3.1).

Standard management is the relevant comparator

3.4 The committee heard from the clinical experts, and from consultees after consultation on the appraisal consultation document that standard management (lifestyle measures) is the relevant comparator because orlistat is not often used in clinical practice. The committee accepted that orlistat should not be considered the only comparator for the reasons discussed in section 3.2. It concluded that standard management was therefore the main comparator in the appraisal.

Duration of treatment

Treatment for obesity is likely to be recurrent or ongoing

3.5 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 clinical expert also noted that long-term treatment with naltrexone–bupropion is likely to be necessary for many people, to maximise the likelihood of maintaining weight loss. The committee concluded that this would likely lead to long-term or recurrent treatment with naltrexone–bupropion for many people.

Analysis

A full intention-to-treat analysis is more appropriate

3.6 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 analysis, 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 or not a post-baseline weight measurement was taken). 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 as a result of people stopping treatment because of 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

3.7 The committee considered the key 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 people who were obese or overweight. 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 people who were obese or overweight but everyone had an intensive standard management 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 but were of short duration. The company presented the results for the modified ITT population and the committee was aware of the limitations of this analysis (see section 3.6). The committee noted that in the full ITT analysis in the clarification response, naltrexone–bupropion was also 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 but that the long-term effectiveness of naltrexone–bupropion was unknown.

Non-intensive standard management alongside pharmacological treatment is more likely in UK practice

3.8 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 standard management 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

3.9 The marketing authorisation for naltrexone–bupropion is for people who are overweight (BMI of 27 kg/m^2 to 30 kg/m^2) with a comorbidity, and for those who are obese (BMI over 30 kg/m^2). 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 people who are overweight.

Company's economic model

Using a discrete event simulation model was reasonable

3.10 The company presented a discrete event simulation (DES) model that compared naltrexone–bupropion plus standard management with orlistat

plus standard management and standard management alone. Because standard management was the main comparator in the appraisal (see section 3.4), the most relevant analyses were those comparing naltrexone–bupropion plus standard management with standard management alone. The committee agreed with the ERG that a DES approach was reasonable, but was concerned that the initial model did not reflect the full treatment pathway for people with obesity. After consultation, the company incorporated a transition to bariatric surgery, which may be a subsequent treatment option for some people (see section 3.1) but it was unable to capture episodes of retreatment which the committee had concluded is a likely scenario for many people (see section 3.5). The company noted that there were limited clinical data to inform such a scenario in the model and the committee accepted this reasoning.

The model was implemented correctly and is appropriate for decision-making

3.11 The ERG had concerns about how the initial economic model was implemented using Discrete Integrated Condition Event (DICE) methodology in Excel, which caused extremely slow run times. It was also concerned that not enough simulations were run to produce stable deterministic and probabilistic results and that the probabilistic analyses did not cover all the main input parameters. The company recognised the limitations of implementing the model in Excel and using DICE. After consultation, the company re-implemented the DES model in Visual Basic for Applications, increased the number of simulations, and extended the probabilistic analyses to explore the main input parameters. The committee heard from the ERG that the revised model ran more efficiently and that the ERG was able to reproduce similar results. The ERG believed that the company's validation of the model, comparing the old and new implementations in terms of the incremental cost-effectiveness ratio (ICER) and other outcomes, gave confidence in the results. The committee concluded it was satisfied that the model was fit for purpose and the results are appropriate for decision-making.

Model assumptions

The baseline characteristics reflect the population under consideration

3.12 The company's initial 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 preferred the COR trials as its sources for the baseline characteristics. The committee recalled its earlier conclusion that the trial population was representative of the population seen in practice in England (see section 3.8) and therefore agreed with the ERG that the baseline characteristics in the model should reflect those in the COR trials. In response to consultation, the company incorporated the committee's preference and the committee was satisfied that the model reflected a population that would be seen in England.

Using data from the COR-I and COR-DM trials and a full ITT analysis to inform time-to-treatment discontinuation is appropriate

3.13 The company's estimates for time-to-treatment discontinuation (TTD) were based initially on the results from the pooled COR trials and the indirect treatment comparison with orlistat, which also used the modified ITT population. The committee reiterated its views about the inappropriateness of using a modified ITT population (see section 3.6). The ERG commented that it is inappropriate to pool the data because of statistical and clinical heterogeneity between the trials. 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. Because such intensive standard management is unlikely to be seen in practice (section 3.8), the committee agreed with the ERG's view that COR-BMOD should be considered separately to the other regimens and that it was inappropriate to pool data from the COR trials because of statistical and clinical heterogeneity. The committee also noted that to derive the 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 analysis. The committee agreed with the ERG's reasoning that applying a scaling factor may lead to bias. In its response to consultation, the company accepted the committee's preference to use only the COR-I and COR-DM trials to inform TTD and removed the scaling factor for naltrexone–bupropion to orlistat. The company also used the full ITT analysis to estimate TTD. The committee was satisfied that the TTD estimates are appropriate for decision-making.

