Cost Effectiveness of Buprenorphine hydrochloride/ naloxone hydrochloride dihydrate (Suboxone®) for opioid dependence.

The NCPE has issued a recommendation regarding the use of Suboxone® for this indication. The NCPE does not consider Suboxone® to be cost effective compared to methadone for the treatment of opioid dependence.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (Reckitt Benckiser Pharmaceuticals) economic dossier on the cost effectiveness of Suboxone®. 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 examine 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 2014**

Summary

Reckitt Benckiser Pharmaceuticals (RBP) submitted a dossier for buprenorphine hydrochloride/naloxone hydrochloride dehydrate (Suboxone®) on 2nd January 2014. Suboxone® is indicated for opioid dependence in patients over 15 years old. Suboxone® contains buprenorphine, a partial opioid agonist and naloxone an opioid antagonist.

1. Comparative Effectiveness Summary

- The comparator included in the pharmacoeconomic evaluation was methadone. Methadone is the primary opioid maintenance treatment provided for opioid dependence in Ireland and is therefore an appropriate comparator.
- The evidence submitted to support efficacy was not combined in any formal way through meta-analysis and the evidence chosen for the pharmacoeconomic evaluation did not appear to be supported by a systematic literature review; the NCPE had concerns that all the relevant data was not included. One study was used to inform the number of opioid negative tests and this was Kamien *et al*. 2008. This 17-week, double-blind, double-dummy trial compared buprenorphine-naloxone (8/2 mg and 16/4 mg) with methadone (45 mg and 90 mg)(N=268). More patients discontinued from buprenorphine/naloxone than from methadone. The percentage of opiate-negative urine samples over time did not differ by drug or dosage. The percentage of patients with ≥12 consecutive opioid-negative urine samples did not differ by drug. Induction success, compliance, non-opioid drug use, retention and Addiction Severity Index scores did not differ among groups.
- The review group have included the Cochrane reviews to further inform the evidence on efficacy as the most recent was published in February 2014. The Cochrane reviews compare buprenorphine alone to placebo and methadone. The Cochrane Review (2008) authors concluded that buprenorphine is less effective than methadone delivered at adequate dosages. In the updated

2014 Cochrane Review the authors concluded that buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials. When buprenorphine is delivered flexibly and at low doses, fewer people are retained compared to methadone. If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use); however, fixed doses are rarely used in clinical practice so the flexible dose results are more relevant to patient care. Methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use.

2. Safety

- The adverse effects of Suboxone® are largely similar to opioid agonists and include headache, withdrawal syndrome, pain, nausea, insomnia and sweating. Hepatic transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred in patients on Suboxone® and caution is advised in patients with mild to moderate hepatic dysfunction. Suboxone® is contraindicated in patients with severe hepatic dysfunction.

3. Cost-Effectiveness analysis

- A cost utility analysis comparing Suboxone® to methadone was submitted by the company. Health benefits were measured in QALYs and are informed by utilities of patients from a study comparing Suboxone® and methadone and do not specifically include disutilities from adverse events. Costs are included from the Irish healthcare system. The population considered included the licensed population i.e. all patients 15 years and over who are opioid dependent and have agreed to opioid addiction treatment. Subgroups were not included as part of the analysis. The perspective of the HSE (payer) was presented. Two scenarios were presented to estimate the cost effectiveness when treatment is provided in

the HSE drug treatment clinic setting and in the community setting.

- The model was run for a one year time horizon with a one day cycle length. The model considered treatment in the GP setting (community) and in the specialised clinic setting as two separate scenarios. The model structure is limited in managing patients who may move in and out of the treatment service. The 'OFF treatment' state does not allow for patients moving back on treatment and only to 'Dead' or remaining in the state. The time horizon of the model does not adequately capture the chronic nature of addiction and as such overestimates cost effectiveness when the benefit and costs are applied to a shorter time horizon.

