August 2001 Volume 6 - Number 8

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

8

Advances in the Neurobiology of Norepinephrine and its Relevance to Psychiatric Disorders

CNS Spectrums is indexed by EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis, and is the official journal of the International Neuropsychiatric Ass.

https://doi.org/10.1017/S1092852900001280 Published online by Cambridge University Press

* *Individual responses to ARICEPT® may include improvement, stabilization, or decline.*

† The most common adverse events in pivotal clinical trials with ARICEPT® were nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. Pivotal clinical trials of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Nevertheless, cholinesterase inhibitors may be expected to increase gastric acid secretion. Therefore, patients (especially those at increased risk for developing ulcers—eg, having a history of ulcer disease, receiving concurrent nonsteroidal anti-inflammatory drugs) should be monitored closely for gastrointestinal bleeding. In pivotal clinical trials, syncopal episodes have been reported in association with ARICEPT® (2% vs 1% for placebo).

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She sees it as a bedtime story.

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Please see brief summary of prescribing information on adjacent page.

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EL208A99CR

60-Day Planner

MEETINGS DEADLINES REMINDERS

September

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2 (–7) IUPS Satellite Symposium: Synaptic Transmission in the Central Nervous System, Queensland, Australia *contact:* Tel: 61-26-249-2602 steve.redman@anu.edu.au	*3* *Labor Day—USA*	*4 (–7)* 6th International Congress of Neuroimmunology: Edinburgh, Scotland *contact:* Tel: 20-8-875-2440 2001@Neuroimmunology-Congress.org	*5 (–8)* University of Cape Town: Neuropsychology Course, Cape Town, South Africa *contact:* Tel: 21-406-6381 selliott@curie.ct.ac.za	*6*	*7*	*8 (–12)* European Brain and Behavior Society: 33rd Annual General Meeting, Marseille, France *contact:* Incf.cnrs-mrs.fr//EBBS-EBPS-2001/welcome.html
9	*10 (–12)* 4th Milano International Symposium: Epidemiology of Sleep Disorders, Milan, Italy *contact:* Tel: 2-29-40-1409 mgacongr@tin.it	*11 (–14)* 13th Meeting of the World Society of Stereotactic and Functional Neurosurgery: Adelaide, Australia *contact:* Tel: 61-29-956-8333 confact@conferenceaction.com.au	*12 (–15)* 4th Congress of the International Society for Neurosurgical Technology and Instrument Inventions: Cairns, Australia *contact:* Tel: 61-70-385-5414 judyw@im.com.au	*13 (–15)* Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine: Long Beach, CA *contact:* Tel: 847-384-4309	*14* National Institutes of Health: National Advisory Mental Health Council, Bethesda, MD *contact:* Tel: 301-443-5047 jsteinbe@nih.gov	*15*
16 12th International Congress of the World Federation of Neurosurgical Societies: Sydney, Australia *contact:* Tel: 61-29-241-1478 reply@icmsaust.com.au	*17*	*18*	*19*	*20 (–22)* 4th International Congress on the Mechanics and Treatment of Neuropathic Pain: San Francisco, CA *contact:* Tel: 716-275-4392 office@cpe.rochester.edu	*21* 16th World Congress on Psychosomatic Medicine: Gothenburg, Sweden *contact:* Tel: 46-3143-1012 icpm.2001@swefair.se	*22* Neuro-Psychiatric Update: New York, NY *contact:* Tel: 617-572-3597 npupdates@hhc.com
23 *30* 126th Annual Meeting of the American Neurological Association: Chicago, IL **(Sept 30–Oct 3)** *contact:* Tel: 612-545-6284 Fax: 612-545-6073	*24 (–29)* World Congress of Neuroinformatics: Vienna, Austria *contact:* Tel: 4-315-880-11-499 frattay@mail.zserv.tuwein.ac.at	*25*	*26* **October *CNS* closes & ships to printer**	*27*	*28*	*29 (–Oct 4)* Annual Meeting of the Congress of Neurological Surgeons: Burr Ridge, IL *contact:* Tel: 877-517-1CNS info@1cns.org