It is difficult to predict and model weight regain trajectory after stopping treatment

3.14 The company's model was based on a previous one by Ara et al. (2012). The ERG explained that the company had deviated from the assumptions used in Ara et al. The company assumed that after stopping all treatment, people regained weight to a predicted BMI (that is, the BMI predicted for the person if they had not lost weight after having naltrexone–bupropion in the trial) rather than returning to their baseline weight. In their response to the appraisal consultation document, the company maintained its preference for its original approach because it follows evidence from the natural history model synthesised by Ara et al. that there is a correlation for age and BMI, and it did not want to deviate from evidence that other factors can influence BMI. The committee heard that the ERG agreed with the company in part, but because it found conflicting and implausible predictions for patients whose condition responded and those whose condition did not respond it preferred to apply the conservative option of a return to a baseline BMI. The committee heard from the ERG that a return to a baseline BMI significantly increased the ICER for naltrexone–bupropion in the company's initial model, and therefore the company's assumption could favour naltrexone–bupropion. The clinical expert explained that it is difficult to predict what an individual's future BMI would be after treatment had stopped but that, irrespective of treatment for obesity, there is a natural increase in BMI with time. The committee concluded there is uncertainty on the most appropriate BMI trajectory after treatment has stopped and it is difficult to model. It also concluded that the effect of this on the modelling results was unclear but that the

company's approach was likely to favour naltrexone–bupropion.

Cost-effectiveness results

Naltrexone–bupropion may not be an appropriate use of NHS resources

3.15 The committee noted that the ICER for naltrexone–bupropion with standard management compared with standard management alone is £23,750 per quality-adjusted life year (QALY) gained. It also noted that the model showed a small incremental benefit for naltrexone–bupropion (a QALY gain of 0.0434). Because of the small QALY gain, the committee expected that the ICER would be very sensitive to changes in the QALY estimate. It noted the company estimated that an additional 0.009 incremental QALY benefit would reduce the ICER to below £20,000 per QALY gained, and it considered that this showed the sensitivity of the ICER to small changes in the QALYs. The committee considered that the ICER was uncertain for a number of reasons. It recalled that the model was unable to capture episodes of retreatment, which the committee had concluded is a likely scenario for many people (see section 3.5), and it was unclear how this would affect the ICER. It also recalled that there is uncertainty about how to model weight regain after treatment has stopped (see section 3.14) and that the effect of different approaches on the modelling results was unclear, but the company's approach was likely to favour naltrexone–bupropion (see section 3.14). The committee concluded that the combination of these factors means that there is considerable uncertainty about the true ICER for naltrexone–bupropion.

3.16 The committee referred to section 6.3.3 of NICE's guide to the methods of technology appraisal. This states that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources take into account a number of factors including the degree of certainty around the ICER. The committee concluded that there is substantial uncertainty around the ICER for the reasons outlined in section 3.15.

3.17 The committee also referred to section 6.2.14 of the guide, which states

that the committee 'will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases. Therefore, the committee may require more robust evidence on the effectiveness and cost effectiveness of technologies that are expected to have a large impact on NHS resources.' The committee recalled the high prevalence of obesity (see section 3.1) and that, as a consequence, there was potential for the impact of introducing the treatment to be large. The committee recognised the high unmet need for pharmacological treatments but, recognising the potentially large impact on NHS resources, it took a cautious approach in making its recommendations. Because of the uncertainty around the ICER, the potentially large patient population and long duration of treatment, the committee needed to be certain that naltrexone–bupropion will provide value to the NHS. Therefore, it was unable to recommend naltrexone–bupropion as a cost-effective treatment for use in the NHS.

3.18 The committee was aware that the company believed that the cost effectiveness of naltrexone–bupropion was inherently underestimated because its model captured only 3 obesity-related diseases (myocardial infarction, stroke and type 2 diabetes), whereas weight is a known risk factor for many other diseases. Also, the company's model did not include the increased risk of death after a myocardial infarction or stroke or the relationship between BMI and mortality risk beyond the first 15 years of the time horizon. The committee accepted that the effects of these on the cost-effectiveness estimates were unknown and ideally would have been included in the company's model. However, the committee was not persuaded that this would change its conclusions about the cost effectiveness of naltrexone–bupropion.

Other considerations

Naltrexone–bupropion is considered an innovative technology

3.19 The committee recalled that naltrexone–bupropion offers a different mechanism of action to current treatment (orlistat) and may be better tolerated than orlistat (see section 3.2). The committee accepted that

naltrexone–bupropion could be considered innovative but, for the reasons discussed in sections 3.15 to 3.18, it was unable to recommend naltrexone–bupropion for use in the NHS.

Conclusion

3.20 The committee noted that the ICER for naltrexone–bupropion with standard management compared with standard management alone was £23,750 per QALY gained. It identified a number of uncertainties around the modelling assumptions and considered that there is considerable uncertainty about the true ICER for naltrexone–bupropion. It noted that the patient population is potentially very large and treatment is long-term. Because of the uncertainty about the true ICER and the potentially high impact on NHS resources, the committee needed to be certain that naltrexone–bupropion will provide value to the NHS. Therefore it was unable to recommend naltrexone–bupropion as a cost-effective treatment for use in the NHS.

4 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.

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ISBN: 978-1-4731-2649-7