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Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

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https://doi.org/10.1017/S0317167100116956 Published online by Cambridge University Press

PrLYRICA®
PREGABALIN

SUMMARY PRODUCT

Classification Analgesic Agent

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules, 25 mg, 50 mg, 75 mg, 150 mg, 300 mg	Lactose monohydrate *For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults: LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with: • Diabetic peripheral neuropathy and • Postherpetic neuralgia

Geriatrics (>65 years of age): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **WARNINGS AND PRECAUTIONS,** *Geriatrics (>65 years of age)*). ***Pediatrics (<18 years of age):*** The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended (see **WARNINGS AND PRECAUTIONS,** *Pediatrics*).

CONTRAINDICATIONS

Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

Tumorigenic Potential In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice (see **Preclinical Toxicology**). The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans. In clinical studies across various patient populations, comprising 6396 patient-years of exposure in 8666 patients ranging in age from 12 to 100 years, new or worsening-preexisting tumors were reported in 57 patients. The most common malignant tumor diagnosed was skin carcinoma (17 patients) followed by breast carcinoma (8 patients), prostatic carcinoma (6 patients), carcinoma not otherwise specified (6 patients) and bladder carcinoma (4 patients). Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA (pregabalin), it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment. **Ophthalmological Effects** In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see **Post-Marketing Adverse Drug Reactions**). Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated, and 2% of placebo-treated patients. At this time, clinical significance of the ophthalmologic findings is unknown. Patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment, including discontinuation of pregabalin, should be considered. More frequent assessments should be considered for patients who are already routinely monitored for ocular conditions. **Peripheral Edema** In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5508) compared with 2% of patients (42/2384) in the placebo group. In these studies, 0.5% (28/5508) of pregabalin patients and 0.2% (4/2384) of placebo patients withdrew due to peripheral edema (see **ADVERSE REACTIONS**, *Peripheral Edema*). In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA (pregabalin) and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents. Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients. **Weight Gain** Pregabalin treatment was associated with weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain (see **ADVERSE REACTIONS**, *Weight Gain*). Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender or age. Weight gain was not limited to patients with edema (see **WARNINGS AND PRECAUTIONS, Peripheral Edema**). Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown. Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg. While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}). **Dizziness and Somnolence** In controlled neuropathic pain studies, pregabalin caused dizziness in 23% of patients (424/1831) compared to 7% in placebo (58/857). Somnolence was experienced by 14% (256/1831) and 4% (33/857) of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses. In these studies, dizziness and somnolence led to withdrawal of 3.5% and 2.6% of the pregabalin-treated patients, respectively. For the remaining patients (359 and 208, respectively) who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 43% and 58% of the patients, respectively (see **ADVERSE REACTIONS**, Tables 2 and 4, and **Post-Marketing Adverse Drug Reactions**). Accordingly, patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental and/or motor performance adversely (see **CONSUMER INFORMATION**). **Abrupt or Rapid Discontinuation** Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see **ADVERSE REACTIONS**, *Adverse Events Following Abrupt or Rapid Discontinuation*). **Sexual Function/Reproduction** Impairment of Male Fertility Preclinical Data In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250 or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. The clinical significance of female fertility findings in animals is unknown. Human Data In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin 600 mg/day for 3 months (one complete sperm cycle). Pregabalin did not exhibit significant detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis, when compared with placebo (n=16). However, due to the small sample size and short-term exposure to pregabalin (only one complete sperm cycle), no conclusions can be made regarding possible reproductive effects of pregabalin during long-term exposure. Effects on other male reproductive parameters in humans have not been adequately studied. **Special Populations** *Renal* Because pregabalin is eliminated primarily by renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). *Adjustment of Dose in Renally-Impaired Patients* In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in **DOSAGE AND ADMINISTRATION, Dosing Considerations**). **Preclinical Data** Pregabalin was not teratogenic in mice, rats or rabbits. Pregabalin induced fetal toxicity in rats and rabbits at ≥39 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day [$AUC_{0\text{-}24}$ of 123 µg•hr/mL]. In the prenatal-postnatal toxicity study, pregabalin induced offspring developmental toxicity in rats at ≥5 times the maximum recommended human exposure. No developmental effects occurred at 2 times the maximum recommended human exposure (see **PRODUCT MONOGRAPH**). **Human Data** *Pregnant Women* There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Labour and Delivery* The effects of pregabalin on labour and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥47 times the mean human exposure [$AUC_{0\text{-}24}$ of 123 µg•hr/mL] at the maximum recommended clinical dose of 600 mg/day (see **PRODUCT MONOGRAPH**). *Nursing Women* It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see **PRODUCT MONOGRAPH**). *Pediatrics (<18 years of age)* The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established. *Geriatrics (>65 years of age)* Of the 1831 patients who received pregabalin in neuropathic pain studies, 528 were 65 to 74 years of age, and 452 were 75 years of age or older. No significant differences in efficacy were observed between these patients and younger patients. Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. In general, the incidence of adverse events did not increase with age. *Creatine Kinase Elevations* Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur. *Laboratory Changes, Decreased Platelet Count* Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x 10^3/µL, compared to 11 x 10^3/µL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/µL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events. *ECG Changes, PR Interval Prolongation* Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block. *Information for Patients* **Dizziness and Somnolence** Patients should be counseled that LYRICA (pregabalin) may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual and/or motor performance adversely. **Visual Disturbances** Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see **WARNINGS AND PRECAUTIONS, Ophthalmologic Effects**). **Abrupt or Rapid Discontinuation** Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache or diarrhea. **Edema and Weight Gain** Patients should be counseled that LYRICA may cause edema and weight gain. Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure. **Muscle Pain, Tenderness or Weakness** Patients should be instructed to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Concomitant Treatment with CNS Depressants, Alcohol** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence. Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol. **Pregnant Woman** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast-feeding or intend to breast-feed during therapy. **Animal Studies in Male Reproduction** In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity (see **WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction**). The clinical significance of this finding is uncertain; however, men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. **Skin** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see **PRODUCT MONOGRAPH**). Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA. **Preclinical Toxicology** ***Carcinogenesis*** A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000 or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. In an investigative study in female B6C3F1 mice, chronic treatment (24 months) with pregabalin at 1000 mg/kg caused an increased incidence of hemangiosarcoma, consistent with previous studies, but not at 50 or 200 mg/kg. Discontinuation of treatment after 12 months at 1000 mg/kg did not significantly reduce the incidence of hemangiosarcoma at 24 months. Evidence of carcinogenicity was not seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150 or 450 mg/kg in males and 100, 300 or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance in humans of this finding in mice is unknown. ***Mutagenesis*** Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests. Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes. **Dermatopathy** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular lesions** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown. **Monitoring and Laboratory Tests** Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with LYRICA (pregabalin) (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview **Clinical Trial Adverse Drug Reactions** In all controlled and uncontrolled trials, more than 8666 patients have received LYRICA (pregabalin), with 83% of exposure at dosages of 300 mg/day or above and 32% at dosages of 600 mg/day or higher. Approximately 4010 patients had at least 6 months of exposure, 2415 had at least 1 year of exposure, and 939 had at least 2 years of exposure to pregabalin. In controlled trials, 1831 patients with neuropathic pain received pregabalin. *Most Common Adverse Events in All Controlled Clinical Studies of Neuropathic Pain* The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema and dry mouth. Adverse events were usually mild to moderate in intensity. *Discontinuation Due to Adverse Events* In all controlled studies, the discontinuation rate due to adverse events was 14% for patients receiving pregabalin and 7% for patients receiving placebo. The most common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were ataxia (1%) and asthenia, confusion, headache and nausea (<1% each). In controlled neuropathic pain studies, the discontinuation rate due to adverse events was 11% for pregabalin and 5% for placebo. The most common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were confusion (1%) and asthenia, peripheral edema and ataxia (<1% each). *Incidence of Adverse Events in Controlled Clinical Studies of Neuropathic Pain* In summaries of adverse events, investigator's terms for individual adverse events have been grouped into a smaller number of standardized categories using the COSTART IV dictionary. The prescriber should be aware that the percentages in Table 1 through Table 6 cannot be used to predict the frequency of adverse events 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. *Adverse Events From Controlled Clinical Studies of Neuropathic Pain* Diabetic Peripheral Neuropathy Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with diabetic peripheral neuropathy receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 979 patients received pregabalin and 459 patients received placebo for up to 13 weeks.

