PREGABALIN **FDA APPROVAL 2005**

Class: Anti-epileptic.

Indications: Adjunctive treatment for partial seizures with or without secondary generalization, peripheral neuropathic pain (diabetic neuropathy and post-herpetic neuralgia), †generalized anxiety disorder.[1,2]

Pharmacology

Pregabalin, like **gabapentin**, is a chemical analog 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 $\alpha 2\delta$ 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 hemodialysis. It has no known pharmacokinetic drug interactions.

Pregabalin is approved for peripheral neuropathic pain on the basis of RCTs in painful diabetic neuropathy and post-herpetic neuralgia.[9-12] 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. In relation to pain and sleep, slower flexible-dose titration (≤4 weeks) ultimately produces similar benefit to a fixed-dose regimen, and is better tolerated. However, the onset of analgesia is delayed with the flexible-dose scheme because of the lower daily dose (75mg b.i.d. compared with 150mg b.i.d.) during the first week.[12] In four RCTs, the NNT to achieve at least 50% pain relief ranged from 3.3 to 5.6. Patients who had previously failed to respond to **gabapentin** were excluded from three of these trials.[9-11]

There are no studies of pregabalin in cancer-related neuropathic pain, nor direct comparisons with **gabapentin** or other neuropathic pain treatments. Pregabalin 300mg had 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.[13]

Bio-availability ≥90% PO.

Onset of action 24min postdental extraction pain; <24h neuropathic pain; 2 days epilepsy.[9,13,14]

Time to peak plasma concentration 1h.

Plasma halflife 5–9h, increasing to >2 days in severe renal impairment (creatinine clearance <15ml/min) and in hemodialysis patients.[8]

Duration of action >12h.

Cautions

Renal impairment, CHF (New York Heart Association Class III or IV).

Undesirable effects

For full list, see manufacturer's PI.

Undesirable effects are dose-related and are generally mild–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, diplopia, dysarthria, tremor, ataxia, increased appetite, weight gain, dry mouth, decreased libido, impotence, edema.

Dose and use for neuropathic pain
- start with 75mg b.i.d.
- if necessary, at intervals of 3–4 days, increase to 150mg b.i.d. → 225mg b.i.d. → 300mg b.i.d. (maximum recommended dose)
- in debilitated patients, start with 25–50mg b.i.d.; and, if necessary, increase the dose correspondingly cautiously.

The intervals between dose increases are pragmatic rather than pharmacokinetic. In one RCT, the effective doses were:
- 150mg b.i.d. in about 1/4 of patients
- 225mg b.i.d. in about 1/3
- 300mg b.i.d. in another 1/3.[12]

Dose reduction is necessary in renal impairment. For patients on hemodialysis, the regular dose should be adjusted according to the creatinine clearance, and a supplementary single dose given after each dialysis (Table 4.1).

Table 4.1 Impact of renal impairment on starting and maximum doses (manufacturer's recommendations)

Creatinine clearance (ml/min)	Starting dose	Maximum dose
>60	75mg b.d.	300mg b.d.
31–60	25mg t.i.d.[a]	150mg b.d.
15–30	25–50mg q.d.	150mg q.d.
<15	25mg q.d.	75mg q.d.
Supplementary single dose after every 4h of hemodialysis	25mg	150mg

a. 37.5mg capsules not available, necessitating t.i.d. regimen.

Note: because epileptic seizures are often sporadic, more time is needed to assess the initial response, i.e. a minimum of 1 week.

Stopping pregabalin
To avoid precipitating pain or seizures, pregabalin should be withdrawn gradually over several weeks.

Supply
All preparations are Schedule V controlled substances.

Lyrica® (Pfizer)
Capsules 25mg, 50mg, 75mg, 100mg, 150mg, 300mg, 28 days @ 75mg, 150mg, 300mg b.i.d. = $112, $114 and $114 respectively; 28 days @ 50mg, 100mg, 200mg t.i.d. = $168, $171 and $342 respectively.

Note: because of unit costs, if the total daily dose is given t.i.d. rather than b.i.d., the overall cost is considerably greater.

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