HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 May 2007

LYRICA 25 mg capsules
Pack of 56 capsules (CIP: 365 127-0)
Pack of 84 capsules (CIP: 365 135-3)
Pack of 100 capsules (CIP: 565 814-1)
LYRICA 50 mg, capsules
Pack of 84 capsules (CIP: 365 128-7)
Pack of 100 capsules (CIP: 565 815-8)
LYRICA 75 mg, capsules
Pack of 56 capsules (CIP: 365 129-3)
Pack of 100 capsules (CIP: 565 816-4)
LYRICA 100 mg, capsules
Pack of 84 capsules (CIP: 365 130-1)
Pack of 100 capsules (CIP: 565 817-0)
LYRICA 150 mg, capsules
Pack of 56 capsules (CIP: 365 131-8)
Pack of 100 capsules (CIP: 565 818-7)
LYRICA 200 mg, capsules
Pack of 84 capsules (CIP: 365 132-4)
Pack of 100 capsules (CIP: 565 819-3)
LYRICA 300 mg, capsules
Pack of 56 capsules (CIP: 365 133-0)
Pack of 100 capsules (CIP: 565 820-1)

Applicant: PFIZER

Pregabalin
List I
N03AX16

Marketing Authorisation (MA) date: September 6, 2004

Amendments to MA:
'Generalised Anxiety Disorder in adults' indication extension: March 20, 2006
'Central neuropathic pain in adults' indication extension: September 07, 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the 'Central neuropathic pain in adults' indication extension.

This opinion does not cover indications in epilepsy and generalised anxiety disorder.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Pregabalin

1.2. Indications

Neuropathic pain:
Lyrica is indicated in the treatment of peripheral **and central** neuropathic pain in adults.

Epilepsy:
Lyrica is indicated in combination in the treatment of partial epileptic seizures with or without secondary generalisation in adults.

Generalised anxiety disorder:
Lyrica is indicated in the treatment of generalised anxiety disorder (GAT) in adults.

1.3. Dosage

Dosage varies from 150 to 600 mg per day in two or three part doses.

Lyrica may be taken with or without food.

Neuropathic pain:
Pregabalin treatment may be introduced at a dose of 150 mg per day. Depending on the patient's response and tolerance, the dosage may be increased to 300 mg per day after a 3–7-day interval, and may if necessary be increased to the maximum dose of 600 mg per day after a further 7-day interval.

Use in patients with renal impairment: a reduced dosage may be set on an individual basis in view of the creatinine clearance (see SPC).

Use in patients above 65 years of age: a reduced dosage of pregabalin may be necessary in elderly patients (see SPC).

Interruption of pregabalin treatment:
According to current clinical practice, if pregabalin treatment has to be interrupted, it is recommended to do so gradually over a period of at least one week, whatever the indication.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

N : Nervous system
N03 : Antiepileptics
N03A : Antiepileptics
N03AX : Other antiepileptics
N03AX16 : Pregabalin

2.2. Medicines in the same therapeutic category

Another antiepileptic indicated for neuropathic pain in adults:

- Carbamazepine: TEGRETOL 20 mg/ml, oral suspension; TEGRETOL 200 mg, scored tablets; TEGRETOL L.P. 200 mg and 400 mg, scored, film-coated, slow-release tablets.

2.3. Medicines with a similar therapeutic aim

Tricyclic antidepressants indicated for neuropathic pain in adults:

- Imipramine – TOFRANIL
- Desipramine – PERTOFRAN
- Clomipramine – ANAFRANIL (indication extension of June 12, 2001, unlisted product).

Opioid analgesics:

- Tramadol – medicinal products indicated in the treatment of moderate to severe pain.
- Opiate analgesics.

3 ANALYSIS OF AVAILABLE DATA

For the extension of indication 'central neuropathic pain in adults,' the company included the Marketing Authorisation pivotal study 1008-00-125 in the dossier.

Objectives:
The aim of this study was to evaluate the efficacy and safety of pregabalin compared with placebo in patients with central neuropathic pain due to spinal cord lesion.

Methodology:
This was a placebo-controlled, parallel-group, randomised, double-blind study.

