Scottish Medicines Consortium

pregabalin, 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg capsules (Lyrica ®) No. (389/07)

Pfizer Limited

6 July 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pregabalin (Lyrica ®) is not recommended for use within NHS Scotland for the treatment of central neuropathic pain in adults.

In a randomised controlled trial pregabalin was superior to placebo in terms of the primary efficacy variable, the weekly mean pain score.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the SMC.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of central neuropathic pain in adults.

Dosing information

150mg to 600mg per day given in either two or three divided doses.

Product availability date

7 September 2006

Summary of evidence on comparative efficacy

Pregabalin is an anti-epileptic that decreases central neuronal excitability by binding to an auxiliary subunit of a voltage-gated calcium channel in the central nervous system. It also reduces the release of several neurotransmitters including glutamate, noradrenaline and substance P though the significance of the latter effects is unknown.

One randomised double-blind, placebo-controlled trial has been conducted in 137 adult patients with spinal cord injury of at least one-year duration with a non-progressive (chronic) stage of at least six months duration, and with central pain (defined by the International Association for the Study of Pain classification) that started after the spinal cord injury, and persisted continuously for at least three months, or with remissions and relapses for at least six months. Patients were required to have a score of at least 40mm on the 100mm visual analogue scale of the Short Form-McGill Pain Questionnaire (SF-MPQ) at both the screening and randomisation visits. Patients taking NSAIDs, opioid analgesics, non-opioid analgesics, anti-epileptic drugs (excluding gabapentin) and antidepressant medications were allowed to enter the study if they had been stable for at least one month before the study and would remain so during the study. Seventy patients were randomised to pregabalin (starting dose 150mg/day, increased weekly to 600mg/day, if needed and tolerated; given twice daily), and 67 patients to placebo, for a treatment period of 12 weeks. The primary efficacy assessment was the endpoint weekly mean pain score (defined as the mean of the last seven post-randomisation entries of the daily pain diary while on study drug including the day after the last day of dosing) using a self-assessed 11-point numerical rating scale (0=no pain to 10=worst possible pain). Secondary efficacy assessments included the SF-MPQ which yields a sensory, affective and total score for pain descriptors.

The mean baseline and endpoint scores for pregabalin were 6.54 and 4.62, and for placebo were 6.73 and 6.27, respectively. Pregabalin was significantly superior to placebo for the primary endpoint; treatment difference 1.53, 95% confidence intervals (CI) 0.92, 2.15. There was a significant difference in the proportion of subjects who had a ≥ 30% reduction in mean pain score from baseline to endpoint in the pregabalin group (29/69; 42%) compared to the placebo group (11/67;16%). Similarly the proportion of subjects who had a ≥ 50% reduction in mean pain score from baseline to endpoint was significantly higher in the pregabalin group (15/69; 22%) compared to placebo group (5/67; 8%). Based on the 30% and 50% responder rates the number needed to treat (NNT) was 3.9 and 7.1, respectively.

The sensory, affective and total scores of the SF-MPQ recorded statistically significant treatment differences in favour of pregabalin beginning at week one, which continued, at each time point collected, to the end of the treatment period at week 12. Differences (95% CI) between endpoints (placebo-pregabalin) were 3.4 (1.3, 5.4), 1.54 (0.62, 2.47) and 4.9 (2.1, 7.7) for sensory, affective and total scores.

An open label study recruited 104 patients who met the inclusion criteria and definitions of the double-blind study and who had received study medication under double-blind conditions. Patients were given pregabalin, starting at a fixed dose of 150mg/day and dose adjustment up to 600mg/day was allowed as needed to achieve maximum efficacy, whilst maintaining tolerability. Mandatory temporary discontinuations (drug holidays) occurred every three months during open-label treatment with pregabalin. The main criterion to assess the efficacy of pregabalin was the SF-MPQ on day 1 and at each clinic visit starting at week 4 and up to week 40. The mean (standard deviation) change from baseline (last available value in the double blind study) to endpoint in sensory, affective, and total scores of the SF-MPQ was -0.7 (5.8), -0.3 (2.8), and -1.0 (8.1), respectively.

Summary of evidence on comparative safety

The incidence of all-cause treatment-emergent adverse events was 75% (50/67) for the placebo group and 96% (67/70) for the pregabalin group, and the incidence of adverse events considered related to study medication was 49% (33/67) and 83% (58/70) respectively.

In the double-blind study, somnolence and dizziness, which were generally mild to moderate, were reported in 41% and 24% of patients on pregabalin respectively, compared with 9% each on placebo. Four patients (5.7%) discontinued treatment in the pregabalin group due to somnolence compared with no patients in the placebo group. No patients discontinued because of dizziness. In the pregabalin group the median time to onset of somnolence was eight days and the median duration was 53 days. In the open label study the incidence of somnolence was 19%.

Summary of clinical effectiveness issues

There are no comparative trials of pregabalin with other agents used in the treatment of central neuropathic pain therefore it is not possible to determine the comparative efficacy of pregabalin. The NNT (50% pain relief) for pregabalin in peripheral neuropathic pain has been reported as 4.2 (3.4-5.4) compared with a NNT for gabapentin in mixed neuropathic pain of 5.1 (4.1-6.8). In the double-blind central neuropathic pain study the NNTs for pregabalin were 7.1 (50% pain relief) and 3.9 (30% pain relief).

