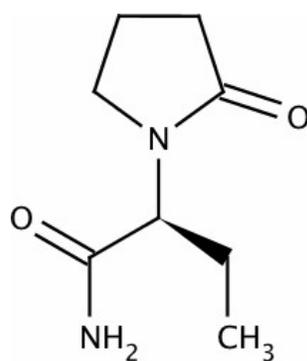


CINAPS COMPOUND DOSSIER

Levetiracetam



9/3/2010

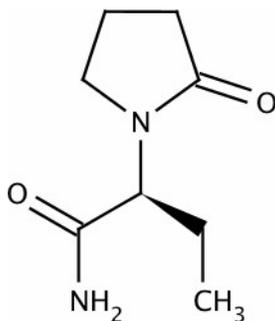
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I. Compound Information

Common name: Levetiracetam

Structure:



Pubchem ID: 5284583 **Mol. Formula:** C₈H₁₄N₂O₂ **FW:** 107.209

CASRN: 102767-28-2 **Polar surface area:** 63.4 **logP:** -0.3

IUPAC name: (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide

Other names: Keppra®

Drug class: Anticonvulsant, nootropic

Medicinal chemistry development potential: High

II. Rationale

Ila. Scientific Rationale / Mechanism

Levetiracetam is a clinically approved anti-epileptic agent. As one of a novel class of atypical anti-epileptic agents, levetiracetam is thought to act via binding to the synaptic vesicle protein SV2A that contributes to the mechanism of vesicular exocytosis and release of neurotransmitter although the effect of drug interaction with this protein remains unclear.¹⁻² Levetiracetam also inhibits presynaptic P/Q-type calcium channels in the dentate gyrus and it has been postulated that this may be a significant factor in the drug-induced inhibition of post-synaptic AMPA and NMDA currents that contribute to the anti-epileptic efficacy of levetiracetam.³

Many publications of clinical and non-clinical studies have demonstrated a crucial role for levetiracetam in the attenuation of L-DOPA-induced dyskinesias in Parkinson's patients.⁴⁻¹⁰ Little discussion is provided on the potential mechanism of action for levetiracetam in the amelioration of treatment related dyskinesias. However, it is very clear from the non-clinical literature that levetiracetam is only effective against fully primed, L-DOPA-induced dyskinesia and is ineffective against acutely induced dyskinetic effects of dopamine replacement therapy. This is supported by the fact that in the clinical setting, levetiracetam is mainly of utility in severe cases of treatment-related dyskinesia and that effective dose levels range from 50 to 3,000 mg per day.^{5, 7} Presumably the mechanism of effect in this setting is a modulation of synaptic release of newly synthesized dopamine in the remaining dopaminergic neurons but there is currently no documented direct data to support this mechanism.

Ilb. Consistency

There are two points of inconsistency in the application of levetiracetam as a neuroprotective agent attenuating the onset and progress of Parkinson's disease. Firstly, the generalized activity of levetiracetam in the amelioration of the overshoot of dopamine activity during replacement therapy does not provide any direct support for the theory that levetiracetam alone would provide any protection of the declining dopaminergic neurons. Secondly, and more directly, in a C57BL/6 mouse model of neuroprotection (using young mice: 5 weeks old, 19 g), levetiracetam conferred no protective effect on the MPTP-induced loss of cells in the substantia nigra expressing the dopamine transporter.¹¹ While there are several limitations to this study design in terms of the semi-quantitative autoradiographic method of cell "counting" and the detection of the dopamine transporter rather than the more common immunohistochemical staining for tyrosine hydroxylase, the results from this study do not support a strong neuroprotective potential for levetiracetam alone. In addition, levetiracetam was reported to have induced Parkinsonian symptoms in a 58-year old male patient with Huntington's Disease¹² and a 36-year

old male patient with a molecular diagnosis of Huntington's Disease.¹³ While this might raise concerns about the utility of levetiracetam as a neuroprotectant, it should not be over-looked that there are only two published case reports. Furthermore, Huntington's Disease patients already present with non-Parkinsonian CNS pathology and this may produce significant complications in the translation of these case studies to patients with a "pure" Parkinsonian pathology or diagnosis.