The efficacy and safety of pregabalin, administered at a dosage of 600 mg, 300 mg or 150 mg divided into two doses per day, were evaluated over a 12-week period in patients with central neuropathic pain due to spinal cord lesion (tetraplegia or paraplegia).

The study was conducted in several phases:

- An initial one-week phase preceded patient randomisation;
- A 12-week phase: the first 3 weeks were a period of forced titration – increasing doses of 150, 300 and 600 mg of pregabalin were administered in two part doses per day and adjusted at weekly intervals according to the patients' response and tolerance.

Inclusion criteria:

- Spinal cord lesion dating back at least one year and non-progressive (in chronic phase) for at least 6 months;
- Patients over 18 years of age with central neuropathic pain associated with spinal cord lesion;
- Visual analogue score of > 40 mm / 100 mm In the Short Form McGill Pain Questionnaire (SF-MPQ).
- During the initial phase, the patient must have completed at least 4 pain assessments and obtained a mean pain score of at least 4 on the Lickert 0–10 scale.[1]

[1] Lickert 11-point scale (0 = no pain; 10 = maximum pain).

Patients could be undergoing treatment with analgesics, tricyclic antidepressants and anti-inflammatory drugs, on condition that the treatment was stable and had been introduced before the commencement of the study.
Patients with pain of uncertain origin and patients requiring unauthorised treatment during the study were not included.

Primary endpoint: final mean pain score on Lickert's scale. This score was calculated from the mean of the daily scores obtained during the last 7 days of study treatment.
The treatment responder rates were also assessed, i.e. the percentages of patients who achieved a reduction of more than 30% or 50% on their initial mean pain score. These responder rates were analysed by logistic regression.

Results:
The results of the ITT analysis of this study are set out in the table below:

	Placebo	**Pregabalin**
N (ITT)	67	69
150 mg/day)	3/67 (4.5 %)	5/70 (7.1 %)
300 mg/day	5/67 (7.5 %)	11/70 (15.7 %)
600 mg/day	59/67 (88.1 %)	54/70 (77.1 %)
Initial mean pain score (Lickert's scale)	6.727	6.540
Final mean pain score (Lickert's scale)	6.273	4.623
Adjusted mean change	- 0.433	- 1.967
	Difference = 1.533 CI 95% [0.916; 2.150] p < 0.001	
≥ 30% responders (%)	16.4 %	42.0 %
	Odds ratio = 25.6% CI 95% [10.9%; 40.3%] p = 0.001	
≥ 50% responders (%)	7.5 %	21.7 %
	Odds ratio = 14.3% CI 95% [2.7%; 25.9%] p = 0.019	

Primary endpoint:
After 12 weeks of treatment, the reduction in the mean pain score on Lickert's scale was significantly greater in the pregabalin-treated patients than in the patients treated with placebo (adjusted mean change in score on Lickert's scale: -1.967% in the pregabalin group against -0.433% in the placebo group).

The percentages of patients who achieved a reduction of more than 30% or more than 50% in their global pain score after 12 weeks of treatment were significantly higher among the pregabalin-treated patients than among the patients treated with placebo.

Adverse events:
In the pregabalin group 95.7% of patients had an adverse event, compared with 74.6% of patients in the placebo group.
Among these patients, adverse events potentially associated with the treatments affected 82.9% of patients in the pregabalin group compared with 49.3% of patients on placebo.

The most frequently observed adverse events were as follows:

	Placebo	Pregabalin
Somnolence	9 %	41.4 %
Dizziness	9 %	24.3 %
Asthenia	6 %	15.7 %
Dry mouth	3 %	15.7 %
Constipation	6 %	12.9 %
Oedema	0 %	12.9 %

Severe adverse events were observed in 8 patients, 5 in the pregabalin group compared with 3 in the placebo group. In the pregabalin group, these events included one faecaloma, one cellulitis, one haemodilution, one oedema and one thrombocytopenia.

Discontinuations of treatment following an adverse event involved 21.4% of pregabalin patients compared with 13.4% of placebo patients. Most of these discontinuations of treatment in the pregabalin group were associated with somnolence (5.7%), oedema (5.7%) and asthenia (4.3%).

Conclusion:
This study showed that the efficacy of pregabalin was significantly greater than that of placebo in patients with central neuropathic pain associated with spinal cord lesion.

