Naltrexone/bupropion (Mysimba®) for the management of weight in adults

The NCPE has issued a recommendation regarding the cost-effectiveness of naltrexone/bupropion (Mysimba®). Following assessment of the applicant's submission, the NCPE recommends that naltrexone/bupropion (Mysimba®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Orexigen Therapeutics Ireland Limited) economic dossier on the cost effectiveness of naltrexone/bupropion (Mysimba®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **May 2018**

Summary

Orexigen Therapeutics Ireland Limited submitted an economic dossier on the cost-effectiveness of naltrexone/bupropion (Mysimba®) for the management of weight in adults on the 6th November 2017. The product obtained European marketing approval in 2015 and is available as naltrexone 8mg + bupropion 90mg in a prolonged release tablet. The dose is escalated from one tablet daily to two tablets twice daily (naltrexone 32mg + bupropion 360mg daily) over four weeks.

Overweight and obesity are associated with a wide range of health problems including short term complications such as fatigue, back and joint pain, breathlessness and diminished physical activity. Longer term complications include diabetes mellitus, cholelithiasis, hypertension, hyperlipidaemia with associated cardiovascular disease and cancer. Psychological complications of obesity include low self-esteem, poor self-image and reduced self-confidence. In adults (age over 18 years) obesity is defined by a BMI ≥ 30 kg/m² and overweight by a BMI between 25 and 29.9 kg/m².

Naltrexone is an opioid receptor antagonist and bupropion is a noradrenaline – dopamine reuptake inhibitor. Bupropion stimulates pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (which controls hunger) of the hypothalamus resulting in the release of alpha-melanocyte stimulating hormone (α-MSH) which in turn binds to and stimulates melanocortin 4 receptors (MC4-R). When α-MSH is released, POMC neurones release β-endorphin to mu-opioid receptors on POMC neurones mediating a negative feedback mechanism resulting in a reduction in the release of α-MSH. Naltrexone blocks this inhibitory feedback loop facilitating a more potent and longer lasting activation of POMC neurones thereby amplifying the effect of bupropion on energy balance.

It is indicated as an 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/m² or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of one or more weight related co-morbidities including type II diabetes mellitus, dyslipidaemia or controlled hypertension.

Treatment with naltrexone/bupropion should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

1. Comparative effectiveness

The submitted clinical evidence for naltrexone/bupropion consisted of four phase III studies where 2,510 patients were randomised to naltrexone/bupropion and 1,448 to placebo. The COR-1 study included adults with uncomplicated obesity or who were overweight with dyslipidaemia or hypertension. The study investigated the safety and efficacy of two doses of naltrexone/bupropion i.e. naltrexone 32mg/day + bupropion 360 mg/day (n=583) and naltrexone 16 mg/day + bupropion 360 mg/day (n=578) versus placebo (n=581). Weight loss in the naltrexone/bupropion arms began early and reached a maximum between 28 and 36 weeks and was sustained through week 56 of the trial. The mean difference in percentage change of weight loss from baseline as compared with placebo was -3.7% (for the naltrexone 16mg + bupropion 360mg dose) and -4.8% for the naltrexone 32 mg + bupropion 360 mg dose. A significantly greater proportion of patients in the naltrexone/bupropion groups achieved a decrease in bodyweight of ≥ 5% as compared with placebo (48% [32mg/360mg] and 39% [16mg/360mg] versus 16%; $p<0.0001$ for both comparisons.

The COR-II study was a phase III multicentre, randomised, parallel-arm, double blind, placebo controlled trial where patients aged 18 – 65 years with a BMI ranging between 30 – 45 kg/m² and uncomplicated obesity or a BMI between 27 – 45 kg/m² and controlled hypertension and/or dyslipidaemia were randomised in a 2:1 ratio to naltrexone 32mg/day + bupropion 360mg/day (n=1,001) or placebo n=495 [4]. Naltrexone/bupropion patients with < 5% weight loss at visits between 28 and 44 weeks were re-randomised (double blind 1:1 ratio) to continue receiving naltrexone/bupropion (n=123) or to escalate to naltrexone 48mg + bupropion 360 mg daily (n=128). The co-primary endpoints were percentage of change in total body weight and proportion of patients with ≥ 5% decrease in total body weight at week 28. The proportion of patients with ≥ 5% decrease in body weight from baseline was significantly greater in the naltrexone/bupropion group at 55.6% versus 17.5%;$p<0.001$ and the mean difference between the treatment groups was -4.6%;$p<0.001$.

The COR-BMOD study was a phase III randomised, double blind, placebo controlled study where patients were randomised to naltrexone 32mg/day + bupropion 360mg/day or placebo and all patients received intensive behavioural modification (BMOD). Patients were aged 18 – 65 years with a BMI ranging between 30 – 45 kg/m² and uncomplicated obesity or a BMI between 27 – 45 kg/m² and controlled hypertension and/or dyslipidaemia. The primary outcomes were percentage change in total body weight and proportion of patients with ≥ 5% decrease in total body weight at week 56. Patients in the naltrexone/bupropion + BMOD group achieved a mean weight loss of 9.3% as compared to 5.1% for patients with placebo + BMOD ($p<0.001$). The proportion of patients who achieved a ≥ 5% reduction in baseline weight was greater in the naltrexone/bupropion group (66.4%) as compared with the placebo group where 42.5% achieved a ≥ 5% weight loss at week 56 ($p<0.001$).