III. Efficacy (Animal Models of Parkinson's Disease)

IIIa. Animal Models: Rodent

There is a single study reported with levetiracetam in which neuroprotective efficacy was assessed. Five-week old C57BL/6 mice were treated with antiepileptic agents (including levetiracetam) prior to, during and following an acute exposure to MPTP (i.p.; four doses at 1 hour intervals). At 10 days following the start of anti-epileptic treatment (1 week after MPTP) post-mortem assessment of dopamine-transporter positive cells by semi-quantitative autoradiography showed no neuroprotective effects of any anti-epileptic except for lamotrigine.¹¹

IIIb. Animal Models: Non-human Primates

There have been no reports of levetiracetam providing protective effects in any non-human primate model of Parkinson's disease or neuronal loss.

Models of levetiracetam-induced attenuation of L-DOPA-induced dyskinesias have been published but they have little value in supporting the neuroprotective efficacy of levetiracetam.^{4, 6,}

10, 14

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

There are no clinical reports of levetiracetam providing neuroprotective effects or attenuation of the onset of Parkinsonian symptoms. Many authors have reported both focused studies and case reports of levetiracetam ameliorating the L-DOPA-induced dyskinesias^{5, 7-9, 12} but, as noted above, the relevance of these to neuroprotective efficacy remains unclear.

IVb. Epidemiological Evidence

No epidemiological evidence was found for a neuroprotective effect of levetiracetam in Parkinson's disease or any other neurodegenerative disorder.

V. Relevance to Other Neurodegenerative Diseases

The relevance of levetiracetam to other neurodegenerative disorders is unclear. Two case reports^{7, 13} of Parkinsonian symptoms in Huntington's Disease patients treated with levetiracetam suggest a complicated interplay between these CNS pathologies.

VI. Pharmacokinetics

Via. General ADME

Levetiracetam exhibits time- and dose-independent pharmacokinetics, with an elimination half-life of 6-8 h in adults. It has minimal (<10%) plasma protein binding and its distribution volume corresponds to body water.¹⁵ The major metabolic pathway is enzymatic hydrolysis of the acetamide group, a process that does not involve the cytochrome P450 system. It is excreted in the urine as the unchanged compound and the acidic metabolite, accounting for 66% and 24% of the dose, respectively.¹⁶

Standard pharmacokinetic parameters from a 24 subject clinical study are presented in Table 1 below.¹⁷

TABLE 1: Single dose bioequivalence of levetiracetam extended-release (XR) and immediate-release (IR) tablets

Parameter	Levetiracetam IR (500mg)	Levetiracetam XR (100 mg)
C _{max} (µg/mL)	19.7	17.4
T _{max} (h)	0.9	4
AUC(0-t) (µg-h/mL)	317	307
AUC _∞ (µg-h/mL)	325	313

Vib. CNS Penetration

Levetiracetam is targeted for CNS indications and acts at intracellular SV2A proteins within the CNS. As evidenced by the many clinical and non-clinical studies discussed above, levetiracetam readily penetrates the CNS owing, in part, to its low protein binding in the plasma (<10%). After i.p. administration, levetiracetam has been found to rapidly cross the blood-brain barrier in rats.¹⁸⁻¹⁹

Vic. Calculated log([brain]/[blood])

-0.84 (Clark Model²⁰)

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

The safety and tolerability of levetiracetam are best summarized by the package insert from the currently available clinical form Keppra®, UCB Pharmaceuticals Inc.. An abridged excerpt from the package insert is included below. Only those sections relating to adverse effects are included. Sections not presented here (such as hematology or hepatic toxicity) list no adverse effects of levetiracetam in the package insert.

Neuropsychiatric Adverse Reactions

Keppra XR Tablets

In some patients experiencing partial onset seizures, Keppra XR causes somnolence, dizziness, and behavioral abnormalities.

In the Keppra XR double-blind, controlled trial in patients experiencing partial onset seizures, 7.8% of Keppra XR-treated patients experienced somnolence compared to 2.5% of placebo-treated patients. Dizziness was reported in 5.2% of KEPPRA XR-treated patients compared to 2.5% of placebo-treated patients.

A total of 6.5% of Keppra XR-treated patients experienced non-psychotic behavioral disorders (reported as irritability and aggression) compared to 0% of placebo-treated patients. Irritability was reported in 6.5% of Keppra XR-treated patients. Aggression was reported in 1.3% of Keppra XR-treated patients.

