Chair's presentation Naltrexone–bupropion (prolongedrelease) for managing overweight and obesity (ID757)

2nd Appraisal Committee meeting

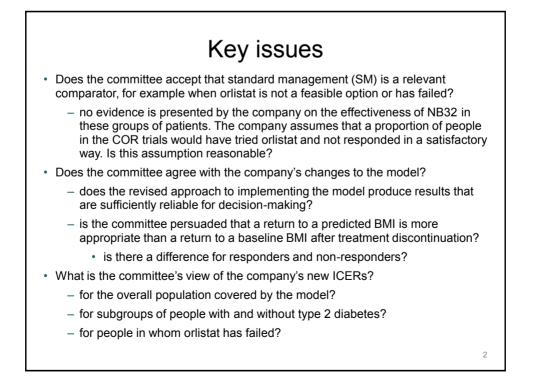
Committee A

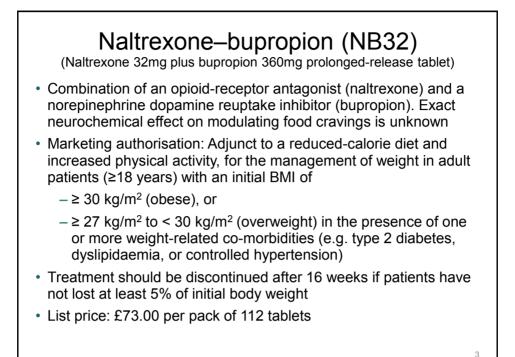
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ERG: Kleijnen Systematic Reviews

Company: Orexigen Therapeutics

8th June 2017





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

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

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

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

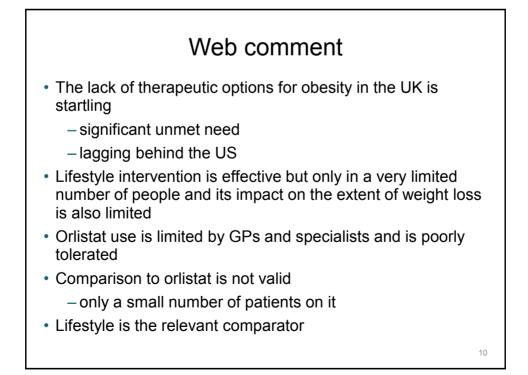
ACD consultation comments

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

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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



Oceaning (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

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

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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/m²)

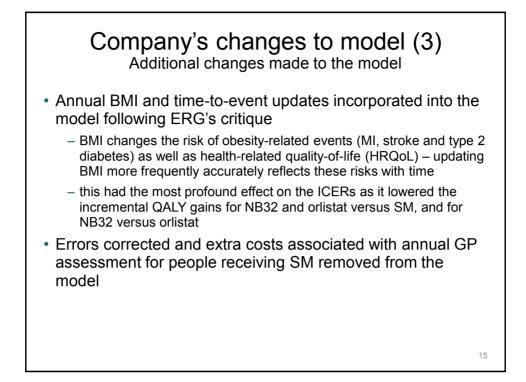
Treatment effectiveness and discontinuation

- 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

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 nonresponders 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 new base case results deterministic results based on 15,000 simulations

	Total		Incremental		ICER			
Technologies	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)								

Company's new base case results Subgroup analysis								
Non-type 2 dia	Non-type 2 diabetes subgroup							
	Total		Incremental		ICER			
Technologies	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 diabete	Type 2 diabetes subgroup							
	Total		Incremental		ICER			
Technologies	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		
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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

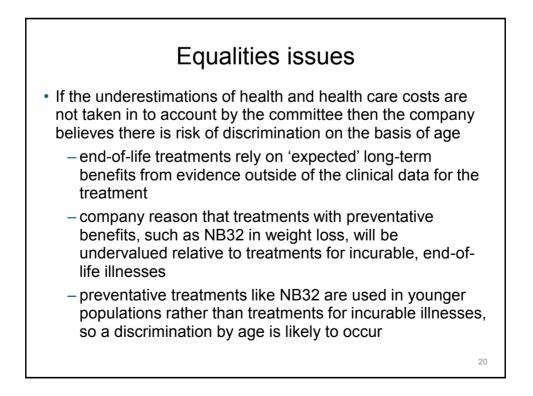
Technologies	Total		Increm		
	Costs	QALYs	Costs	QALYs	ICER
SM	£6,527	13.6404			
NB32	£7,557	13.6845	£1,030	0.0442	£23,324
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Limitations of the analysis

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

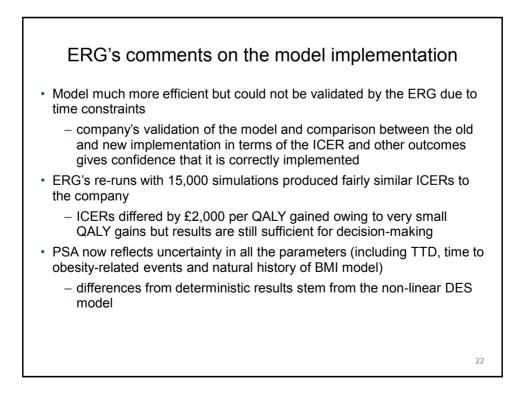
- Only 3 obesity diseases are captured; MI, stroke and T2DM; when weight is a known risk factor for over 60 further health events including numerous cancers, hypertension, hyperlipidaemia, joint/spinal complaints, and sleep apnoea
- The increased risk of death upon incidence of MI or stroke is not included
- 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



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



ERG's comments on the modelling assumptions

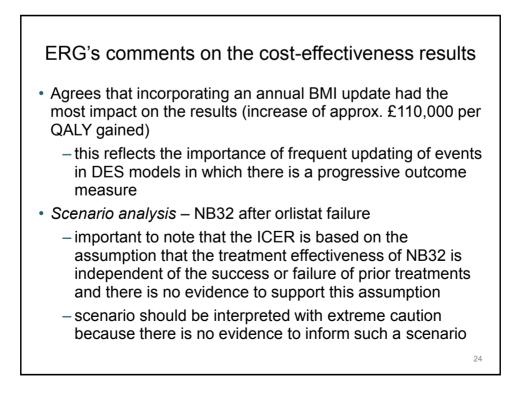
Underestimation of benefits for NB32

 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





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?