# Chair's presentation
# Naltrexone–bupropion (prolonged-release) for managing overweight and obesity (ID757)

2nd Appraisal Committee meeting

Committee A

Lead team: Mohit Misra, Rita Faria and Pamela Rees

ERG: Kleijnen Systematic Reviews

Company: Orexigen Therapeutics

8th June 2017

1

## Key issues

- Does the committee accept that standard management (SM) is a relevant comparator, for example when orlistat is not a feasible option or has failed?
  - no evidence is presented by the company on the effectiveness of NB32 in these groups of patients. The company assumes that a proportion of people in the COR trials would have tried orlistat and not responded in a satisfactory way. Is this assumption reasonable?
- Does the committee agree with the company's changes to the model?
  - does the revised approach to implementing the model produce results that are sufficiently reliable for decision-making?
  - is the committee persuaded that a return to a predicted BMI is more appropriate than a return to a baseline BMI after treatment discontinuation?
    - is there a difference for responders and non-responders?
- What is the committee's view of the company's new ICERs?
  - for the overall population covered by the model?
  - for subgroups of people with and without type 2 diabetes?
  - for people in whom orlistat has failed?

2

# Naltrexone–bupropion (NB32)

(Naltrexone 32mg plus bupropion 360mg prolonged-release tablet)

- Combination of an opioid-receptor antagonist (naltrexone) and a norepinephrine dopamine reuptake inhibitor (bupropion). Exact neurochemical effect on modulating food cravings is unknown
- Marketing authorisation: Adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial 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)
- Treatment should be discontinued after 16 weeks if patients have not lost at least 5% of initial body weight
- List price: £73.00 per pack of 112 tablets

3

# Randomised placebo-controlled trials

| Trial name | Population | Intervention | Co-Primary Outcomes |
|---|---|---|---|
| **COR-I**<br>**Phase III multicentre, double-blind**<br>**Location: USA** | Adults with uncomplicated obesity or who were overweight with dyslipidaemia or hypertension | Naltrexone 32mg per day + bupropion 360mg per day (NB32)<br>Naltrexone 16mg per day + bupropion 360mg per day | Mean percent change in body weight and proportion of patients with ≥5% decrease in body weight at week 56 |
| **COR-II**<br>**Phase III, multicentre, parallel-arm, double-blind**<br>**Location: USA** | As above | NB32 | Mean percent change in body weight and proportion of patients with ≥5% decrease in body weight at week 28 |
| **COR-BMOD**<br>**Phase III multicentre, double-blind**<br>**Location: USA** | As above | NB32 + intensive behaviour modification (BMOD) | Mean percent change in body weight and proportion of patients with ≥5% decrease in body weight at week 56 |
| **COR-DM**<br>**Phase III multicentre, double-blind**<br>**Location: USA** | Adults with T2DM and BMI ≥27 and ≤45kg/m$^2$ | NB32 | As above |

***Note***: NB32 and placebo are all given as adjunct to standard management (SM) or intensive SM [BMOD] in COR-BMOD. COR, Contrave obesity research; DM, diabetes mellitus; BMOD, intensive behaviour modification; T2DM, Type 2 diabetes mellitus

4

# ACD recommendations

- 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

5

# Key conclusions in ACD

**Clinical effectiveness**

- Orlistat is the only relevant active comparator
- NB32 offers a different mechanism of action to orlistat, may be better tolerated, and could be considered innovative
- Obesity is a chronic condition and treatment with NB32 could be recurrent or long-term for many people
- Adjunctive standard care in the COR trials is applicable to practice in England, except for the intensive standard care regimen in COR-BMOD
- Full-ITT analyses are more appropriate than the modified ITT analyses proposed by the company
- NB32 was more effective than placebo in the 4 COR trials using full-ITT analyses
- Indirect treatment comparison (ITC): most appropriate analyses (excluding COR-BMOD, no pooling of NB32 trials, and using the full-ITT population) suggest similar efficacy between NB32 and orlistat but orlistat may be more effective in changing mean weight in people with type 2 diabetes
- Appraisal should focus on people who are obese because of limited data to inform a decision on those who are overweight