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60-Day Planner

October

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	*2*	*3*	*4 (–6)*	*5 (–7)*	*6*
				International Society for the Study of Personality Disorders: 7th International Congress, New York, NY *contact:* Tel: 212-305-3334 Fax: 212-781-6047	2nd Congress of the Hellenic Stroke Society: Athens, Greece *contact:* Tel: 30-31-260-645 Fax: 30-31-260-645 nicart@med.auth.gr	
7	*8*	*9*	*10 (–13)*	*11 (–13)*	*12*	*13 (–17)*
	Columbus Day—USA		Mental and Behavioral Dysfunction in Movement Disorders: Montreal, Canada *contact:* Tel: 514-848-1133 Fax: 514-288-6469 bedard.marc-andre@uquam.ca	1st Canadian Colloquium on Dementia: Toronto, Canada *contact:* Tel: 416-340-5304 Fax: 416-340-4198 rkeren@home.com	Johns Hopkins: Neuroradiology Review With Case Reviews, Baltimore, MD *contact:* Tel: 410-955-2959 Fax: 410-955-0807 cmenet@jhmi.edu	European College of Neuropsychopharmacology: 14th Congress, Istanbul, Turkey *contact:* Tel: 31-30-253-8567 Fax: 31-30-253-8568
14	*15*	*16*	*17*	*18*	*19*	*20*
			The Royal College of Pathologists: What's New in Pediatric Neuropathology, London, UK *contact:* Tel: 2-74-516-700 Fax: 2-74-516-701 info@rcpath.org			
21 (–26)	*22*	*23*	*24*	*25 (–27)*	*26*	*27*
World Conference Sleep Odyssey 2001: Punta del Este, Uruguay *contact:* Tel: 59-80-92-43-414 x3409 Fax: 59-82-92-48-784 sleep2001@fmed.edu.uy				Neuromuscular Disorders in Pediatrics: St. Louis, MO *contact:* Tel: 800-553-2712 Fax: 314-776-4395 cme@slu.edu		New York University School of Medicine: Review of Practice Guidelines for Treatment of Psychiatric Disorders, New York, NY *contact:* www.med.nyu.edu/cme/
28	*29*	*30*	*31*			
			November *CNS* closes & ships to printer	37th Annual Turkish Neurological Congress: Antalya, Turkey **(Oct 31–Nov 4)** *contact:* Tel: 90-46-23-258-309 Fax: 90-46-23-269-192 mozmenoglu@usa.net	Harry Benjamin International Gender Dysphoria Association: 17th Symposium, Galveston, TX **(Oct 31–Nov 4)** *contact:* Tel: 612-625-1500 Fax: 612-626-8311	

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CNS SPECTRUMS

The International Journal of Neuropsychiatric Medicine

ADRENERGIC RECEPTORS AND THEIR EFFECT ON THE CNS

page 656

"Few β_1-selective agonists have been developed due to a lack of significant therapeutic indications. Dobutamine is the main compound used experimentally, but shows little ability to penetrate the brain. However, dobutamine's CNS effects have been observed following systemic administration, suggesting that some drug does cross the BBB. As discussed, a number of β_3-AR selective agonists have been developed. Because there are few β_3-ARs in the brain, there has been little interest in whether they can cross the BBB. However, the structures of most of these compounds suggest that they will achieve at least partial brain penetration."

NOREPINEPHRINE MODULATION AND REGULATION IN NEUROPSYCHIATRIC DISORDERS

page 663

"Much early work was based on NE metabolite measurements, which initially suggested decreased NE activity in depression, though later studies found significant variability in metabolite measurements between patients. Studies of LC number and tyrosine hydroxylase (TH) expression suggest that the LC/NE system is profoundly affected in depressed patients. Furthermore, there is evidence that NE is hypersecreted in plasma and CSF in patients with unipolar depression and generalized anxiety."

MONOAMINE AND NOREPINEPHRINE TRANSPORTERS: DEVELOPING NOVEL THERAPIES

page 671

"With regard to NETs, immunofluorescence studies in mammalian cells reveal that NE reduces PKC-activated internalization of NETs. Amphetamine also triggers the internalization of DATs via a dynamin-dependent pathway, thereby providing a novel mechanism by which amphetamine can elevate extracellular levels of DA. Together, these studies point to the fact that acute substrate occupancy influences transporter phosphorylation and trafficking, possibly by altering the accessibility and sensitivity of monoamine transporters to protein kinases, phosphatases, and transporter regulatory proteins."

