Cost Effectiveness of pregabalin (Lyrica®) for the treatment of neuropathic pain in adults.

The NCPE has performed a re-evaluation of the use of pregabalin for this indication. Pregabalin may be considered cost effective given certain assumptions.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the applicant's (Pfizer Healthcare Ireland) economic dossier on the cost effectiveness of pregabalin. 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 that 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 that 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 ***Date June 2015***

Summary

Pregabalin (Lyrica®) is currently used in Ireland for the treatment of adults with neuropathic pain. In accordance with the Health Act (Pricing and Supply of Medical Goods) 2013 (section 18(4)), the HSE has requested the NCPE to examine the cost effectiveness of the drug for this indication. Pfizer Healthcare Ireland (PHI) submitted a dossier on the cost effectiveness of pregabalin (Lyrica®) for neuropathic pain on September 12th 2014.

1. Comparative Effectiveness and Safety

The evidence submitted by PHI for the comparative effectiveness of pregabalin was adapted from a guideline document ('CG173') produced by NICE. This guideline examined the overall pharmacological management of neuropathic pain. The evidence was derived from a network meta-analysis of randomised controlled trials of monotherapy with various agents in the treatment of neuropathic pain. Comparative effectiveness was presented in terms of the probability of achieving a 30-49% or ≥50% reduction in pain with each treatment.

Evidence was presented for a range of drugs including gabapentin, duloxetine, tramadol and amitriptyline, treatments which are comparators relevant to the HSE. Evidence was not provided for the additionally relevant treatments capsaicin cream and topical lidocaine (medicated plaster); no evidence was submitted for capsaicin cream, and the efficacy of topical lidocaine, for the purposes of a scenario analysis, was assumed by PHI to equal that of placebo.

There was a 57% probability of pain reduction associated with pregabalin use, as compared to a 53% probability for each of amitriptyline and gabapentin use, and a 36% probability of pain relief following placebo use. After tramadol (42%), pregabalin had the highest probability (41%) of a ≥50% pain reduction, compared with amitriptyline and gabapentin (each 38%).

Evidence on comparative safety was presented for two specific side effects which included dizziness and nausea. The review group consider this to be an incomplete summary of the adverse effect profile. Regarding overall safety data, pregabalin and gabapentin were associated with withdrawal from treatment due to overall adverse events to a similar level of probability (19% and 18%, respectively) while amitriptyline had a higher probability of withdrawal (24%).

2. Cost-Effectiveness analysis

A cost utility analysis was presented to provide evidence for the cost effectiveness of pregabalin versus other treatments for neuropathic pain. The perspective of the HSE (payer) was presented

A decision tree model was constructed in TreeAge Pro® and was based on the model constructed by NICE for the development of guideline CG173. The model time horizon was 20 weeks. This time horizon was chosen by NICE for the model within CG173 as the clinical trial data considered by NICE did not extend beyond twenty weeks for all of the treatments considered. However, the NCPE considers this time horizon to be short with respect to the present decision problem given the typically chronic nature of neuropathic pain. The limited length of time of the trials should be considered by clinicians in their prescribing practice.

Absolute costs and quality-adjusted life years (QALYs) associated with pregabalin, placebo, and the comparators gabapentin, duloxetine, and tramadol, were presented as the base-case analysis. Costs and QALYs for the use of topical lidocaine (though lidocaine efficacy was assumed equal to placebo) and amitriptyline were presented as scenario analyses. Incremental costs and QALYs were presented for the comparison of pregabalin to (i) gabapentin, and (ii) amitriptyline, as requested.

QALYs were calculated using the probabilities of 30-49% or ≥50% pain reduction and the probabilities of experiencing nausea, dizziness, or withdrawal from treatment due to adverse events, which were derived from the evidence synthesis. The probability estimates were combined with health-state utility and adverse event disutility values which were taken from the literature as per the NICE guideline CG173. The cost associated with pregabalin was based on a daily dose of 400mg, which represented the weighted mean of the doses used in the trials which provided the efficacy data. The review group consider that doses lower than 400mg are more likely to be applied in the Irish community setting. As such, the cost effectiveness model may not accurately represent the real-life costs and QALYs associated with pregabalin use. The review group notes that a scenario analysis by NICE, in the development of CG173, found that a 'typical' daily dose of 300mg of pregabalin was

associated with lower cost effectiveness of pregabalin and favoured the use of other treatments.

Results

Pregabalin was found to be cost effective versus both of its nearest comparators, gabapentin and amitriptyline, at a willingness-to-pay threshold of €45,000/QALY. In the case of the comparison to gabapentin, pregabalin resulted in an incremental QALY of 0.005 and an incremental cost of €100, producing an ICER of €19,655/QALY. For the comparison to amitriptyline, pregabalin resulted in an incremental QALY of 0.009 and an incremental cost of €362, producing an ICER of €41,184.

Sensitivity analysis

One way and probabilistic sensitivity analyses were included in the submission to explore the uncertainty in the model.

- A one way sensitivity analysis (OWSA) varied a wide range of parameters and found that the model was particularly sensitive to the probability of withdrawal from treatment due to adverse events associated with pregabalin or its comparators. For example, in the comparison of pregabalin to amitriptyline, where treatment withdrawal rates were assumed to be at the upper end of the probability range, the cost effectiveness of pregabalin exceeded the willingness-to-pay threshold: a probability of amitriptyline withdrawal of 41% resulted in an ICER of €68,217/QALY; a probability of pregabalin withdrawal of 26% resulted in an ICER of €110,544/QALY.

- A cost-effectiveness acceptability curve was provided by PHI to illustrate the cost effectiveness of each treatment at different willingness-to-pay thresholds. Amitriptyline was found to be the treatment with the highest probability of cost-effectiveness up until a willingness-to-pay threshold of €45,000 per QALY, at which point pregabalin demonstrated an equal probability of cost-effectiveness to that of amitriptyline. Also at this threshold, gabapentin represents the next highest probability of cost-

effectiveness.

The probability of cost effectiveness of pregabalin versus gabapentin at a threshold of €45,000/QALY was 54%. The probability of cost effectiveness of pregabalin versus amitriptyline at this threshold was 53%.

3. Budget Impact Analysis

The most recent PCRS data available to the NCPE (November 2013-October 2014) showed that the 12-month cost of pregabalin across the GMS, DP and LTI schemes amounted to €33.5million. Given the availability of generic pregabalin from 2015 onwards, PHI estimate that the total drug costs of pregabalin under the community drug schemes are expected to reduce. However, as Lyrica® maintains a patent on the use of pregabalin for neuropathic pain (though not for generalised anxiety disorder or for epilepsy) in Ireland until July 2017, the applicant was asked to submit a budget impact scenario whereby Lyrica® holds 100% of the pregabalin market share for the treatment of pain until mid-2017. Under this scenario, PHI estimate that the total costs of pregabalin to the HSE will reduce from €28million in 2015 to €17million in 2019, assuming sales do not increase during this time. However, the cumulative budget impact over these five years remains significant, falling in the region of €105million.

4. Conclusion

The NCPE Review Group concludes that pregabalin (Lyrica®) may be cost effective versus amitriptyline and gabapentin, however, the model is based on dose and duration assumptions which may not reflect standard practice.