6

# Key conclusions in ACD

**Cost-effectiveness**

- Model structure (discrete event simulation [DES]) was appropriate but episodes of retreatment and a transition to bariatric surgery should be included
- Implementation using Discrete Integrated Condition Event [DICE] methodology caused slow run times and limited the number of simulations - an alternative approach would be more practical for decision-making
- Baseline characteristics may not reflect the population under consideration - Committee preferred the ERG's estimates using the COR trials
- Weight regain towards baseline BMI is more appropriate than a predicted return to BMI
- Inappropriate to use modified ITT population and pooled trial results to estimate time to treatment discontinuation (TTD)
  - estimates for NB32 TTD were scaled to orlistat treatment at an earlier assessment point
  - committee preferred the ERG's assumptions on treatment effectiveness and TTD
- Deterministic and probabilistic ICERs not sufficiently reliable for decision-making
- Unable to assess the cost effectiveness of NB32 and could not therefore recommend it as an option for use in the NHS

7

# ACD consultation comments

- Royal College of Pathologists
- Royal College of Physicians
- Web (1 response received)
- Company (Orexigen Therapeutics)

8

# Royal College of Pathologists and Royal College of Physicians

- Clear unmet clinical need for novel pharmacological approaches to treatment of overweight and obesity, as part of an integrated weight management pathway
  - strong patient voice for this
  - orlistat is the only current treatment and is poorly tolerated by many people
- Evidence demonstrates that NB32 is more effective than placebo (SM) and there is similar clinical efficacy to orlistat
- Disappointing that a reliable assessment of cost-effectiveness could not be made
  - acknowledged that economic analysis needs more work
- Orlistat is not the only relevant comparator
  - use could be supported in those who do not respond to, or are intolerant of, orlistat

9

# Web comment

- The lack of therapeutic options for obesity in the UK is startling
  - significant unmet need
  - lagging behind the US
- Lifestyle intervention is effective but only in a very limited number of people and its impact on the extent of weight loss is also limited
- Orlistat use is limited by GPs and specialists and is poorly tolerated
- Comparison to orlistat is not valid
  - only a small number of patients on it
- Lifestyle is the relevant comparator

10

# Company (Orexigen Therapeutics)

- New model and analysis provided
- Still a DES model but re-implemented in more efficient framework (VBA)
- Run times dramatically reduced and stable results produced with 15,000 simulations
- New base case using some of the committee's and ERG's preferred assumptions
- Results are also presented for people with and without type 2 diabetes

11

# Company's comments on the decision problem

## Standard management is a relevant comparator

**When orlistat is not a feasible option**

- Orlistat use is limited due to side-effects and has a poor uptake in the NHS
- A pairwise comparison to SM is relevant to determine cost-effectiveness for a subset of people for whom this option is relevant

**When orlistat has failed**

- *Evidence* - reasonable to assume that a proportion of people in the COR trials could have failed on orlistat before entering the studies
- Previous treatment with orlistat is unlikely to impact on NB32 efficacy as they have a different mechanism of action

**Comparison to SM provides the most credible evidence**

- Clinical comparison to orlistat is limited due to assumptions imposed in the ITC
- It is highly plausible that the relative benefit of NB32 is underestimated compared to orlistat in the ITC (and therefore the economic model) due to heterogeneity in the studies and no stopping rule being applied

12

# Company's changes to model (1)

## Capturing the committee's preferred modelling assumptions

**Baseline characteristics**

- Baseline characteristics of patients in the COR trials modelled
- BMI natural history model now reflects baseline BMI from COR trials (36 kg/m$^2$)

**Treatment effectiveness and discontinuation**

- Used full-ITT population from COR-I and COR-DM trials only instead of the modified-ITT population for the pooled population
- Scaled estimates for TTD removed

**Weight regain following treatment discontinuation**

- No adjustment made for a return to baseline BMI over 3 years (as Ara et al.)
- A return to baseline assumes stable weight for 3 years from a treatment that had no noticeable effect
- Evidence from Ara et al. natural history models shows that BMI increases with age
- Company does not want to incorporate an assumption that diverts from evidence

13

# Company's changes to model (2)

## Capturing the committee's preferred modelling assumptions

**Treatment pathway**

- Bariatric surgery
  - Data from a 2016 British Medical Journal press release was used to incorporate transition to bariatric surgery
  - Assumptions: average instant weight loss (24.225%), failure (12.5%), fatal surgery (0.1%), surgery only possible after 2 years of meeting criteria, cost of surgery (£4,886) and provision is greater in type-2 diabetics than non-type 2 diabetics
- Retreatment of pharmacological adjunct