HOW DOES THE NOREPINEPHRINE SYSTEM RESPOND TO ANTIDEPRESSANTS?

page 679

"Antidepressants have been shown to reverse the attenuated cerebral blood flow in the frontal cortex and induce neurogenesis in the hippocampus, possibly via a neurotrophic factor-dependent mechanism. Indeed, the NE system densely innervates these structures, and antidepressant-induced alterations occur within a time course of about 2 weeks, which is congruent with their therapeutic effects. Given that PTSD patients often experience flashbacks, and that patients with anxiety disorders may have phobias linked to traumatic events, these structures do seem relevant to the clinical condition. Extensive research on anxiety and affective disorders has focused on the frontal cortex, hippocampus, and serotonin system, all of which are regulated by the NE system."

USING POSTMORTEM BRAIN TISSUE TO INVESTIGATE PSYCHIATRIC ILLNESS

page 697

"Despite the lack of effect of NE depletion on mood in normal subjects, rapid pharmacologic depletion of NE in patients taking noradrenergic antidepressants causes a rapid relapse of depression. This latter finding demonstrates that NE is critical to the therapeutic action of noradrenergic antidepressants. Most recently, and of considerable significance, a well-controlled study demonstrated that depletion of catecholamines (NE and DA) in euthymic, unmedicated subjects who had a history of major depression resulted in a relapse into depression. Together, these studies demonstrate that NE depletion by itself is insufficient to induce depressive symptoms, but depletion in a susceptible individual will induce depressive symptoms. Hence, there is strong evidence for a direct role of NE in depression pathobiology."

RADIOLIGANDS, PET, AND SPECT

page 704

"For quantifying receptor and transporter density, PET and SPECT imaging techniques provide important advantages over other methods, especially in humans. Serial studies in the same subject are possible; this arrangement avoids the intersubject variation inherent in cross-sectional studies, as subjects can serve as their own control. Because human subjects can be identified and selected prospectively, important variables such as clinical diagnosis, comorbid illness, and drug exposure can be accurately assessed. Although serial studies of noradrenergic neurochemistry in cerebrospinal fluid or blood samples are possible, they lack spatial signal resolution and a defined, direct relationship to CNS activity. The ability to perform noninvasive serial studies in vivo and access to well-defined study populations may resolve controversies about the roles of the noradrenergic system in the etiology, pathophysiology, and therapy of depression and other psychiatric disorders."

EFFICACY OF NORADRENERGIC AGENTS

page 710

"In a recent large-scale, multicenter, placebo-controlled study involving adult patients, reboxetine proved particularly effective in the treatment of panic disorder. It significantly reduced the number of major panic attacks and phobic symptomatology experienced by patients. There is suggestion of a role for the noradrenergic antidepressants in other disorders, including ADHD and social phobia."

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KEPPRA™ (levetiracetam)

250 mg, 500 mg and 750 mg tablets **℞ only**

BRIEF SUMMARY (for full prescribing information, consult package insert)

INDICATIONS AND USAGE: Keppra (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

CONTRAINDICATIONS: This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra tablets.

