

Pregabalin for epilepsy

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Pregabalin is a new oral adjunctive therapy for the treatment of partial seizures in adults with or without secondary generalisation. It has a pharmacological profile similar to gabapentin.
- In randomised controlled trials pregabalin has been added to existing treatment in patients who have not achieved adequate seizure control while on up to three other anti-epileptic drugs. The lowest effective dose of pregabalin was 150mg/day and the most effective 600mg/day. These studies were of short duration (12 weeks).
- Results from one open label study (up to 2 years duration) have yet to be fully published but indicate that tolerance to pregabalin is unlikely to occur. 33% of patients in the study discontinued therapy due to lack of efficacy; 39% of these had an increase in seizure frequency.
- There are no studies comparing pregabalin to other newer treatments for epilepsy. There are no data available assessing whether patients who have not responded to, or who have had a limited response to gabapentin will respond to pregabalin therapy.
- NICE technology appraisal no. 76 recommends that combination anticonvulsant therapy only be used if monotherapy fails. The Appraisal reviewed newer antiepileptic treatments, with the exception of pregabalin, which was not marketed at the time of the review.
- Pregabalin can be taken in either two or three divided doses. Both are efficacious in controlling seizures, though it is more cost effective to use the twice daily dosing regimen

Introduction

Pregabalin was launched in July 2004 as an adjunctive therapy in adults with partial seizures with or without secondary generalisation. Treatment should be started at 150mg/day and can be increased to 300mg/day after one week if necessary. The maximum 600mg/day can be used after an additional week if necessary. Pregabalin is also licensed as an oral treatment of peripheral neuropathic pain in adults.

Pregabalin is an alpha₂-delta (α₂-δ) ligand that has analgesic, anxiolytic and anticonvulsant activity. α₂-δ is an auxiliary protein associated with voltage-gated calcium channels. Pregabalin binds to this protein, thereby reducing calcium influx at nerve terminals and the subsequent release of neurotransmitters. Pregabalin is not active at GABA_A and GABA_B receptors. Pregabalin has a pharmacological profile similar to that of gabapentin, with increased potency (3-10 fold).¹

Evidence

There are two fully published **dose-response studies (O34 and O11)** that have compared pregabalin with placebo as adjunctive therapy in patients with highly refractory disease. The patients in these trials had epilepsy for a mean duration of over 20 years and, despite treatment of up to three anti-epileptic drugs (AEDs) a median baseline seizure frequency of 10 per month. Both trials lasted 12 weeks. Study O34 compared 50mg (n=88) 150mg (n=86), 300mg (n=90) and 600mg (n=89) of pregabalin given in two divided doses with placebo (n=100).² Study O11 compared 150mg (n=99) and 600mg (n=92) of pregabalin given in three divided doses, with placebo (n=96).³

Two main outcome measures were used:

RRatio: a measure of the percentage change from baseline in seizure frequency. Zero indicates no change, whilst - 100 indicates a complete elimination in seizures. An RRatio of - 33 indicates a 50% improvement.

Brand Name, (Manufacturer): *Lyrica, (Pfizer)*

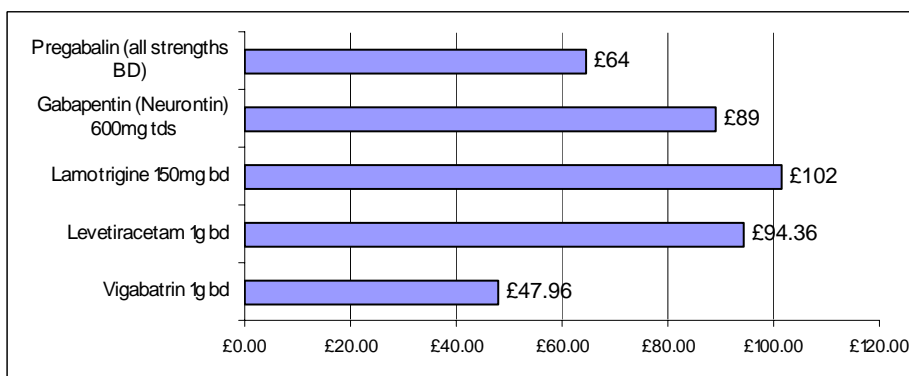
BNF Therapeutic Class: 4.8.1

Licensed Indications: Adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Dosage and Administration: 150mg per day initially, increasing to 300mg per day after one week if necessary. The maximum 600mg per day may be achieved after an additional week.

Marketed: July 2004 (secondary care), September 2004 (primary care).

Cost Comparisons: Cost for 28 days treatment [*MIMS October 2004-NB: pregabalin costs are the same regardless of capsule strength*]



N.B. Doses shown for general comparison and do not imply therapeutic equivalence

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Responder rate: the percentage of patients with over 50% reduction in seizure frequency compared to placebo.