*NB32 after orlistat failure*

  - Scenario explored where people treated with orlistat are presented as non-responders at 12 weeks and then can have either SM or NB32

*Retreatment with the same treatment*

  - No data on frequency, timing or efficacy of NB32 used as a retreatment
  - No scenario explored but if there is no relationship between treatment effectiveness and retreatment assumed, then the new base case ICER gives a fair estimate of retreatment

14

# Company's changes to model (3)

Additional changes made to the model

- Annual BMI and time-to-event updates incorporated into the model following ERG's critique
  - BMI changes the risk of obesity-related events (MI, stroke and type 2 diabetes) as well as health-related quality-of-life (HRQoL) – updating BMI more frequently accurately reflects these risks with time
  - this had the most profound effect on the ICERs as it lowered the incremental QALY gains for NB32 and orlistat versus SM, and for NB32 versus orlistat
- Errors corrected and extra costs associated with annual GP assessment for people receiving SM removed from the model

15

# Company's new base case results

deterministic results based on 15,000 simulations

| Technologies | Total | | Incremental | | ICER | |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | Versus baseline [SM] | Incremental |
| **SM** | £6,502 | 13.6300 | | | | |
| **Orlistat** | £6,802 | 13.6698 | £300 | 0.0398 | £7,536 | £7,536 |
| **NB32** | £7,531 | 13.6734 | £729 | 0.0035 | **£23,750** | **£207,274** |

**Probabilistic results** (1,000 iterations):
NB32 vs SM: **£24,539**
NB32 vs orlistat: **£138,618**
(due to the sensitivity in the ICER for NB32 versus orlistat, an increase of 0.0017 QALYs caused a reduction in the ICER of approximately £68,656)

16

# Company's new base case results

## Subgroup analysis

| Non-type 2 diabetes subgroup | | | | | | |
|---|---|---|---|---|---|---|
| **Technologies** | Total | | Incremental | | ICER | |
| | Costs | QALYs | Costs | QALYs | Versus baseline [SM] | Incremental |
| **SM** | £4,300 | 14.0335 | | | | |
| **Orlistat** | £4,572 | 14.0669 | £272 | 0.0334 | £8,153 | £8,153 |
| **NB32** | £5,311 | 14.0797 | £738 | 0.0128 | **£21,897** | **£57,899** |

| Type 2 diabetes subgroup | | | | | | |
|---|---|---|---|---|---|---|
| **Technologies** | Total | | Incremental | | ICER | |
| | Costs | QALYs | Costs | QALYs | Versus baseline [SM] | Incremental |
| **SM** | £11,435 | 12.7100 | | | | |
| **Orlistat** | £11,785 | 12.7639 | £350 | 0.0539 | £6,507 | £6,507 |
| **NB32** | £12,467 | 12.7496 | £681 | -0.0143 | **£26,049** | **Dominated** |

17

# Company's new scenario analysis

## NB32 after orlistat has failed (vs SM)

- Model set to a 12-week time horizon and people present as non-responders with orlistat at primary assessment – all other assumptions remained the same as in the new base case
- People can then either have SM or NB32 after orlistat failure – mean results for each arm derived
  1. orlistat for 12 weeks followed by SM
  2. orlistat for 12 weeks followed by NB32
- Incremental analysis from the 2 sets of results represent the scenario of NB32 as an alternative to SM in people who have failed on orlistat

| **Technologies** | **Total** | | **Incremental** | | **ICER** |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **SM** | £6,527 | 13.6404 | | | |
| **NB32** | £7,557 | 13.6845 | £1,030 | 0.0442 | **£23,324** |

18

# Limitations of the analysis

**Company believes that the cost-effectiveness of NB32 is inherently underestimated:**

- Only 3 obesity diseases are captured; MI, stroke and T2DM; when weight is a known risk factor for over 60 further health events including numerous cancers, hypertension, hyperlipidaemia, joint/spinal complaints, and sleep apnoea
- The increased risk of death upon incidence of MI or stroke is not included
- The relationship between BMI and mortality risk is not captured beyond the first 15 years of the time horizon
- If data on *any* of these known limitations were incorporated, the expected health benefit of NB32 could be better demonstrated. An additional 0.009 incremental QALY benefit would reduce the revised base case ICER below £20,000