Immediate-Release Keppra Tablets

In controlled trials of immediate-release Keppra tablets in patients experiencing partial onset seizures, immediate-release Keppra causes the occurrence of central nervous system adverse reactions that can be classified into the following categories: (1) somnolence and fatigue, (2) coordination difficulties, and (3) behavioral abnormalities.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.8% of immediate-release Keppra-treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients.

A total of 3.4% of immediate-release Keppra-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients.

Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment.

In controlled trials of patients with epilepsy experiencing partial onset seizures, 5 (0.7%) immediate-release Keppra-treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient.

A total of 13.3% of immediate-release KEPPRA patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, etc.) compared to 6.2% of placebo patients.

Other Adverse Reactions

Keppra XR Tablets

In the well-controlled clinical study using Keppra XR in patients with partial onset seizures, the most frequently reported adverse reactions in patients receiving KEPPRA XR in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were irritability and somnolence.

The following treatment-emergent adverse reactions occurred in at least 5% of epilepsy patients treated with Keppra XR participating in the placebo-controlled study and were numerically more common than in patients treated with placebo: nausea (5% vs 3%), influenza (8% vs. 4%), nasopharyngitis (7% vs. 5%), somnolence (8% vs. 3%), dizziness (5% vs. 3%), and irritability (7% vs. 0%). In this study, either KEPPRA XR or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Discontinuation Or Dose Reduction in a Keppra XR Well-controlled Clinical Study

In the well-controlled clinical study using Keppra XR, 5.2% of patients receiving Keppra XR and 2.5% receiving placebo discontinued as a result of an adverse event. The adverse reactions that resulted in discontinuation and that occurred more frequently in Keppra XR-treated patients than in placebo-treated patients were asthenia, epilepsy, mouth ulceration, rash and respiratory failure. Each of these adverse reactions led to discontinuation in a Keppra XR-treated patient and no placebo-treated patients.

Immediate-Release Keppra Tablets

In well-controlled clinical studies of immediate-release KEPPRA tablets as adjunctive therapy to other AEDs in adults with partial onset seizures, the most frequently reported adverse reactions, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness.

Table 2 lists treatment-emergent adverse reactions that occurred in at least 1% of adult epilepsy patients treated with immediate-release KEPPRA tablets participating in placebo-controlled studies and were numerically more common than in patients treated with placebo. In these studies, either immediate-release KEPPRA tablets or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 2: Incidence (%) of Treatment-Emergent Adverse Reactions in the Placebo-controlled, Add-on Studies in Adults Experiencing Partial Onset Seizures by Body System

Body System

<i>Adverse Reaction</i>	<i>Immediate-release Keppra</i>	<i>Placebo</i>
Body as a Whole		
Asthenia	15	9
Headache	14	13
Infection	13	8
Pain	7	6
Digestive System		
Anorexia	3	2
Nervous System		
Somnolence	15	8
Dizziness	9	4
Depression	4	2
Nervousness	4	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Hostility	2	1
Paresthesia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Diplopia	2	1

(Adverse reactions occurred in at least 1% of Immediate-release Keppra-treated patients and occurred more frequently than in placebo-treated patients.)

In addition, the following adverse reactions were seen in other well-controlled studies of immediate-release Keppra tablets: balance disorder, disturbance in attention, eczema, hyperkinesia, memory impairment, myalgia, personality disorders, pruritus, and blurry vision.

Postmarketing Experience

In addition to the adverse reactions listed above for immediate-release Keppra tablets, the following adverse events were identified during post-approval use of immediate-release Keppra tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The listing is alphabetized: abnormal liver function test, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), thrombocytopenia and weight loss. Alopecia has been reported with immediate-release Keppra use; recovery was observed in majority of cases where immediate-release Keppra was discontinued.

(Abridged from the DailyMed Website: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=13216#Section_5.3)

VIIb. Drug Interaction Potential

The drug interaction potential for levetiracetam is low owing to the fact that there is minimal cytochrome P450-based metabolism of levetiracetam. This has been an issue of careful consideration in the clinical use of levetiracetam for the treatment of epilepsy as it is primarily used as adjunct therapy.

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