Table 1. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

		Pregabalin (mg/day)			
Body System Preferred Term	Placebo (n = 459) %	75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Body as a whole					
Infection	6.1	3.9	7.5	8.4	4.6

Body System Preferred Term	Placebo (n = 459) %	Pregabalin (mg/day) 75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Asthenia	2.4	3.9	1.9	4.4	7.3
Pain	3.9	5.2	4.2	2.5	4.9
Accidental injury	2.8	5.2	2.4	2.2	5.7
Back pain	0.4	0.0	2.4	1.2	1.9
Chest pain	1.1	3.9	1.4	1.2	1.6
Face edema	0.4	0.0	0.9	0.9	2.2
Digestive system					
Dry mouth	1.1	2.6	1.9	4.7	6.5
Constipation	1.5	0.0	2.4	3.7	6.0
Diarrhea	4.8	5.2	2.8	1.9	3.0
Flatulence	1.3	2.6	0.0	2.2	2.7
Vomiting	1.5	1.3	0.9	2.2	1.1
Hemic and lymphatic system					
Ecchymosis	0.2	2.6	0.5	0.6	0.3
Metabolic and nutritional disorders					
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Edema	0.0	0.0	1.9	4.0	1.9
Hypoglycemia	1.1	1.3	3.3	1.6	1.1
Nervous system					
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Neuropathy	3.5	9.1	1.9	2.2	5.4
Ataxia	1.3	6.5	0.9	2.2	4.3
Vertigo	1.1	1.3	1.9	2.5	3.5
Confusion	0.7	0.0	1.4	2.2	3.3
Euphoria	0.0	0.0	0.5	3.4	1.6
Thinking abnormal[a]	0.0	1.3	0.0	0.9	3.0
Abnormal gait	0.0	1.3	0.0	0.6	2.7
Reflexes decreased	1.7	3.9	0.5	1.2	1.4
Amnesia	0.2	2.6	0.9	0.0	2.2
Hypesthesia	0.7	2.6	0.0	0.0	0.8
Hyperalgesia	0.2	2.6	0.0	0.0	0.3
Respiratory system					
Dyspnea	0.7	2.6	0.0	1.9	1.9
Skin and appendages					
Pruritus	1.3	2.6	0.0	0.9	0.0
Special senses					
Blurred vision[b]	1.5	2.6	1.4	2.8	1.5
Conjunctivitis	0.2	2.6	1.4	0.6	0.3

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.

b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Diabetic Peripheral Neuropathy Approximately 9% of patients receiving pregabalin and 4% receiving placebo discontinued from controlled diabetic peripheral neuropathy studies due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 2.

Table 2. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

	Number (%) of Patients				
		Pregabalin (mg/day)			
COSTART Preferred Term	Placebo (n = 459)	75 (n = 77)	150 (n = 212)	300 (n = 321)	600 (n = 369)
Dizziness	2 (0.4)	0 (0.0)	3 (1.4)	6 (1.9)	21 (5.7)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	15 (4.1)

Postherpetic Neuralgia Table 3 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with postherpetic neuralgia receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 852 patients received pregabalin and 398 patients received placebo for up to 13 weeks.