WARNINGS: Neuropsychiatric Adverse Events: Keppra use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities. In controlled trials of patients with epilepsy, 14.8% of Keppra treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of Keppra treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence. In controlled trials of patients with epilepsy, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced. A total of 3.4% of Keppra treated patients experienced coordination difficulties (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued Keppra treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of preexisting ataxia. Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment. In controlled trials of patients with epilepsy, 5 (0.7%) of Keppra treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) Keppra treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In one patient experiencing psychotic depression occurring within a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of Keppra patients experienced other behavioral symptoms (reported as agitation, hostility, anxiety, apathy, emotional lability, depersonalization, depression, etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized. In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months. **Withdrawal Seizures:** Antiepileptic drugs, including Keppra, should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS: Hematologic Abnormalities: Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 10^9/mm^3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%) were seen in Keppra treated patients in controlled trials. A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤1.0 x 10^9/L) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts. **Hepatic Abnormalities:** There were no meaningful changes in mean liver function tests (LFT) in controlled trials; lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%). No patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) epilepsy patient receiving open treatment. **Information For Patients:** Patients should be instructed to take Keppra only as prescribed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised that Keppra may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery or engage in other hazardous activities until they have gained sufficient experience on Keppra to gauge whether it adversely affects their performance of these activities. **Laboratory Tests:** Although most laboratory tests are not systematically altered with Keppra treatment, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests. **Use in Patients With Impaired Renal Function:** Caution should be taken in dosing patients with moderate and severe renal impairment and patients undergoing hemodialysis. Dosage should be reduced in patients with impaired renal function receiving Keppra and supplemental doses should be given to patients after dialysis (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function). **Drug Interactions:** *In vitro* data on metabolic interactions indicate that Keppra is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, warfarin, digoxin, oral contraceptive) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients. Drug-Drug Interactions Between Keppra and Existing Antiepileptic Drugs (AEDs): Potential drug interactions between Keppra and existing AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of existing AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam. **Other Drug Interactions:** Oral Contraceptives: Keppra (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam. Digoxin: Keppra (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam. Warfarin: Keppra (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam. Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of Keppra on probenecid was not studied. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis: Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m^2 or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied. Mutagenesis: Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* 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 (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay. Impairment of Fertility: No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis). **Pregnancy: Pregnancy Category C:** In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (approximately 4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day. When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study. Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Keppra should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women exposed to Keppra physicians are encouraged to register patients, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free). **Labor and Delivery:** The effect of Keppra on labor and delivery in humans is unknown. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Keppra is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in patients below the age of 16 have not been established. **Geriatric Use:** Of the total number of subjects in clinical studies of levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Keppra in these patients. A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses for 10 days showed no pharmacokinetic differences related to age alone. Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. **Use in Patients With Impaired Renal Function:** Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. The dosage should be reduced in patients with impaired renal function receiving Keppra and supplemental doses should be given to patients after dialysis (see DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

ADVERSE REACTIONS: In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness. Table 1 lists treatment-emergent adverse events that occurred in at least 1% of patients with epilepsy treated with Keppra participating in placebo-controlled studies and were numerically more common in patients treated with Keppra than placebo. In these studies, either Keppra or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity. The prescriber should be aware that these figures, obtained when Keppra was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied. **Table 1: Incidence (%) of Treatment-emergent Adverse Events in Placebo-controlled, Add-on Studies by Body System (Adverse Events Occurred in at Least 1% of Keppra-treated Patients and Occurred More Frequently than Placebo-treated Patients)** Keppra (N=769) vs Placebo (N=439): **Body System/Adverse Event: Body as a Whole:** Asthenia (15% vs 9%); Headache (14% vs 13%); Infection (13% vs 8%); Pain (7% vs 6%). **Digestive System:** Anorexia (3% vs 2%). **Nervous System:** Amnesia (2% vs 1%); Anxiety (2% vs 1%); Ataxia (3% vs 1%); Depression (4% vs 2%); Dizziness (9% vs 4%); Emotional Lability (2% vs 0%); Hostility (2% vs 1%); Nervousness (4% vs 2%); Paresthesia (2% vs 1%); Somnolence (15% vs 8%); Vertigo (3% vs 1%). **Respiratory System:** Cough Increased (2% vs 1%); Pharyngitis (6% vs 4%); Rhinitis (4% vs 3%); Sinusitis (2% vs 1%). **Special Senses:** Diplopia (2% vs 1%). Other events reported by 1% or more of patients treated with Keppra but as or more frequent in the placebo group were: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain. **Time Course of Onset of Adverse Events:** Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra. **Discontinuation or Dose Reduction in Well-Controlled Clinical Studies:** In well-controlled clinical studies, 15.0% of patients receiving Keppra and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in Table 2. **Table 2: Adverse Events Most Commonly Associated With Discontinuation or Dose Reduction in Placebo-controlled Studies in Patients With Epilepsy** Keppra (N=769) vs Placebo (N=439): [Number (%)]: Asthenia [10 (1.3%) vs 3 (0.7%)]; Convulsion [23 (3.0%) vs 15 (3.4%)]; Dizziness [11 (1.4%) vs 0]; Somnolence [34 (4.4%) vs 7 (1.6%)]; Rash [0 vs 5 (1.1%)]. **Comparison of Gender, Age and Race:** The overall adverse experience profile of Keppra was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