19

# Equalities issues

- If the underestimations of health and health care costs are not taken in to account by the committee then the company believes there is risk of discrimination on the basis of age
  - end-of-life treatments rely on 'expected' long-term benefits from evidence outside of the clinical data for the treatment
  - company reason that treatments with preventative benefits, such as NB32 in weight loss, will be undervalued relative to treatments for incurable, end-of-life illnesses
  - preventative treatments like NB32 are used in younger populations rather than treatments for incurable illnesses, so a discrimination by age is likely to occur

20

## ERG's comments on the decision problem/clinical evidence

**Use of NB32 after orlistat failure**

- No evidence presented for this population
  - size of the population unclear - orlistat use prior to the 4 weeks before entering the COR trials was not documented
  - therefore unclear what the relative effectiveness of NB32 compared to standard management is in this population
- No evidence presented to justify assumption that previous orlistat treatment is not expected to affect NB32 treatment effectiveness
  - efficacy of NB32 also relies on being an adjunct to SM and patient's behaviour – NB32 and orlistat are part of a multi-component treatment and assuming independence may result in biased model outcomes
- **ITC for NB32 vs orlistat**
  - ERG fails to see why the limitations of the ITC would necessarily favour either NB32 or orlistat

21

## ERG's comments on the model implementation

- Model much more efficient but could not be validated by the ERG due to time constraints
  - company's validation of the model and comparison between the old and new implementation in terms of the ICER and other outcomes gives confidence that it is correctly implemented
- ERG's re-runs with 15,000 simulations produced fairly similar ICERs to the company
  - ICERs differed by £2,000 per QALY gained owing to very small QALY gains but results are still sufficient for decision-making
- PSA now reflects uncertainty in all the parameters (including TTD, time to obesity-related events and natural history of BMI model)
  - differences from deterministic results stem from the non-linear DES model

22

## ERG's comments on the modelling assumptions

Underestimation of benefits for NB32

- ERG agrees that the model may be an oversimplification of reality and believes that the costs and HRQoL implications of other conditions and mortality should have been incorporated in the model, to be able to inspect the true impact on model outcomes

Return to a predicted BMI rather than a baseline BMI after treatment discontinuation

- Company applies a non-conservative assumption that is not in line with Ara et al.
- ERG agrees that the Ara et al. model produces an implausible conclusion that non-responders to treatment would achieve long-term benefit
- ERG considers it equally implausible that responders only have a benefit for the time they are on treatment and for the 3 years after discontinuation, at which point they would revert back to the predicted BMI trajectory
- Without further evidence or clinical opinion ERG deems it appropriate to stick with its conservative assumption of a return to baseline BMI

23

## ERG's comments on the cost-effectiveness results

- Agrees that incorporating an annual BMI update had the most impact on the results (increase of approx. £110,000 per QALY gained)
  - this reflects the importance of frequent updating of events in DES models in which there is a progressive outcome measure
- *Scenario analysis* – NB32 after orlistat failure
  - important to note that the ICER is based on the assumption that the treatment effectiveness of NB32 is independent of the success or failure of prior treatments and there is no evidence to support this assumption
  - scenario should be interpreted with extreme caution because there is no evidence to inform such a scenario

24

# Key issues

- Does the committee accept that standard management (SM) is a relevant comparator, for example when orlistat is not a feasible option or has failed?
  - no evidence is presented by the company on the effectiveness of NB32 in these groups of patients. The company assumes that a proportion of people in the COR trials would have tried orlistat and not responded in a satisfactory way. Is this assumption reasonable?
- Does the committee agree with the company's changes to the model?
  - does the revised approach to implementing the model produce results that are sufficiently reliable for decision-making?
  - is the committee persuaded that a return to a predicted BMI is more appropriate than a return to a baseline BMI after treatment discontinuation?
    - is there a difference for responders and non-responders?
- What is the committee's view of the company's new ICERs?
  - for the overall population covered by the model?
  - for subgroups of people with and without type 2 diabetes?
  - for people in whom orlistat has failed?

25