Scottish Medicines Consortium

pregabalin 25mg, 50mg, 75mg, 100mg, 150mg, 200mg and 300mg capsules (Lyrica®) No. (157/05)

Pfizer Ltd

09 April 2009

The Scottish Medicines Consortium (SMC) 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 second resubmission

pregabalin (Lyrica®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in adults.

The clinical evidence of efficacy in patients with peripheral neuropathic pain who are refractory to treatment was based on open-label, uncontrolled, non-randomised studies, with small patient numbers and different methodologies.

Pregabalin is restricted to use in patients who have not achieved adequate pain relief from, or have not tolerated, conventional first and second line treatments for peripheral neuropathic pain. Treatment should be stopped if the patient has not shown sufficient benefit within 8 weeks of reaching the maximally tolerated therapeutic dose.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of peripheral neuropathic pain

Dosing information

Initially 150mg daily, then increased to 300mg daily after 3 to 7 days according to individual patient response and tolerability, and increased again if needed to a maximum dose of 600mg daily after another 7 days. The daily dose may be given in two or three divided doses.

Product availability date

July 2004

Summary of evidence on comparative efficacy

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

This resubmission focused on the use of pregabalin in patients with peripheral neuropathic pain who are treatment-refractory. The company submitted evidence from six non-randomised studies in treatment-refractory patients and a total of 22 double-blind randomised studies which included some patients refractory to gabapentin and other agents.

Ten of the 22 studies were registration studies. Five studies recruited patients with diabetes who had glycated haemoglobin (HbA1C) ≤11% and distal symmetrical sensorimotor polyneuropathy for ≥1 year duration. Four studies recruited patients with postherpetic neuralgia of ≥3 and 6 months duration after healing of the herpes zoster skin rash. A further double-blind study recruited patients with either diabetic peripheral neuropathy or postherpetic neuralgia. In all studies patients had a score of ≥40mm on the 100mm visual analogue pain scale of the Short-Form McGill Pain Questionnaire (SF-MPQ) and during the week before randomisation, had at least four daily pain scores ≥4 assessed on an 11-point scale (where 0=no pain and 10=worst possible pain). Five of these studies included patients who had not responded to gabapentin and five excluded these patients.

Patients were randomised to placebo or pregabalin (75 to 600mg daily in two or three divided doses) with one study including amitriptyline as an active treatment arm. The primary endpoint, weekly mean pain score (assessed via the 11-point Likert scale) at endpoint, was compared in the intention to treat population between placebo and active treatments via an analysis of covariance which adjusted for weekly mean pain score at baseline.

In the eight-week, active comparator study, pregabalin 600mg daily was not significantly different from placebo in the primary analysis of mean pain scores at end-point. The difference between amitriptyline 75mg daily and placebo was significant. This pattern was repeated for the proportion of patients achieving a response (≥50% reduction in pain scores) and patients' and clinicians' global impression of pain. In no analysis was the result significant for pregabalin but not amitriptyline.

Pregabalin 300mg and 600mg were associated with significantly lower weekly mean pain scores at endpoint compared with placebo in most other studies, except for the 300mg dose in one diabetic neuropathy study. Weekly mean pain scores with pregabalin 150mg were generally lower than placebo, but differences between this dose and placebo were not consistently significant. In these studies, responders were defined as patients who had a 50% reduction in mean weekly pain score compared with baseline. Similar efficacy patterns were observed in this secondary endpoint.

Of the other 12 double-blind, randomised, placebo-controlled studies, ten did not exclude patients who had not responded to gabapentin, doses were both fixed and flexible and five allowed concomitant neuropathic pain medications. Thus the design and inclusion criteria in these studies varied and the outcomes presented a mixed picture with a few studies showing no significant benefit of pregabalin (150 to 600mg) treatment over placebo.