DOSAGE AND ADMINISTRATION: Keppra is indicated as adjunctive treatment of partial onset seizures in adults with epilepsy. In clinical trials, daily doses of 1000 mg, 2000 mg and 3000 mg, given as twice a day dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose (see CLINICAL STUDIES in package insert), a consistent increase in response with increased dose has not been shown. Treatment should be initiated with a daily dose of 1000 mg/day, given as twice daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Long term experience at doses greater than 3000 mg/day is relatively minimal, and there is no evidence that doses greater than 3000 mg/day confer additional benefit. Keppra is given orally with or without food. **Patients With Impaired Renal Function:** Keppra dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose are shown in the Table below. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

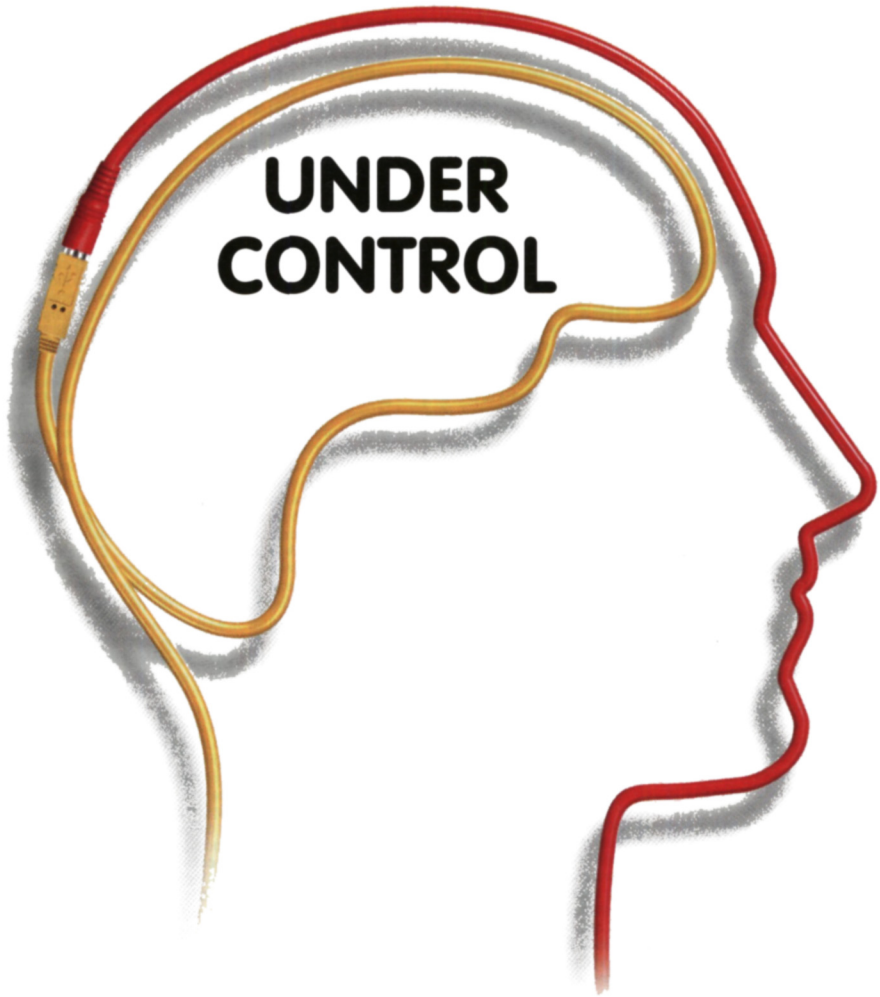
$$CLcr = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Dosing Adjustment Regimen for Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 h
Mild	50 – 80	500 to 1,000	Every 12 h
Moderate	30 – 50	250 to 750	Every 12 h
Severe	< 30	250 to 500	Every 12 h
ESRD patients using dialysis	—	500 to 1,000	Every 24 h*