The COR-DM study was a phase III, randomised, double-blind, placebo-controlled 56 week study where patients were randomised to naltrexone 32mg/day + bupropion 360 mg/day (n=335) or placebo (n=170) in a 2:1 ratio The primary outcomes were percentage change in total body weight and proportion of patients with ≥ 5% decrease in total body weight at week 56. Patients treated with naltrexone/bupropion lost significantly more weight than placebo treated patients i.e. 5% versus 1.8% respectively ($p<0.001$). More patients in the active treatment group achieved a ≥ 5% reduction in body weight at week 56 i.e. 44.5% versus 18.9% ($p<0.001$).

2. Safety

Safety data in relation to naltrexone/bupropion is derived mainly from the four phase III clinical trials. In the COR-I study drug related adverse events occurred in over 50% of patients resulting in treatment discontinuation in approximately 20% of participants. Discontinuation generally occurred early i.e. by weeks 4 and 8. The most frequent adverse event was nausea in 27.2% in the lower dose combination and 29.8% in the higher dose combination of naltrexone/bupropion as compared with 5.3% in the placebo group. Headache, constipation, dizziness, vomiting and dry mouth were also more frequent in the naltrexone/bupropion treatment groups. A transient increase of around 1.5 mmHg in mean systolic and diastolic blood pressure was followed by a reduction of around 1 mmHg below

baseline in the treatment groups. Combination treatment was not associated with increased depression or suicidality events compared with placebo.

The COR-II study adverse effects were similar to those described above and over 24% of patients reported an adverse event leading to treatment discontinuation. As in COR-I treatment discontinuation tended to occur early in the trial which had a completion rate of 54% across the treatment groups. Similarly in the COR-BMOD trial over 25% of patients treated with naltrexone 32mg + bupropion 360 mg discontinued treatment and nausea was the most common adverse event. At week 56 systolic blood pressure fell an average of 3.9±0.7 mmHg from baseline in the placebo + BMOD group compared with a smaller 1.3±0.5 mmHg reduction in the naltrexone/bupropion group (p=0.002). Diastolic blood pressure also declined more in the placebo group.

In the COR-DM study 29.4% of patients discontinued naltrexone/bupropion therapy because of adverse events with nausea being the most frequent side effect. No difference was observed between the groups in relation to depression, suicidal ideation or hypoglycaemia. In the NB-404 study 20.7% of subjects discontinued medication because of adverse events.

The NB-CVOT (LIGHT) study aimed to determine whether the combination of naltrexone and bupropion increased major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal stroke or non-fatal myocardial infarction as compared with placebo in patients with obesity. However the NCPE review group note that the cardiovascular safety of naltrexone/bupropion remains to be established.

3. Cost effectiveness

A de novo individual-level economic model was developed for this pharmacoeconomic assessment and built in Excel. The model harnesses many assumptions and key input data from Ara et al. including the natural history models for BMI lifetime patterns and BMI risks estimated using the General Practice Research Database (GPRD). The key modelling assumptions made include the following (a) following cessation of naltrexone/bupropion

standard management would continue (b) for patients who discontinue adjuvant therapy but continue to receive non-pharmacological standard management, weight gain was assumed to only commence when standard management was discontinued (c) weight is regained linearly over a 3 year period (d) BMI was assumed to revert to the natural history model predicted BMI given the intrinsic correlation known between age and BMI (e) within the model it is possible for patients to experience a primary and secondary cardiovascular event (myocardial infarction or stroke) as well as developing type two diabetes mellitus. The average duration of treatment with naltrexone/bupropion in the model is taken from the NB-CVOT study where all patients had discontinued treatment by 156 weeks. After discontinuation of naltrexone/bupropion the assumption is made in the model of weight regain based on the following (i) weight regain begins immediately after a patient discontinues all treatment and that (ii) weight is regained linearly over a 3 year period.

The primary sources of evidence was derived from the COR clinical trial programme followed by the NB-CVOT study. Health outcomes were expressed as quality adjusted life years i.e. QALYs however the submission did not include the impact of adverse events on health related quality of life. Drug costs were presented as costs per patient per pack. The price presented for naltrexone 8 mg/day + bupropion 90 mg/day was €90.28 per pack of 112 tablets having taken into account mark-up, rebates and pharmacy fees. As the daily dose is naltrexone 32 mg + bupropion 360 mg the cost is €90.28 per 28 day course resulting in a cost of €1,176 per patient per year. Should the patient discontinue treatment at 16 weeks the cost would be €361.12. A discount rate of 5% was applied in line with current guidelines and results in the base case represent the perspective of the Health Service Executive (HSE).

The base case incremental cost-effectiveness ratio (ICER) was €30,575/QALY (incremental costs €1,312.83; incremental QALYs 0.0429). Probabilistic sensitivity analysis (PSA) for naltrexone/bupropion versus standard management resulted in an ICER of €33,685/QALY however the NCPE review group considered that uncertainty around the ICER estimates were not fully illustrated by the submitted sensitivity analyses.

4. Budget impact

The applicant estimates the number of eligible patients at 57,777 however not all of these will receive treatment. The estimated numbers that would be treated with naltrexone/bupropion increase from 215 patients in year one to 1,534 patients in year five. The gross budget impact presented in the dossier includes drug acquisition cost plus the costs of adverse events. This results in an estimated gross drug budget of €70,179 in year one increasing to €937,432 in year five. The cumulative 5 year gross drug budget impact was estimated at €2,565,000. As naltrexone/bupropion is not expected to displace any existing treatments, the net budget impact is assumed to be the same as the gross budget impact.

5. Conclusion

The cardiovascular safety of naltrexone/bupropion (Mysimba®) remains uncertain and requires further evaluation. The uncertainty associated with the cost-effectiveness estimate was not adequately explored in the current submission. The NCPE recommends that naltrexone/bupropion (Mysimba®) should not be considered for reimbursement.