LEVETIRACETAM (Systemic)

Indications

Accepted

Epilepsy, partial seizures (treatment adjunct)¾Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾170.21 1

Solubility¾Very soluble in water (104 grams/100 mL); freely soluble in chloroform (65.3 grams/100 mL); freely soluble in methanol (53.6 grams/100 mL); soluble in ethanol (16.5 grams/100 mL); sparingly soluble in acetonitrile (5.7 grams/100 mL); and practically insoluble in n-hexane. 1

Precautions to Consider

Carcinogenicity

There was no evidence of carcinogenicity in a study in rats receiving 50, 300 and 1800 mg of levetiracetam per kg of body weight (mg/kg) per day for 104 weeks. The 1800 mg/kg per day dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg per square meter of body surface area (mg/m2) basis and it also provided systemic exposure (area under the time-concentration curve[AUC]) approximately 6 times that achieved in humans receiving the MRHD. 1

Mutagenicity

Mutagenicity was not demonstrated in the Ames test or in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an in vitro analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an in vivo mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (L057) was not mutagenic in the Ames test or the in vitro mouse lymphoma assay. 1

Pregnancy/Reproduction

Fertility¾No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg per day (approximately 6 times the maximum recommended human dose on a mg/m2 or exposure basis). 1

Pregnancy¾Adequate and well-controlled studies in humans have not been done. Studies in animals have shown that levetiracetam causes developmental toxicity at doses similar to or greater than human therapeutic doses. Doses ³ 350 mg/kg per day (approximately equivalent to the maximum recommended human dose (MRHD) of 3000 mg on a mg/m 2 basis) was associated with increased

incidences of minor fetal skeletal abnormalities and retarded offspring growth when administered to female rats throughout pregnancy and lactation. Doses of 1800 mg/kg per day (6 times the MRHD on a mg/m2 basis) was associated with increased pup mortality and offspring behavioral alterations. The developmental no effect dose was 70 mg/kg per day (0.2 times the MRHD on a mg/m 2 basis). 1

Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ³ 600 mg/kg per day (approximately 4 times MRHD on a mg/m2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg per day (12 times the MRHD on a mg/m2basis). The developmental no effect dose was 200 mg/kg per day (1.3 times MRHD on a mg/m2basis). Maternal toxicity was also observed at 1800 mg/kg per day. 1

Pregnant rats fed levetiracetam doses of 3600 mg/kg per day (12 times the MRHD) during the period of organogenesis produced offspring with decreased fetal weights and an increased incidence of fetal skeletal variations. 1

No adverse developmental or maternal effects in rats treated during the last third of gestation and throughout lactation at doses up to 1800 mg/kg per day (6 times the MRHD on a mg/m2basis). 1

FDA Pregnancy Category C 1

Note: Note: To facilitate monitoring of fetal outcomes of pregnant women exposed to levetiracetam, physicians are encouraged to register patients in the Antiepileptic Drug Pregnancy Registry before fetal. outcome is known 1.

Labor and delivery¾The effect of levetiracetam on labor and delivery is not known 1.

Breast-feeding

It is not known whether levetiracetam is distributed into breast milk. However, problems in humans have not been documented. 1

Pediatrics

Appropriate studies on the relationship of age to the effects of levetiracetam have not been performed in the pediatric population in children up to the age of 16. Safety and efficacy have not been established. 1

One pharmacokinetic study in 24 patients 6 to 12 years of age showed that the apparent clearance of levetiracetam was approximately 40 % higher than that in adults following oral administration of a single 20 mg/kg dose 1.

Geriatrics

Appropriate studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of levetiracetam in the elderly. However, elderly patients are more likely to have age-related renal function impairment which may require adjustment of dosage or dosing interval in patients receiving levetiracetam. 1

Pharmacogenetics

. Due to the lack of important racial differences in creatinine clearance and the renal excretion of levetiracetam, pharmacokinetic differences due to race are not expected. Cross study comparisons between a small number of whites and Asians showed comparable pharmacokinetics. 1

Clearances adjusted for body weight, but not maximum concentration and area under the curve, were comparable between men and women. 1

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Studies to assess potential pharmacokinetic interactions with levetiracetam have shown no clinically relevant interactions with digoxin, oral contraceptives, or warfarin to date 1.

Similarly, potential interactions with existing antiepileptic agents, including phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, and primidone, have not been demonstrated 1.

Probenecid

(no interaction between probenecid and levetiracetam was observed; however, probenecid decreased the renal clearance of ucb L057 [inactive metabolite of levetiracetam] by 60%. 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Hemoglobin

Hematocrit

Neutrophil count

Red blood cell count

White blood cell count

(minor decrease in values. 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Hypersensitivity to levetiracetam 1

Risk-benefit should be considered when the following medical problems exist

>> Renal function impairment

(reduction in total body clearance of levetiracetam; dosage reduction is recommended. 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Note: Adverse events were usually mild to moderate in intensity. 1

Those indicating need for medical attention