*Following dialysis, a 250 to 500 mg supplemental dose is recommended.

https://doi.org/10.1017/S1092852900001280 Published online by Cambridge University Press



EFFICACY AND TOLERABILITY IN AN EASY-TO-USE AED—ADD-ON THERAPY STARTS WITH KEPPRA™

EFFECTIVE CONTROL OF PARTIAL ONSET SEIZURES

- Provides up to 4 out of 10 refractory patients with ≥50% partial onset seizure reduction
- Clinical improvement has been seen within 2 weeks[1]

GENERALLY WELL TOLERATED

- The most common adverse events associated with Keppra™ in combination with other AEDs were somnolence, asthenia, infection, and dizziness. Of these, most appeared to occur during the first 4 weeks of treatment
- No dose relationship was observed for the most common adverse events over the entire treatment period in Phase III clinical studies[1]

EASY TO START, EASY TO MANAGE

- Starting dose of 1000 mg/day (500 mg bid) is effective for many patients
- If needed, the dose can be increased by an additional 1000 mg/day at 2 week intervals up to a maximum dose of 3000 mg/day
- No drug/drug interactions with AEDs included in well-controlled studies, a combination oral contraceptive, warfarin, or digoxin

Keppra™
levetiracetam
250 • 500 • 750 mg tablets

SIMPLIFYING SEIZURE CONTROL

Keppra™ use is associated with the occurrence of central nervous system adverse events including somnolence and fatigue, coordination difficulties, and behavioral abnormalities, and with minor, but statistically significant, hematological abnormalities. Keppra™ dosing must be individualized according to renal function status.

Please consult brief summary of prescribing information on adjacent page.

Reference: 1. Data on file, UCB Pharma, Inc.

ucb Pharma

K156-0301

https://doi.org/10.1017/S1092852900001280 Published online by Cambridge University Press

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Feature Articles

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 6 • Number 8
August 2001

CNS Spectrums is a peer review journal and is indexed in EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis. *CNS Spectrums* is endorsed by, and is the official journal of, the International Neuropsychiatric Ass., with members in 30 countries.

CNS Spectrums
(ISSN 1092-8529)
is published monthly by
MedWorks Media,
333 Hudson Street, 7th Floor
New York, NY 10013.

Periodicals postage paid
at New York, NY, and at
additional mailing offices.

One year subscription rates:
domestic $90;
foreign $145;
in-training $50.
For subscriptions:
Fax: 212-328-0600
E-mail:
jrr@medworksmedia.com

Postmaster:
Send address changes to
CNS Spectrums
c/o PPS Medical Marketing Group
264 Passaic Ave.
Fairview, NJ 07004-2595

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 6 • Number 8
August 2001

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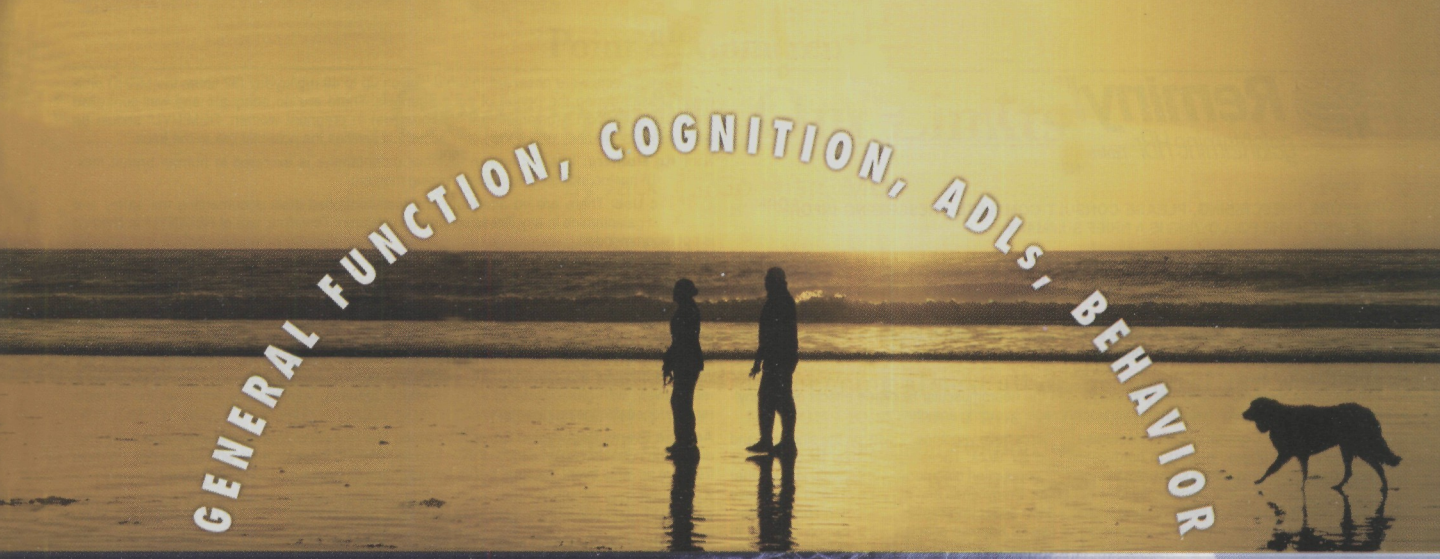