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

Body System Preferred Term	Placebo (n = 398) %	Pregabalin (mg/day) 75 (n = 84) %	150 (n = 302) %	300 (n = 312) %	600 (n = 154) %
Body as a whole					
Infection	3.5	14.3	8.3	6.4	2.6
Headache	5.3	4.8	8.9	4.5	8.4
Pain	3.8	4.8	4.3	5.4	4.5
Asthenia	4.0	3.6	5.0	2.6	5.2
Accidental injury	1.5	3.6	2.6	3.2	5.2
Flu syndrome	1.3	1.2	1.7	2.2	1.3
Face edema	0.8	0.0	1.7	1.3	3.2
Malaise	1.0	2.4	0.3	0.6	0.0
Cardiovascular system					
Vasodilatation	1.3	2.4	1.0	0.6	0.0
Digestive system					
Dry mouth	2.8	7.1	7.0	6.1	14.9
Constipation	2.3	3.6	4.6	5.4	5.2
Diarrhea	4.0	2.4	4.3	3.5	4.5
Flatulence	1.0	2.4	1.3	1.6	3.2
Vomiting	0.8	1.2	0.7	2.9	2.6
Metabolic and nutritional disorders					
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Weight gain	0.3	1.2	1.7	5.4	6.5
Edema	1.3	0.0	1.0	2.2	5.8
Hyperglycemia	0.8	2.4	0.3	0.0	0.0
Nervous system					
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Ataxia	0.5	1.2	2.0	5.4	9.1
Abnormal gait	0.5	0.0	2.0	3.8	7.8
Confusion	0.3	1.2	2.3	2.9	6.5
Thinking abnormal[a]	1.5	0.0	1.7	1.3	5.8
Incoordination	0.0	2.4	1.7	1.3	2.6
Amnesia	0.0	0.0	1.0	1.3	3.9
Speech disorder	0.0	0.0	0.3	1.3	3.2
Insomnia	1.8	0.0	0.7	2.2	0.0
Euphoria	0.0	2.4	0.0	1.3	1.3
Nervousness	0.5	0.0	1.0	0.3	2.6
Tremor	1.5	1.2	0.0	1.0	2.6
Hallucinations	0.0	0.0	0.3	0.3	3.2
Hyperesthesia	0.3	2.4	0.3	0.0	1.3
Respiratory system					
Bronchitis	0.8	0.0	1.3	1.0	2.6
Pharyngitis	0.8	0.0	2.6	0.6	0.6
Rhinitis	1.8	1.2	0.7	0.6	3.2
Skin and appendages					
Rash	3.0	2.4	2.0	2.9	5.2
Special senses					
Blurred vision[b]	2.5	1.2	5.0	5.1	9.1
Diplopia	0.0	0.0	1.7	1.9	3.9
Abnormal vision	0.3	0.0	1.0	1.6	5.2
Urogenital system					
Urinary tract infection	1.5	0.0	2.3	1.6	3.2

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.

b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Postherpetic Neuralgia Approximately 14% of patients receiving pregabalin and 7% receiving placebo discontinued from controlled postherpetic neuralgia studies due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 4.

Table 4. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Postherpetic Neuralgia

	Number (%) of Patients				
		Pregabalin (mg/day)			
COSTART Preferred Term	Placebo (n = 398)	75 (n = 84)	150 (n = 302)	300 (n = 312)	600 (n = 154)
Dizziness	3 (0.8)	0 (0.0)	11 (3.6)	12 (3.8)	12 (7.8)
Somnolence	1 (0.3)	0 (0.0)	6 (2.0)	12 (3.8)	10 (6.5)
Confusion	1 (0.3)	0 (0.0)	2 (0.7)	5 (1.6)	8 (5.2)
Peripheral edema	1 (0.3)	0 (0.0)	2 (0.7)	5 (1.6)	5 (3.2)
Ataxia	0 (0.0)	0 (0.0)	1 (0.3)	5 (1.6)	4 (2.6)
Abnormal gait	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	4 (2.6)
Hallucinations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	4 (2.6)
Dry mouth	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)

Incidence of Most Common Dose-Related Treatment-Emergent Adverse Events Most common dose-related treatment-emergent adverse events are presented in Table 5 (diabetic peripheral neuropathy) and Table 6 (postherpetic neuralgia).

Table 5. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Event Preferred Term	Placebo (n = 459) %	Pregabalin (mg/day) 75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Asthenia	2.4	3.9	1.9	4.4	7.3
Dry mouth	1.1	2.6	1.9	4.7	6.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Constipation	1.5	0.0	2.4	3.7	6.0
Blurred vision[a]	1.5	2.6	1.4	2.8	5.7

a Investigator term; summary level term is amblyopia.