- EQ-5D or SF-6D data was not available from the pivotal RCTs therefore the utilities were drawn from the literature. A systematic literature review was not provided. The utility values used were that from Harris *et al.* (2005) which was a randomised, open-label, 12-month trial of 139 heroin-dependent patients in an Australian community setting receiving individualised treatment regimens of buprenorphine or methadone. The study aimed to estimate the cost effectiveness of buprenorphine as an alternative to methadone maintenance treatment for heroin dependence in a primary care setting. Health-related QOL (HRQOL) was one of the primary outcomes of the study and was measured using the Australian Quality of Life instrument (AQoL). There was no statistically significant difference in the utility between buprenorphine and methadone. In the absence of a systematic review of the available evidence the review group considered that the exclusion of other relevant data could lead to bias in favour of Suboxone®.

- The main efficacy outcome used in the model was the number of opioid positive and negative urine tests for patients (Kamien *et al*. 2008). Retention rates were also included. The retention rate is assumed to be constant for both methadone and Suboxone®. Mattick *et al*. indicates that there is no statistical difference in retention rates although patients in the study (N=405)

remained on methadone longer. The assumption that methadone has better retention rates has not been explored in the dossier; evidence from the Cochrane Reviews indicates that patients stay on methadone longer than buprenorphine. A mortality rate is applied for methadone and not for buprenorphine however there is no robust supporting evidence for this assumption. The review group ran the model without the mortality rate for methadone and it had little overall impact.

Results

- For treatment provided in the clinic setting the cost and QALYs associated with Suboxone® were estimated by the company to be €26,290 for 0.619 QALYs, and for methadone to be €26,828 for 0.588 QALYs. The ICER was estimated to be cost saving €-17,337/QALY i.e. Suboxone® dominates methadone (less expensive and more effective). The review group do not consider this ICER to be robust due to the concerns with the inputs and in particular the rate of opiate negative urine tests, the utility inputs and the mortality risk for methadone only. The review group reran the model using the base case urine negative/positive of 50%/50% (as per the company model) for both buprenorphine and methadone, equal utility gain for Suboxone® and methadone (i.e. no difference) and under these assumptions methadone dominates Suboxone®. When treatment is provided in the community setting (through pharmacies) the costs and QALYs were estimated by the company to be €3,558 for 0.619 QALYs and for methadone to be €2,737 for 0.588 QALYs. The ICER for Suboxone® was estimated to be €26,480/QALY. The review group reran the model using the same input changes as for the scenario in the clinic setting and the ICER increased to €374,315/QALY.

Sensitivity analysis

- A one way sensitivity analysis (OWSA) varied the following parameters; price of Suboxone®, daily average dose of Suboxone®, utility and negative opioid urine tests. The primary driver of the model was the negative urinalysis rate. The review group reran further analysis changing the key parameters, utility, number of opioid negative urine tests and the retention

rate and when adjusted to be the same as methadone, methadone dominates Suboxone®.

- The probability of cost effectiveness at a threshold of €45,000/QALY under the assumptions that both methadone and Suboxone® work similarly is 0%.

4. Budget Impact Analysis

Suboxone® contains buprenorphine and naloxone and is available in two strengths; buprenorphine 8mg/ naloxone 2mg and buprenorphine 2mg/naloxone 0.5mg and in pack sizes of 28. The price to wholesaler of Suboxone® is €81.66 and €24.28 respectively. The drug is for sublingual use and is dissolved under the tongue.

The estimated drug cost to the HSE clinic is €83,791 in 2014, €113,995 in 2015, €156,798 in 2016, €220,065 in 2017 and €319,531 in 2018. The estimated drug cost to the PCRS through the community schemes is €90,494 in 2014, €123,115 in 2015, €169,342 in 2016, €237,670 in 2017 and €345,094 in 2018. The gross budget impact for Suboxone® in the community, including patient care fees, controlled drug fees, dispensing fees is €146,093 in 2014, €198,756 in 2015, €273,385 in 2016, €383,692 in 2017 and €557,116 in 2018.

The company have estimated the net budget impact to be €127,432 in 2014, €173,367 in 2015, €238,463 in 2016, €334,680 in 2017 and €485,952 in 2018. The review group have recalculated this including only drug costs, as the fees should cancel out if patients are put on one replacement therapy instead of another. The recalculated net budget impact for community and clinic drug costs would be €138,038 in 2014, €187,797 in 2015, €258,310 in 2016, €362,535 in 2017 and €526,397 in 2018.

5. Conclusion

The company have not demonstrated a robust cost effectiveness case for Suboxone® compared to methadone.