The safety profile of pregabalin observed in this study seems to be comparable to that observed in the other indications for this medicinal product. However, in the treatment of central neuropathic pain due to spinal cord lesion, the incidence of adverse events in general, and of adverse events involving the central nervous system (CNS) and somnolence in particular, was higher than the incidence observed in other indications of Lyrica.

According to the European public assessment report (EPAR):
- The observed effect size in this study in terms of pain reduction is in the same order of magnitude as observed in the studies assessing pregabalin in peripheral neuropathic pain. Similarly, in terms of responders (≥ 50%) the difference observed between the placebo and pregabalin groups is in the same order of magnitude, although the percentage itself was smaller in this study than was observed for peripheral neuropathic pain.
- Additional adverse events might possibly be associated with medicines combined with pregabalin (particularly baclofen and benzodiazepines).

This study demonstrated the efficacy of pregabalin compared with placebo only in the context of central neuropathic pain associated with spinal cord lesion.

The Transparency Committee notes, however, that several other aetiologies are at the root of so-called central neuropathic pain. It cannot therefore draw any conclusions regarding the size of pregabalin's effect on other types of central neuropathic pain than those due to spinal cord injury.

Moreover, the Transparency Committee regrets the lack of any direct comparison of pregabalin with an active medicinal product, particularly tricyclic antidepressants.

The Transparency Committee notes, however, that Lyrica was the only medicinal product evaluated in the 'central neuropathic pain in adults' indication during a recent trial conducted according to rigorous methodology.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The term neuropathic pain covers all types of pain associated with a lesion or dysfunction of the nervous system. These types of pain may be linked to lesions of the central nervous system, the most frequent causes being spinal cord injury, cerebral vascular accidents and multiple sclerosis. The clinical presentations are very often complex; different symptoms may coexist in the same patient, combining continual and/or paroxysmal spontaneous pain and provoked pain: allodynia and hyperalgesia.[2]

Characterised by their chronic evolution and resistance to medical treatment, these types of pain may have a major psychosocial impact and affect the patient's quality of life.
These medicinal products are symptomatic treatments for central neuropathic pain.
The efficacy/safety ratio is modest.
Alternative medicinal products exist.

In view of its frequency and psychosocial repercussions (fatigue, anxiety and depression), neuropathic pain is a moderate public health burden. The burden caused by pain of central origin, however, is low, because of the smaller number of patients concerned.

The need for improved pain management may be considered a public health priority, as identified by GTNDO (National Technical Group for Defining Public Health Objectives). For neuropathic pain, the therapeutic need is partly covered by the available treatments.

Given the existing treatments, LYRICA is not expected to have an impact in terms of morbidity (including quality of life) insofar as in the only trial available it was compared solely with placebo and its safety profile is unfavourable.

In addition, it is not certain that the results of this trial can be transposed into clinical practice, because the profile of patients treated in real practice is likely to differ from that of the trial patients.

In view of these factors, LYRICA is unlikely to make any additional contribution to meeting the identified public health need.

Consequently, in the current state of knowledge and in view of the existence of other currently available treatments, LYRICA is not expected to benefit public health in this indication.

The actual benefit of LYRICA in the treatment of central neuropathic pain in adults is substantial.

[2] Harden RN. Chronic neuropathic pain. Mechanisms, diagnosis and treatment. The Neurologist 2005;11:111-122

4.2 Improvement in actual benefit

Lyrica does not provide any improvement in actual benefit (IAB level V) over the usual management of central neuropathic pain in adults.

4.3 Therapeutic use[3,4,5,6,7,8,9,10]

A variety of therapeutic approaches have been recommended for neuropathic pain, mainly based on their aetiology, the patient's symptoms, or physiopathological mechanisms. The ideal approach needs to take into account the diversity and considerable disparity in clinical situations which may evolve over time with the same patient.
The most frequent causes of central neuropathic pain are cerebral vascular accidents, multiple sclerosis and spinal cord injury.
Neuropathic pain responds poorly, if at all, to the usual analgesic treatments (NSAIDs, paracetamol and salicylates).
Medicinal analgesic treatments for neuropathy are based, by common consent, on the use of tricyclic antidepressants or antiepileptics acting on the sodium or calcium channels. The efficacy of these treatments is moderate. Their safety profile may limit their prescription. It is still difficult to identify the responders to these different treatments.