Additional supporting data came from a published, uncontrolled, 15 month open-label safety study in 81 patients recruited from previous pregabalin studies (73 had received pregabalin and 8 placebo). Patients had a score o ≥40mm on the 100mm visual analogue pain scale of the Short-Form McGill Pain Questionnaire (SF-MPQ) and were intolerant of or had experienced lack of efficacy after ≥two weeks of at least minimum doses of tricyclic antidepressants, gabapentin 1,800mg or other third line agents. Patients were given pregabalin 150 to 600mg daily and could continue to receive and adjust other analgesics, to optimise their pain control. Pregabalin was discontinued quarterly for 3 to 28 days until patient's pain worsened, when they could recommence treatment. If the patient did not relapse they were discontinued from the study. Data from 45 patients with painful diabetic peripheral neuropathy and 36 patients with postherpetic neuralgia indicated that mean SF-MPQ scores decreased from respective baseline values of 73mm and 75mm to 47mm and 51mm at the 15-month endpoint, a 34% improvement in mean pain scores from baseline. Four patients were discontinued from the study as they had not relapsed during treatment withdrawal and 56 patients completed 15 months of pregabalin treatment.

Three audits undertaken in the UK in a total of 96 patients were also presented. Patients included in these audits had unsatisfactory response to or could not tolerate other neuropathic agents including gabapentin. All reported some positive benefit for pregabalin.

Summary of evidence on comparative safety

Pregabalin is commonly associated with central nervous system adverse events typical of most antiepileptic drugs. In common with gabapentin it is eliminated as unchanged drug primarily by renal excretion. It does not bind to plasma proteins and does not induce or inhibit hepatic enzymes.

The overall incidence of serious adverse events in the controlled studies was 2.3% with pregabalin versus 2.1% with placebo. In an integrated safety database across a range of indications for pregabalin, the most commonly reported adverse reactions in the pregabalin-treated patients were dizziness (29%) and somnolence (23%).

Peripheral oedema was noted mainly in the elderly, affecting approximately 11% of patients after one to three months of treatment and persisting in 54% of these patients. Weight gain was in general a dose-dependent finding across studies, which was first observed as an adverse event with a median time to onset of two weeks and persists over time.

A meta-analysis of three of the pregabalin placebo-controlled studies found a significantly increased risk of somnolence, dizziness and oedema.

Summary of clinical effectiveness issues

It is recognised that neuropathic pain is often treatment-refractory and patients are frequently treated with a wide range of agents tried until satisfactory pain control is achieved for the individual patient.

There are no direct studies comparing pregabalin to gabapentin in the treatment of neuropathic pain and so relative efficacy is uncertain. In addition, there are limited data in patients unresponsive to gabapentin since many of the double-blind studies excluded patients who had failed to respond to previous treatment with gabapentin ≥1200mg/day and in other studies the patient population was mixed, including responders, non-responders and those who had not been treated with gabapentin. Since the drugs are considered to act in the same way, the exclusion could potentially favour the results of the pregabalin studies and the mixed patient population studies are difficult to interpret with some of these studies showing no significant benefit in mean pain scores or in response rate in the pregabalin arm compared with placebo. The uncontrolled, open-label study in patients intolerant of, or refractory to, other treatments used pregabalin as add-on therapy to other background analgesia. Although this found a reduction in pain score with pregabalin within the first three months, which was maintained for up to 15 months, these results are difficult to interpret due to a number of limitations. The study was of open design with no control for placebo response, was descriptive with no statistical testing to assess efficacy and patients could remain on other analgesic medication with doses adjusted during the study to optimise control.

Data presented from three UK audits were limited by small patient numbers, a significant drop-out rate, not all patients being accounted for and the open design and methodology of these studies making it difficult to draw meaningful conclusions.