ALL AROUND SUCCESS

Now all the benefits of REMINYL can help patients with mild to moderate Alzheimer's disease (AD).[1-4]

The most frequent adverse events that occurred with REMINYL were nausea, vomiting, diarrhea, anorexia, and weight loss.

Available in 4-mg, 8-mg, and 12-mg tablets.

www.reminyl.com

Please see brief summary of prescribing information on adjacent page.

ALL AROUND BENEFITS IN AD

NEW Reminyl®
galantamine HBr Tablets

References: 1. Tariot PN et al. *Neurology*. 2000;54:2269-2276. 2. Raskind MA et al. *Neurology*. 2000;54:2261-2268. 3. Wilcock GK et al. *BMJ*. 2000;321:1-7. 4. Data on file, Janssen.

JANSSEN PHARMACEUTICA PRODUCTS, L.P. ORTHO-McNEIL

 Printed in U.S.A. 01-RM-039-2 April 2001

https://doi.org/10.1017/S1092852900001280 Published online by Cambridge University Press

Reminyl®
galantamine HBr Tablets

Rx only

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

INDICATION
REMINYL® (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS
REMINYL® is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS
Anesthesia: Galantamine is likely to exaggerate the neuromuscular blockade effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

Cardiovascular Conditions: Cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction. In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope.

Gastrointestinal Conditions: Patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). REMINYL® has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss. (See **ADVERSE REACTIONS**)

Genitourinary: Cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions: Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. In clinical trials, there was no increase in the incidence of convulsions with REMINYL® compared to placebo.

Pulmonary Conditions: Galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS
Information for Patients and Caregivers: The recommended administration is twice per day, preferably with morning and evening meal. Dose increases should follow minimum of four weeks at prior dose. Following the recommended dosage and administration can minimize the most frequent adverse events associated with use of the drug. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Special Populations

Hepatic Impairment: In patients with moderately impaired hepatic function, dose titration should proceed cautiously (See **CLINICAL PHARMACOLOGY** in full prescribing information and **DOSAGE AND ADMINISTRATION**). The use of REMINYL® in patients with severe hepatic impairment is not recommended.

Renal Impairment: In patients with moderately impaired renal function, dose titration should proceed cautiously (See **CLINICAL PHARMACOLOGY** in full prescribing information and **DOSAGE AND ADMINISTRATION**). In patients with severely impaired renal function (CL_{cr} < 9 ml/min) the use of REMINYL® is not recommended.

Drug-Drug Interactions

Use with Anticholinergics: Galantamine has the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine: *In vitro* - CYP3A4 and CYP2D6 were the major enzymes involved in the metabolism of galantamine. CYP3A4 mediated the formation of galantamine-N-oxide, whereas CYP2D6 was involved in the formation of O-desmethyl-galantamine. *In vivo* - Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine. Ketoconazole increased the AUC of galantamine by 30%. Erythromycin affected the AUC of galantamine minimally (10% increase). Paroxetine increased the oral bioavailability of galantamine by about 40%.

