Cost Effectiveness of pregabalin (Lyrica®) for the treatment of Generalised Anxiety Disorder.

The NCPE has issued a recommendation regarding the use of pregabalin for the treatment of generalised anxiety disorder. The NCPE Review Group concludes that, at the current price, pregabalin (Lyrica®) is not a cost effective treatment for this indication.

Pregabalin (Lyrica®) is currently used in Ireland for the treatment of generalised anxiety disorder. In accordance with the Health Act (Pricing and Supply of Medical Goods) 2013 (section 18(4)), the HSE has requested the National Centre for Pharmacoeconomics (NCPE) to examine the cost effectiveness of this drug for this indication.

The NCPE has evaluated the Applicant's (Pfizer Healthcare Ireland) dossier on the cost effectiveness of pregabalin (Lyrica®) for this indication. 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.

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 **December 2014**

Cost Effectiveness of Pregabalin (Lyrica®) for the Treatment of Generalised Anxiety Disorder

Pregabalin (Lyrica®) is currently used in Ireland for the treatment of people with generalised anxiety disorder (GAD). 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 submitted a dossier on the cost effectiveness of pregabalin for this indication to the NCPE in September 2014.

1. Comparative Effectiveness and Safety

The comparators are the licensed treatment options for generalised anxiety disorder in Ireland: venlafaxine, duloxetine, paroxetine, and escitalopram. Sertraline and citalopram are included in scenario analysis as unlicensed options.

Efficacy and safety outputs from meta-analyses (random-effects; implemented in WinBUGS®) reported by Mavranezouli *et al* [1] are adopted for this cost utility analysis. Mavranezouli *et al* synthesised data from 39 randomised controlled trials that provided direct or indirect evidence on 'discontinuation due to intolerable adverse events'. Of these, 26 trials also provided direct or indirect evidence on 'conditional response'(≥ 50 % reduction in the Hamilton Anxiety Rating Scale score in those not discontinuing treatment due to adverse events). A further model in each analysis predicted the placebo effect on these outputs using the placebo arms of the trials [1].

Mavranezouli *et al* also investigated 'relapse after initial response'. A systematic literature review identified four placebo-controlled trials that assessed pharmacological treatments in people with GAD. Two assessed selective serotonin reuptake inhibitors (SSRI), one assessed a serotonin-norepinephrine reuptake inhibitor (SNRI) and one assessed pregabalin. For the network meta-analysis, the pregabalin study (Feltner *et al* [2]) was excluded. Reasons given for exclusion included a higher relative risk of relapse of pharmacological treatment vs. placebo in Feltner *et al* [2] than in the other studies, also the inclusion of data from Feltner *et al* increased the heterogeneity of the meta-analysis. In the cost-utility analysis, the estimate from this network meta-analysis was used for all pharmacological treatments, including pregabalin. The Review Group raised concerns regarding the exclusion of Feltner *et al* [2]. In response, the Company investigated the impact of varying the relative risk of relapse with pregabalin in a sensitivity analysis (*see sensitivity analysis*). The probability of relapse

following response in the 'no treatment' node of the model was estimated by pooling data from the placebo arms of all four studies.

Mavranezouli *et al* conclude that, when comparing pharmacological treatments, sertraline had the lowest probability of being discontinued due to adverse events, followed by pregabalin, escitalopram, paroxetine, venlafaxine XL and duloxetine. In terms of conditional response, duloxetine had the highest probability of conditional response followed by sertraline, venlafaxine XL, pregabalin, escitalopram and paroxetine [1].

In this cost-utility analysis, clinical data for escitalopram was used as a proxy for citalopram in the evaluation of citalopram. There is no clinical data to support this assumption.

2. Cost-Effectiveness analysis

The analysis evaluates the cost effectiveness of pregabalin (vs. other pharmacological treatments) for the treatment of people with GAD. A cost-utility analysis was conducted from the perspective the Health Service Executive, Ireland.

A decision tree model was constructed in TreeAge Pro®. The structure of the model was based on that by Mavranezouli *et al* [1]. The model time horizon was 42 weeks, based on an initial pharmacological treatment of 8 weeks, a maintenance period of 26 weeks and to accommodate a switch to second-line treatment if necessary. The Review Group considers the time horizon to be short. Various Guidelines state that treatment for GAD should be continued for at least a one to two years [3, 4]. Approximately 40% of individuals with GAD experience symptoms for more than 5 years [5].

The main model outcomes were 'discontinuation due to intolerable AEs', 'conditional response' and 'relapse after initial response'. Outputs from the data synthesis by Mavranezouli *et al* [1] were adopted for this cost-utility analysis.

For the handling of all utility data, the submission refers to the 2011 NICE CG113 Guidelines [3]. Health state utility values were derived from Allgulander *et al* [6]. Allgulander *et al* evaluated the SF-6D in 273 people with GAD in a double-blind, placebo-controlled, multinational trial of escitalopram. Disutility values associated with the adverse events of

pharmacological treatments were derived from Revicki & Wood [7]. In the model, only intolerable adverse events are associated with a disutility. This disutility was applied for only 2 weeks under the assumption that drug discontinuation would occur within 2 weeks from initiation.

Results

The following incremental cost effectiveness ratios (ICERs) were obtained compared to the licensed and the unlicensed pharmacological comparators:

Licensed comparators	**ICER (€/QALY)**
Pregabalin vs. paroxetine	50,936
Pregabalin vs. duloxetine	122,649
Pregabalin vs. venlafaxine XL	215,344
Pregabalin vs. escitalopram	353,675
Unlicensed comparators	
Pregabalin vs. citalopram	364,771
Pregabalin vs. sertraline	Sertraline dominates

Scenario Analysis

A treatment strategy model was developed, to include cognitive behavioural therapy as a first line treatment. Patients who experience a relapse or who have not responded to cognitive behavioural therapy are assumed to receive first line drug therapy. Likewise, patients who relapse or who have not responded to first line drug therapy are assumed to receive a second line drug.

The cost-effectiveness acceptability curve identifies cognitive behavioural therapy, followed by escitalopram or venlaflaxine (first line drug) followed by pregabalin (second line drug) as the overall most cost-effective strategy for the treatment of GAD.

Sensitivity Analysis

Sensitivity analyses were undertaken to explore the uncertainty in the model; both one way (deterministic) and probabilistic sensitivity analysis were included. Deterministic sensitivity analyses were undertaken on the evaluation that compared pregabalin vs. escitalopram. Of interest, the ICER is sensitive to changes in the efficacy and safety profile of the comparator and the relative risk of relapse with pregabalin. The ICER is also sensitive to the assumed

dose of pregabalin (in this sensitivity analysis the cost of pregabalin, but not the efficacy and safety profile is varied).

The probability of cost effectiveness was investigated at a threshold of €45,000/QALY. When compared solely to escitalopram, there is a 31% probability that pregabalin is cost effective. When all comparators are simultaneously considered, there is a range in probabilities from 10% (placebo) to 26% (escitalopram); the overall probability that pregabalin is cost effective is 13%.

3. Conclusion

The NCPE Review Group concludes that, at the current price, pregabalin (Lyrica®) is not cost effective as a first line treatment for generalised anxiety disorder. Pregabalin may be considered cost effective (as a third line treatment) in patients who have relapsed or who have not responded to cognitive behavioural therapy (first line treatment) and who subsequently have relapsed or have not responded to escitalopram or venlaflaxine (first line drug treatment).

References

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