Greater changes in R Ratios and responder rates were seen in the pregabalin groups compared to placebo. No efficacy for a 50mg dose was shown in trial 034.

Results from trials 034 and 011:

034	RRatio [95% CI]
150mg	-21 [-26.1, -7.2]
300mg	-28 [-33.3, -14.6]
600mg	-37 [-42.9, -24.1]
P<0.0001 for all above	
Placebo	-4
	Responder rate
150mg	27% (p<0.006)
300mg	36% (p<0.001)
600mg	45% (p<0.001)
Placebo	Not stated
011	RRatio
150mg	-11.5 [-20.5, -4.3] (p=0.0007)
600mg	-31.4 [-40.6, -24] (p<0.0001)
Placebo	0.9
	Responder rate
150mg	14.1% (p=0.087)
600mg	43.5% (p<0.0001)
Placebo	6.2%

In the third randomised **safety and efficacy trial (009)** 312 patients, who were not adequately controlled on 1-3 other AEDs and experienced at least six seizures during the eight week baseline period, were randomised to receive pregabalin 300mg twice a day (bd group) (n=103) or 200mg three times a day (tds group), (n=111) or placebo (n=98) for 12 weeks. The trial is not yet fully published: data comes from an abstract and the European Product Assessment Report (EPAR).^{4,5}

The mean percentage change in seizure frequency was - 48.1 (200mg tds), - 35.6 (300mg bd) and - 0.8 (placebo).

Results from trial 009:

Dose	RRatio [95% CI]
200mg	-36.1 [- 46.4, -27] (p<0.0001)
300mg	-28.4 [-38.9, -19] (p<0.0001)
Placebo	0.6

Dose	Responder rate
200mg	49% [CI 28.5, 50.4] (p0.001)
300mg	43% [CI 22.4, 44.7] (p<0.001)
Placebo	9%

One **open-label study** (extension of the efficacy studies) has been described in the EPAR and in one poster.⁶ 1480 patients were enrolled, including those who had chosen to continue after participating in the controlled studies. No primary or secondary efficacy parameters were defined. Efficacy measures were the change in frequency of partial seizures as defined by e.g. responder rates and maximum length of seizure free period. Doses of 75mg to 600mg/day were used, in two or three divided doses. Little information on dose adjustments was given.

A Responder rate of 37% and a median percentage reduction from baseline of 38% was seen during the initial 12 weeks – no further data is available although the responder rate and median percentage change in seizure frequency were maintained over time. The mean increase in the number of seizure-free days was 41%. 8.9% of 1199 patients were seizure-free for six months and 5.8% of 877 patients were seizure-free for 12 months. Tolerance to pregabalin was not considered to be a major concern. 33% of patients discontinued treatment due to lack of efficacy, over two years. 39% of these showed an increase in seizure frequency compared to baseline.

Safety

During the trials 65% of patients taking placebo and 79.6% taking pregabalin experienced adverse events. The most frequently reported side effects were dizziness (29.1% taking pregabalin, compared to 8.7% on placebo) and somnolence (22.6% on pregabalin compared to 7.8% on placebo). These particular side effects may increase the occurrence of accidental injury or falls in the elderly population. Patients are advised to exercise caution until they are familiar with the potential side effects of pregabalin. Other side effects that occurred more in pregabalin treated patients included dry mouth, asthenia, amblyopia, nausea and peripheral oedema.

No clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol.

Oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate have not been shown to have any clinically significant effect on pregabalin clearance. When pregabalin is co-administered with the oral contraceptives norethisterone and/or ethinyl oestradiol steady-state pharmacokinetics of either substance is not affected.

Place in Therapy

Pregabalin has a similar mode of action to gabapentin; there is no data available to assess whether patients who have a limited response or no response to gabapentin, will respond to pregabalin.

Pregabalin is not covered in the NICE guidance no.76 (as it was not licensed at the time of writing): in the absence of any guidance regarding the use of pregabalin, any treatment decision should be based on the clinician's assessment of each individual patient's circumstances.

Pfizer have a formulary summary which states that pregabalin is a rational first choice adjunctive therapy for the treatment of partial seizures in patients who are uncontrolled on either monotherapy or combination treatment with antiepileptic drugs. Pregabalin has not been specifically used in trials as first line adjunctive therapy.

The total daily dose of pregabalin can be taken either twice or three times a day – Pfizer aim to market pregabalin at the twice daily dosing regimen.

The full London New Drugs Group review can be found on [DrugInfoZone](#)

Appendix I: Bibliography

Risk Management Issues:

Pregabalin is also licensed for the treatment of neuropathic pain. The dose titration for this indication is different to that for adjunctive epilepsy treatment (it is quicker). Prescribers should be made aware of this.

Produced for the UK Medicines Information Service

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Appendix I

Bibliography

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