B) Effect of Galantamine on Other Drugs: *In vitro* Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. *In vivo* - The protein binding of warfarin was unaffected by galantamine. Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 24-month oral carcinogenicity study in rats, a trend for an increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day (12 times MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis). Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis).

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis. There are no adequate and well-controlled studies of REMINYL® (galantamine hydrobromide) in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether galantamine is excreted in human breast milk. REMINYL® has no indication for use in nursing mothers.

Pediatric Use: There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of REMINYL® in children is not recommended.

ADVERSE REACTIONS
Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects (nausea, vomiting and anorexia) the principle reason for discontinuing galantamine.

Adverse Events Reported in Controlled Trials: The majority of reported adverse events occurred during the dose-escalation period of the controlled trials. In those patients who experience the most frequent adverse event, nausea, the median duration of the nausea was 5 to 7 days.

Administration of REMINYL® with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of REMINYL® under conditions of every 4 week dose-escalation, were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose. They included nausea (5%, 13% and 17%), vomiting (1%, 6% and 10%), diarrhea (6%, 12% and 6%), anorexia (3%, 7% and 9%) and weight decrease (1%, 5% and 5%) for placebo, 16-mg/day and 24-mg/day treatment groups respectively.

The most common adverse events (adverse events occurring with an incidence of 2% with REMINYL® treatment and in which the incidence was greater than with placebo treatment) for patients in controlled trials who were treated with 16 or 24 mg/day of REMINYL® were: fatigue 5%, syncope 2%, dizziness 9%, headache 8%, tremor 3%, nausea 24%, vomiting 13%, diarrhea 9%, abdominal pain 5%, dyspepsia 5%, bradycardia 2%, weight decrease 7%, anorexia 9%, depression 7%, insomnia 5%, somnolence 4%, anemia 3%, rhinitis 4%, urinary tract infection 8% and hematuria 3%.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with REMINYL® treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rates related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials: The incidence of all adverse events occurring in approximately 0.1% of the patients during clinical trials, except for those adverse events already listed elsewhere in labeling, are defined as: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients; and rare adverse events - those occurring in fewer than 1/1000 patients. **Body As a Whole – General Disorders:** *Frequent:* chest pain; **Cardiovascular System Disorders:** *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure; **Central & Peripheral Nervous System Disorders:** *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia; **Gastrointestinal System Disorders:** *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *rare:* esophageal perforation; **Heart Rate & Rhythm Disorders:** *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T wave inversion, ventricular tachycardia; **Metabolic & Nutritional Disorders:** *Infrequent:* hyperglycemia, alkaline phosphatase increased; **Platelet, Bleeding & Clotting Disorders:** *Infrequent:* purpura, epistaxis, thrombocytopenia; **Psychiatric Disorders:** *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium; **Urinary System Disorders:** *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

OVERDOSAGE
Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics.

DOSAGE AND ADMINISTRATION
The dosage of REMINYL® shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a BID regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL® might provide additional benefit for some patients. The recommended starting dose of REMINYL® is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) should be attempted only after a minimum of 4 weeks at the previous dose. REMINYL® should be administered twice a day, preferably with morning and evening meals. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Doses in Special Populations: Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of REMINYL® in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended. For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance <9 ml/min), the use of REMINYL® is not recommended.

7517303
March 2001, March 2001
US Patent No. 4,663,318

Manufactured by:
Janssen-Cilag SpA
Latina, Italy

Distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary—see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated *in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.* **WARNINGS *Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart attack in patients both with or without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®,cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions *Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL), and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin, and warfarin. ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro.* Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis). **Pregnancy *Pregnancy Category C:*** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/%Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks

Adverse Event	Placebo (n=315)	No titration 5 mg/day (n=311)	One-week titration 10 mg/day (n=315)	Six-week titration 10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® (donepezil HCl) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients with any Adverse Event	**72**	**74**
Body as a Whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

Other Adverse Events Observed During Clinical Trials ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events*—those occurring in at least 1/100 patients; *infrequent adverse events*—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Revised December 2000

Eisai Inc. Teaneck, NJ 07666

Pfizer U.S. Pharmaceuticals New York, NY 10017

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Printed in USA/May 2001

https://doi.org/10.1017/S1092852900001280 Published online by Cambridge University Press