Two published systematic reviews have been identified. One review included data from five double-blind pregabalin studies (three in painful diabetic peripheral neuropathy and two in post-herpetic neuralgia) to calculate numbers needed to treat (NNT) to achieve a 50% reduction in pain scores and numbers needed to harm (NNH) and used these as a basis for an evidence-based treatment algorithm. The authors reported a combined NNT for pregabalin at doses of 150 to 600mg in both pain models of 4.2 (range 3.4 to 5.4). This was reported to be similar to the NNT for gabapentin at all doses and pain models (5.1 (range 4.1 to 6.8). The NNH for pregabalin was considered to represent a relatively high rate of withdrawal and was 11.7 (range 8.3 to 19.9) compared with 26.1 (range 14.1 to 170) for gabapentin. For a treatment algorithm in peripheral neuropathic pain based on pain relief, the NNT are lowest for tricyclic antidepressants, then opioids, then tramadol, then gabapentin/ pregabalin.

The second systematic review was in patients with post-herpetic neuralgia lasting for more than three months. The review included 32 studies and calculated NNT defined by a 50% reduction in pain. Pooled NNT for therapies for established post-herpetic neuralgia (PHN) were reported as tricyclic antidepressants (2.64), opioids (2.67), pregabalin (3.42), gabapentin (4.39) and tramadol (4.76). NNT for topical therapies were reported as 2.0 for lidocaine patch and 3.26 for capsaicin. The European Public Assessment Report (EPAR) also presented results of a meta analysis which suggested that pregabalin had a greater treatment effect in post-herpetic neuralgia than diabetic peripheral neuropathy.

A recent independent meta-analysis of three of the above diabetic peripheral neuropathy studies (n=728; 476 pregabalin and 252 placebo) found pregabalin was associated with a

significant decrease in pain score (weighted mean difference, 1.15 (95% CI: 0.81 to 1.49) and patients in the pregabalin group were significantly more likely to achieve a 50% reduction in mean pain score, relative risk 4.05 (95% CI: 3.01 to 5.46). However, they were also at a significantly increased risk of somnolence, dizziness and oedema.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis of pregabalin in treatment-refractory patients in addition to usual care (a mix of existing treatments, including licensed and 'off-label' medicines) versus usual care alone. Clinical effectiveness estimates were based on four non-randomised clinical trials in this patient group. Resource use and utility data were obtained from surveys of patients in Wales. Assumptions were made about the withdrawal rate from pregabalin over time based on the longest open-label study.

On this basis it was estimated that over 5 years the additional cost per patient would be £2,748 and the additional QALYs would be 0.25. This resulted in an estimate of the net cost per QALY gained of £10,803.

The manufacturer proposed a realistic niche within the licensed indication and sought relevant clinical data. They have supplemented this with UK-based estimates of resource use and utilities.

Sensitivity analysis has identified that the key uncertainty is the clinical data used and unfortunately this has a number of weaknesses, the most important being that a 'before-and-after' study design does not allow differences observed over time to be attributed to the medicine alone. There was a lack of data from the clinical studies for adverse event rates which several SMC clinical experts suggest may make pregabalin attractive. In addition there were some concerns around the use of the last observation carried forward method (LOCF) for missing data, particularly dealing with a disease that fluctuates over time.

The manufacturer provided supplementary sensitivity analysis, however, which provided reassurance that only in extreme scenarios would pregabalin no longer be cost-effective. Additional analysis was also provided to support the use of a 'stopping rule' as a means to ensure cost-effective usage of treatments. Taking the additional analyses into account, the economic case was considered demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Pain Concern
- The Neuropathy Trust

Additional information: guidelines and protocols

The February 2006, NHS Quality Improvement Scotland best practice statement on the management of chronic pain in adults recommends that the following drugs should be considered for the treatment of neuropathic pain: tricyclic antidepressants (the best available evidence is for amitriptyline); anticonvulsants (gabapentin is thought to be effective); and tramadol. Tricyclic antidepressants should be the preferred initial treatment for neuropathic pain.