The EFNS (European Federation of Neurological Societies) guidelines[10] recommend a monotherapy as a first line of treatment, followed in the event of failure by bitherapy combining two medicinal products with different mechanisms of action.

For central neuropathic pain, they recommend amitriptyline, gabapentin and pregabalin as first-line treatments (amitriptyline and gabapentin are not indicated for central neuropathic pain), and lamotrigine and opioids as second-line treatments.

The Transparency Committee, however, highlights the fact that pregabalin is a useful adjunctive therapy in the management of central neuropathic pain in adults.

Use of opioids (oral morphine, or tramadol) may be justified in patients in the early stage of treatment, where treatment has failed, or where there is partial response, particularly where nociceptive pain coexists. The long-term benefits of opioid treatment must be weighed against the appearance of induced hyperalgesia, opioid tolerance and addictive behaviour.

Since the efficacy of treatments is often incomplete, combinations of analgesics with complementary action mechanisms may be proposed.

Optimum therapeutic management of the patient requires regular assessment and adjustments to the treatment strategy as the underlying disease evolves.

The treatment of chronic pain must often include some form of non-medicinal management, based on the use of physical and/or psychotherapeutic treatments.

4.4 Target population

[3]Attal N, Bouhassira D. Traitement pharmacologique des douleurs neuropathiques. EMC 17-023-2005.
[4]Chen H, et al. Contemporary management of neuropathic pain for the primary care physician. Mayo Clin Proc 2004;79:1533-1545
[5]Eisenberg E et al. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293(24):3043-52.
[6]Dworkin RH et al. Advances in Neuropathic Pain. Diagnosis, mechanisms, and Treatment Recommendations. Arch Neurol 2003;60:1524-1534.
[7]Maizels and al. Antidepressants and antiepileptic drugs for chronic non-cancer pain. AAFP, Feb 1, 2005:vol 71 (3).
[8]Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. The Cochrane Collaboration. 2005.
[9]Wiffen P and al. Anticonvulsivant drugs for acute and chronic pain. The Cochrane Collaboration.2005
[10]Attal et al. EFNS guidelines on pharmacological treatment of neuropathic pain. European Journal of Neurology 2006, 13 : 1153-1169.

Data published by the French statistical office INSEE put the adult (age ≥ 18) population of France on January 1, 2007 at 44,751,445.

The prevalence of peripheral and central neuropathic pain may be estimated at 1%,[11] or approximately 450,000 patients in France.

Other articles estimate the prevalence of central and peripheral neuropathic pain at between 2% and 3% of the general population.[12,13]

According to the applicant, the number of patients with central neuropathic pain should be between 79,093 and 80,013 persons. These figures relate to the total number of patients with central neuropathic pain due to multiple sclerosis, cerebral vascular accidents and spinal cord injuries.[14,15,16,17]

Since the aetiologies of central neuropathic pain are not limited solely to multiple sclerosis, cerebral vascular accidents and spinal cord injuries, this target population seems to be an underestimate.

The target population for Lyrica in its 'central neuropathic pain in adults' indication extension is therefore at least 80,000 patients.

4.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication 'central neuropathic pain in adults' and at the posology given in the Marketing Authorisation.

4.1.1. Packaging:

Appropriate for the prescription conditions.

4.1.2. Reimbursement rate: 65 %

[11]EPAR Lyrica.
[12]Gilron et al. Neuropathic pain: a practical guide for the clinician. CMAJ 2006; 175 (3):265-75
[13]Moulin D. The role of opioids in the management of neuropathic pain. Paincare 2004; 4 (2):3-7
[14]ANAES 2001: Conférence de consensus «la sclérose en plaque»
[15]Osterberg et al. Central pain in multiple sclerosis – prevalence and clinical characteristics. European Journal of Pain 2005, 9: 531–542.
[16]Andersen et al. Incidence of central post-stroke pain. Pain 1995; 61: 187-193
[17]CEMKA-EVAL réalisée pour le laboratoire Pfizer: Etude documentaire sur la prévalence des patients souffrant de douleurs neuropathiques en France 2002.