The incidence of somnolence in the double-blind trial (41%) was higher than in peripheral neuropathic pain studies where an incidence of 23% has been reported. However, in the central neuropathic pain study the proportions of pregabalin treated patients receiving concurrent medication with sedating drugs such as muscle relaxants (including baclofen and dantrolene), and benzodiazepines were 54% and 40% respectively. These drugs may have additive CNS effects to those of pregabalin.

There was an imbalance at baseline in terms of the percentage of patients on concomitant pain medication; 69% in the placebo group and 76% in the pregabalin group. More patients in the pregabalin group were taking tricyclic antidepressants (18% of placebo treated and 33% of pregabalin treated patients).

However, opioids and NSAIDs/Cox-2 medications were taken by 48% and 28% of patients in the placebo group and 30% and 19% of patients in the pregabalin group. The company, in the submission to the European Medicines Agency (EMEA), explained these differences as chance imbalances and noted that the imbalances did not consistently favour the pregabalin treatment group. An ancillary analysis of effect size adjusted for use of concurrent medication showed similar results to the primary analysis.

Summary of comparative health economic evidence

The manufacturer presented a one-year cost utility "hidden" Markov model with daily cycles of the evolution of pain states, within which patients were classified as having mild pain, moderate pain or severe pain. The comparator in the analysis was placebo. The economic model was specifically focused on the treatment of central neuropathic pain following spinal cord injury. The base case analysis estimated an average gain of 0.11 QALYs at a cost of £839 to give a cost effectiveness estimate of £7,694 per QALY.

Pregabalin was evaluated against placebo on the basis that there are no other pharmacological treatments licensed for this indication in the UK. However a range of other treatments such as tricyclic antidepressants and anticonvulsants are being currently used within Scotland for central neuropathic pain. These treatments may be less expensive than pregabalin.

Transition probabilities for the initial 12 weeks were drawn from the pivotal randomised controlled trial, with extrapolation to 52 weeks being based upon the one year follow up associated with this trial. The initial distribution of pain scores was taken from the pivotal trial. A time varying percentage reduction was applied to this for each arm. It is unclear whether this was applied across pain states or across pain scores. There was an overall lack of transparency in the model structure.

Quality of life values were drawn from a paper which evaluated pain scores and quality of life through EQ-5D among patients suffering conditions associated with neuropathic pain. Changes to pain scores were assumed to drive results and quality of life values, regardless of any possibly associated co-morbidities. In addition, a standard percentage reduction was applied to pain scores, regardless of the baseline. This may have overestimated the gain in quality of life.

Only the direct drug costs of pregabalin were considered. Adverse events were not considered within the modelling despite pregabalin having higher rates of adverse events in the trial.

Given these issues, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Federation of Neurological Societies (EFNS) published a guideline on pharmacological treatment of neuropathic pain, in 2006. It highlighted the small number of

RCTs conducted in patients with central pain. It concluded that there is level B evidence (probably effective) for the use of lamotrigine, gabapentin, pregabalin or tricyclic antidepressants for post stroke or spinal cord injury pain.

Additional information: previous SMC advice

Following an independent review panel assessment the SMC issued the following advice in July 2006; pregabalin (Lyrica) is not recommended for use within NHS Scotland for the treatment of peripheral neuropathic pain in adults. Comparative clinical and cost effectiveness have not been demonstrated. Further controlled data are needed to establish its place in therapy in patients refractory to or intolerant of other pharmacological treatments.

Additional information: comparators

There are no other drugs licensed for the treatment of central neuropathic pain. The EFNS guideline highlighted lamotrigine, gabapentin, pregabalin or tricyclic antidepressants for the treatment of post stroke or spinal cord injury pain. Lamotrigine and amtriptyline are not licensed for the treatment of any type of neuropathic pain although amtriptyline is commonly used for treatment of peripheral neuropathic pain. Gabapentin is licensed for the treatment of peripheral neuropathic pain and carbamazepine for treatment of paroxysmal pain of trigeminal neuralgia. Responses from experts consulted as part of the SMC process support the use of gabapentin, amtriptyline and carbamazepine for central neuropathic pain.

Cost of relevant comparators

Drug	Dose regimen per day	Cost per year (£)
pregabalin	**150-600mg**	**837 ***
pregabalin	**150-600mg**	**1256****
gabapentin †	900-3600mg	176 -702[a]/2315[b]
gabapentin (Neurontin) †	900-3600mg	579- 2315
carbamazepine †	400-1600mg	42-131
carbamazepine (Tegretol Retard) †	400-1600mg	68-269
amitriptyline †	25-75mg	21-44

*75mg bd – 300mg bd. **50mg tds – 200mg tds.
a. based on using 300mg capsules
b. based on using 600mg tablets.
† These drugs are not licensed for the treatment of central neuropathic pain.
Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 1/5/07

Additional information: budget impact

The manufacturer estimated that the number of patients being treated for central neuropathic pain was between 25% and 75% of patients with spinal cord injury, which translated into between 800 and 2,400 patients being eligible for treatment with pregabalin. Based upon a market share of 10% in year 1, this translated in a direct drug cost estimate of between £50k and £145k. By year 5 with a market share of 30% this was anticipated to increase to between £170k and £510k.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 June 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission. The reference shaded grey is additional to the reference supplied with the submission.

Siddall PJ, Cousins MJ, Otte A et al (2006). Pregabalin in central neuropathic pain associated with spinal cord injury. Neurology 67; 1792-1800

European Medicines Agency. Scientific discussion (EMEA/H/C/000546/II/0007). Accessed on 16/4/07.