PREGABALIN

Class: Anti-epileptic.
Indications: Adjunctive treatment for partial seizures with or without secondary generalisation, peripheral neuropathic pain, †generalised anxiety disorder.[1–2]

Pharmacology

Pregabalin, like **gabapentin**, is a chemical analogue of GABA but does *not* act as a GABA-receptor agonist. Both drugs bind to the α2δ regulatory subunit of presynaptic N- and P/Q-type voltage-gated calcium channels, reducing calcium influx and therefore release of neurotransmitters such as glutamate, substance P and norepinephrine.[3–6] Pregabalin has a binding affinity 6 times greater than that of **gabapentin**, competitively displacing the latter from the α2δ subunit.[7] Intersubject variability in pharmacokinetics is low (<20%). Bio-availability is high and independent of dose. It is not protein-bound and undergoes negligible metabolism. More than 90% is excreted unchanged by the kidneys and it thus cumulates in renal impairment.[8] Half of the drug is removed after 4h of haemodialysis. It has no known pharmacokinetic drug interactions. Pregabalin is licensed for peripheral neuropathic pain following trials in painful diabetic neuropathy and post-herpetic neuralgia.[9–11] Response is dose-related; a quarter of patients on 150mg/day and up to a half of patients receiving 300–600mg/day obtain ≥50% reduction in pain. Patients who had previously failed to respond to **gabapentin** were excluded from these trials. There are no studies of pregabalin in cancer-related neuropathic pain, nor direct comparisons with **gabapentin** or other neuropathic pain treatments. Pregabalin 300mg has a similar but longer lasting analgesic effect to ibuprofen 400mg in postdental extraction pain (i.e. nociceptive pain) when compared in a single-dose placebo-controlled trial.[12]
Bio-availability ≥90% PO.
Onset of action 24min postdental extraction pain; <24h neuropathic pain; 2 days epilepsy.[11-13]
Time to peak plasma concentration 1h.
Plasma halflife 5–9h, increasing to >2 days in severe renal impairment (creatinine clearance <15ml/min) and in haemodialysis patients.[8]
Duration of action >12h.

Cautions

Renal impairment.

Undesirable effects

For full list, see manufacturer's SPC
Undesirable effects are dose-related and are generally mild-to-moderate in severity.
Very common (>10%): Dizziness (about 1/3 of patients), drowsiness (about 1/4); these generally resolve spontaneously after a median of 5–8 weeks.[9–11]
Common (<10%, >1%): Confusion, irritability, euphoria, amnesia, increased appetite, decreased libido, diplopia, dysarthria, tremor, ataxia, weight gain, dry mouth, impotence, oedema.

Dose and use

- starting dose 75mg b.d.
- increase to 150mg b.d. after 3–7 days (*epilepsy 7 days*) if necessary
- increase to 300mg b.d. after a further 7 days if necessary (maximum recommended dose).

The intervals between dose increments were recommended by the MHRA after review of pooled data. They are pragmatic rather than pharmacokinetic. Because epileptic seizures are often sporadic, more time is needed to assess the initial response.

The total daily dose can be given as a t.d.s. regimen, but as each capsule is priced at £1.15 irrespective of strength or pack size, this is more expensive than a b.d. regimen, e.g. 28 days @ 150mg b.d. and 100mg t.d.s. = £64.40 and £96.60, respectively.

Dose reduction is required in renal impairment (Table 1). For patients undergoing haemodialysis, adjust the regular dose according to creatinine clearance and give the supplementary single dose after each dialysis session.

Table 1 Impact of renal impairment on starting and maximum doses (*see also* SPC)

Creatinine clearance (ml/min)	*Starting dose*	*Maximum dose*
>60	75mg b.d.	300mg b.d.
31–60	25mg t.d.s.[a]	150mg b.d.
15–30	25–50mg o.d.	150mg o.d.
<15	25mg o.d.	75mg o.d.
Supplementary single dose after each haemodialysis session	25mg	100mg

[a]37.5mg capsules not available, necessitating t.d.s. regimen.

Stopping pregabalin

To avoid precipitating pain or seizures, pregabalin should be withdrawn gradually over at least 1 week.

Supply

Lyrica® (Pfizer 01304 616161)

Capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg, 28 days @ 150mg b.d. or 300mg b.d. = £64.40.

1 Pande AC *et al*. (2003) Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *American Journal of Psychiatry*. **160:** 533–540.

2 Feltner DE *et al*. (2003) A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *Journal of Clinical Psychopharmacology*. **23:** 240–249.

3 Stahl SM (2004) Anticonvulsants and the relief of chronic pain: pregabalin and gabapentin as $\alpha_2\delta$ ligands at voltage-gated calcium channels. *Journal of Clinical Psychiatry*. **65:** 596–597.

4 Dooley DJ *et al*. (2000) Inhibition of K^+-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. *Neuroscience Letters*. **280:** 107–110.
5 Dooley DJ *et al*. (2000) Stimulus-dependent modulation of [^{3}H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin. *Journal of Pharmacology and Experimental Therapeutics*. **295:** 1086–1093.
6 Maneuf YP *et al*. (2001) Gabapentin inhibits the substance P-facilitated K^+-evoked release of [^{3}H]glutamate from rat caudal trigeminal nucleus slices. *Pain*. **93:** 191–196.
7 Jones DL *et al*. (1998) Systemic gabapentin and S(+)-3-isobutyl-gamma-aminobutyric acid block secondary hyperalgesia. *Brain Research*. **81:** 93–99.
8 Randinitis EJ *et al*. (2003) Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *Journal of Clinical Pharmacology*. **43:** 277–283.
9 Sabatowski R *et al*. (2004) Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain*. **109:** 26–35.
10 Rosenstock J *et al*. (2004) Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. **110:** 628–638.
11 Dworkin RH *et al*. (2003) Pregabalin for the treatment of postherpetic neuralgia. A randomized, placebo-controlled trial. *Neurology*. **60:** 1274–1283.
12 Hill CM *et al*. (2001) Pregabalin in patients with postoperative dental pain. *European Journal of Pain*. **5**: 119–124.
13 Perucca E *et al*. (2003) Pregabalin demonstrates anticonvulsant activity onset by second day. *Neurology*. **60 (suppl. 1):** A145 [abstract P02.122].