The November 2008 Scottish Intercollegiate Guidelines Network (SIGN) publication number 106 (superseding number 44) on the control of pain in cancer recommends that patients with neuropathic pain should have a trial of a tricyclic antidepressant (e.g. amitriptyline or imipramine) and/or an anticonvulsant (e.g. gabapentin, carbamazepine or phenytoin) with careful monitoring of side effects.

The 2008 National Institute for Health and Clinical Excellence (NICE) Clinical Guideline number 66. Type 2 diabetes: The management of type 2 diabetes recommends that neuropathic pain should be initially treated with a tricyclic drug, starting at a low dose and titrating as tolerated. The next step should be to offer a trial of the cheapest (at maximum doses) of duloxetine, gabapentin or pregabalin. This should be stopped if ineffective at maximally tolerated dose. Another of the drugs should be tried if side effects limit dose titration. If the patient remains uncontrolled a trial of opiate should be considered and if the patient is still uncontrolled, they should be referred to a pain management service.

The 2004 NICE Clinical Guideline number 15. Type1 diabetes: diagnosis and management of type 1 diabetes in adults recommends that painful diabetic neuropathy should be initially treated with simple analgesics (paracetamol, aspirin). The next step is a trial of a low- to medium-dose tricyclic antidepressant drug, timed to symptoms. This can be followed by a trial of gabapentin, working up to the maximum tolerated dose or at least 1800mg per day. If gabapentin fails, carbamazepine and phenytoin are alternative choices. If continued chronic pain, consider opiate analgesia and referral to pain management service.

Additional information: comparators

The oral antiepileptic drug, gabapentin is licensed for the treatment of peripheral neuropathic pain. The antiepileptic carbamazepine and the tricyclic antidepressant amitriptyline are used to treat post-herpetic neuralgia but are not licensed for this indication. Topical preparations licensed for treatment of post-herpetic neuralgia include capsaicin (Axsain®) and lidocaine 5% medicated plasters.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Pregabalin	**150 to 600mg daily**	**837 to 1256[#]**
Lidocaine plaster	One to three plasters	878 to 2635
Gabapentin	900 to 1,800mg daily	95 to 1158[+]
Duloxetine	60mg daily	360
Carbamazepine retard	400 to 1,600mg daily	71 to 282
Capsaicin 0.075% cream	Applied three to four times daily	158*
Carbamazepine	400 to 1,600mg daily	39 to 156
Amitriptyline	25 to 75mg daily	12 to 37

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 February 2009. [#]Any dose of pregabalin (150 to 600mg daily) prescribed in two divided doses costs £64/28 days and prescribed in three divided doses costs £97/28 days. [+]When gabapentin is administered as six 300mg capsules per day rather than three 600mg tablets per day the yearly cost of the 1,800mg daily dose is £190 * Costs for capsaicin cream based on the assumption that a 45g tube lasts 28 days.

Additional information: budget impact

The manufacturer's budget impact estimates were based on the use of pregabalin in patients with treatment-refractory peripheral neuropathic pain, estimated at 4.5% of patients with the condition. A 3% net increase in patient numbers each year was included to account for the incident population. The net drug budget impact was estimated at between £402k and £806k by year 5, based on a current and predicted market share of 87% for pregabalin as fourth line or subsequent treatment. The budget impact will be greater if the existing market share is less than the 87% estimated by the manufacturer.

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 19 March 2009.

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 references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Stacey BR, Dworkin RH, Murphy K et al. Pregabalin in the treatment of refractory neutopathic pain: results of a 15-month open-label trial, Pain Med 2008;9:;1202

Finnerup N, Otto M, McQuay H, et al. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005: 1-17.

Hempenstall K, Nurmikko T, Johnson R et al. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med 2005;2(7):628-644

The European Medicines Agency (EMEA) European Public Assessment Report. Pregabalin (Lyrica®) http://www.emea.europa.eu/humandocs/PDFs/EPAR/lycra/084504en6/pdf

Hurley RW, Lesley MR, Adams MCB et al. Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis. Reg Anaes and Pain Med 2008:33;3889