Criteria for Use of Levetiracetam (Keppra®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Indication for therapy

Patient with one of the following conditions:

☐ Patient diagnosed with localization-related epilepsy (producing simple or complex partial seizures with or without secondary generalization)

AND ONE OF THE FOLLOWING

☐ Incomplete seizure control requiring adjunctive therapy

OR

☐ Incomplete seizure control intolerant of first-line antiepileptic drugs(phenytoin, carbamazepine, divalproex sodium)

OR

☐ Concurrent therapy with a drug that is a CYP450 substrate, inducer or inhibitor and has a narrow therapeutic range

Dosing

- Levetiracetam is available as 250 mg, 500 mg, and 750 mg tablets and 100mg/ml oral solution.
- Levetiracetam may be administered without regards to food.
- Initiate levetiracetam at 250 mg BID. After 2 weeks increase to 500 mg BID. If needed, additional dosing increments of 500-1000 mg/day every 2 weeks can be implemented, to a maximum recommended daily dose of 3000 mg or to maximum clinically tolerated dose.
- Adjust dose according to renal function, as follows:

Creatinine Clearance(ml/min)	Dose(mg)	Interval(hours)
>80	500-1500	12
50-80	500-1000	12
30-49	250-750	12
<30	250-500	12
On dialysis	500-1000	24

(250-500 mg supplemental dose post dialysis recommended)

Adverse Effects

- Use of levetiracetam has been associated with neuropsychiatric adverse events, such as somnolence, fatigue, coordination difficulties, and behavioral abnormalities
- The most common adverse events associated with levetiracetam use are asthenia (15%), somnolence (15%), headache (14%), infection (13%), dizziness (9%), and pain (7%). These adverse events appear to occur predominantly during the first 4 weeks of treatment with levetiracetam.

Monitoring

- Therapy with levetiracetam does not require monitoring of blood levels, white blood cell counts or liver function tests
- There are no reported significant drug interactions, thus concurrent therapy with levetiracetam would not be expected to necessitate dose changes in other agents.

Contraindications

❑ Hypersensitivity to levetiracetam

Off Label Uses

See Table 1

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Table 1: Evidence for Off Label Use of Levetiracetam

Myoclonus/Dystonia	***Evidence rating III-I***
Lim 2005[10]	Open label trial of 8 patients over a one year period. One patient with posthypoxic myoclonus improved. The other seven did not improve or worsened.
Shauer 2002[15]	Case report, 16yo male with posthypoxic myoclonus. Improved clinical condition and allowed patient to enter rehab therapy.
Chatterjee 2002[17]	Case report, 38 yo female with paroxysmal kinesiogenic choreoathetosis. Resolution of attacks however patient ceased therapy due to sedation and palpitations.
Zasiewicz 2004[14]	Case report, 56 yo female with Meige's syndrome. Minimal improvement with gabapentin, clorazepate and Botulinum toxin A. Levetiracetam 500 mg TID improved blepharospasm and oral dystonia.
Recio 2005[13]	Case report, 35 yo female with cerebral palsy.
Crest 2004[12]	Open label trial in 6 patients with progressive myoclonic epilepsy. Three patients with marked improvement, 3 patients with no improvement or worsening.
Frucht 2001[16]	Open label trial in eight patients with chronic myoclonus. Two patients discontinued therapy. Three patients experience significant reductions in their myoclonus scores.
Magaudda 2004[11]	Retrospective review of 13 patients with Unverricht-Lundborg disease. Eight patients had measurable improvement on their myoclonus scores.
Bipolar Disorder	***Evidence rating III-I***
Kaufman 2004[4]	Case report. 21 yo female , failed 15 psychotropics. Patient improved over one year of followup.
Grunze 2003[6]	Ten patients with bipolar disease in acute mania. Used as add on therapy with haloperidol 5-10mg/day. Used an on-off design, levetiracetam till day 14, then remove and reintroduce at day 21. Seven of ten patients were responders at day 28 of the trial.
Goldberg 2002[8]	Case report 42 yo male. Previously treated with lithium, divalproex, carbamazepine and SSRI. Modest improvement but significant sedation and nausea which caused DC of agents. No recurrence of mania for 6 weeks on levetiracetam 2500 mg/day
Post 2005[3]	Open label adjunctive treatment of 34 patients [depression(13), mania (7) and cycling (14)]. The 16 patients with manic symptoms showed improvement in 2 weeks, four showed intervening periods of moderate to marked exacerbation.
Migraine	***Evidence Rating II-2 C (for pediatric use)***
Miller 2004[19]	Retrospective review of 19 pediatric patients. Eliminated headache in 10 patients, less severe headache reported in 7 patients no effect in 2 patients.
Pain	***Evidence rating III C***
Price 2004[21]	Case series of three patients, 67 yo male, 75 yo male and 55 yo female. All showed improvement on levetiracetam.
Guay 2003[20]	Summary report of five case series of levetiracetam in various neuropathic pain syndromes. 48% to 60% of patients improved on therapy- outcomes were measured by visual analog scales, pain score or patient rating.
Monotherapy for epilepsy	***Evidence Rating II-2 B***
Alsaadi 2004[29]	Retrospective review of 46 patients over a one year period. At 1 year 45% of patients were seizure free.
Alsaadi 2004[30]	Retrospective review of 14 elderly patients. Eight patients became seizure free by six months
Cohen 2003[31]	Case report of three patients with primary generalized epilepsy. Patients became seizure free for at least 6 months on levetiracetam 1250-3000 mg/day
Ben-Menachem 2000[32]	Randomized adjunctive therapy trial where responder patients(N=86) then underwent withdrawal to monotherapy. A responder rate of 52.9% with a mean reduction in seizure frequency by 74%

TABLE 2: Quality of Evidence [QE]

I	At least one properly done RCT
II-1	Well designed controlled trial without randomization
II-2	Well designed cohort or case-control analytic study
II-3	Multiple time series, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, case reports, expert committees.

TABLE 3: Grade the Recommendation

A	A strong recommendation that the intervention is always indicated and acceptable
B	A recommendation that the intervention may be useful/effective
C	A recommendation that the intervention may be considered
D	A Recommend that a procedure may be considered not useful / effective, or may be harmful.
I	Insufficient evidence to recommend for or against – the clinician will use their clinical judgment