Table 6. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia

Adverse Event Preferred Term	Placebo (n = 398) %	Pregabalin (mg/day) 75 (n = 84) %	150 (n = 302) %	300 (n = 312) %	600 (n = 154) %
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Dry mouth	2.8	7.1	7.0	6.1	14.9
Blurred vision[a]	2.5	1.2	5.0	5.1	9.1
Ataxia	0.5	1.2	2.0	5.4	9.1
Weight gain	0.3	1.2	1.7	5.4	6.5
Abnormal gait	0.5	0.0	2.0	3.8	7.8

a Investigator term; summary level term is amblyopia.

Adverse Events Following Abrupt or Rapid Discontinuation Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**). **Drug Abuse and Dependence/Liability** In a study of recreational users (n=15) of sedative/hypnotic drugs, including alcohol, a single dose of LYRICA (pregabalin) 450 mg received subjective ratings of "good drug effect", "high", and "liking" to a degree that was similar to a single dose of diazepam 30 mg. In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event. However, in clinical trials of diabetic peripheral neuropathy, euphoria was reported as an adverse event by 1.8% of LYRICA-treated patients and 0% of placebo-treated patients, and in clinical trials of postherpetic *neuralgia, euphoria was reported as an adverse event by 0.9% of LYRICA-treated* patients and 0% of placebo-treated patients. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea suggestive of physical dependence (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**). Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour). ***Other Events Observed During the Premarketing Evaluation of LYRICA*** Following is a list of treatment-emergent adverse events reported during premarketing assessment of LYRICA in clinical trials (over 8600 adult subjects) except those already listed in the previous tables or elsewhere in labeling. In the tabulations that follow, a COSTART-based dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 8600 adult individuals exposed to multiple doses of LYRICA who experienced an event of the type cited on at least 1 occasion while receiving LYRICA. It is important to emphasize that although the events reported occurred during treatment with LYRICA, they were not necessarily caused by it. **Less Common Clinical Trial Adverse Drug Reactions (<2%)** Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body System	Adverse Events
Body as a whole	
Frequent	Flu syndrome, back pain, allergic reaction, fever, generalized edema
Infrequent	Neck pain, neoplasm, cellulitis, cyst, chills, malaise, overdose, moniliasis, hernia, viral infection, photosensitivity reaction, pelvic pain, abdomen enlarged, abscess, neck rigidity, lab test abnormal, drug level increased, carcinoma, sepsis, suicide attempt, reaction unevaluable
Rare	Infection fungal, unexpected benefit, chills and fever, body odor, drug level decreased, halitosis, hangover effect, injection site reaction, hormone level altered, hypothermia, infection bacterial, injection site hemorrhage, intentional overdose, mucous membrane disorder, accidental overdose, adenoma, anaphylactoid reaction, ascites, chest pain substernal, death, sarcoidosis, sudden death, immune system disorder, increased drug effect, injection site pain, Lupus Erythematosus syndrome, medication error, sarcoma, shock, tolerance decreased
Cardiovascular	
Frequent	Hypertension, vasodilatation
Infrequent	Palpitation, migraine, tachycardia, peripheral vascular disorder, electrocardiogram abnormal, cardiovascular disorder, angina pectoris, congestive heart failure, hemorrhage, myocardial infarct, hypotension, postural hypotension, ventricular extrasystoles, atrial fibrillation, coronary artery disorder, bradycardia, cerebrovascular accident, arrhythmia, cerebral ischemia, vascular disorder, sinus bradycardia, myocardial ischemia, bundle branch block, AV block first degree, arteriosclerosis, deep thrombophlebitis, phlebitis, arterial anomaly, heart failure, pulmonary embolus, retinal vascular disorder, varicose vein
Rare	Heart arrest, vascular anomaly, occlusion, supraventricular tachycardia, atrial arrhythmia, atrial flutter, cerebral infarct, coronary occlusion, thrombophlebitis, thrombosis, cardiomegaly, extrasystoles, pallor, AV block, AV block second degree, cardiomyopathy, peripheral gangrene, QT interval prolonged, retinal artery occlusion, supraventricular extrasystoles, cerebral hemorrhage, digitalis *intoxication, ventricular arrhythmia, aortic stenosis, bigeminy,* cerebrovascular disorder, left heart failure, ventricular tachycardia, AV block complete, carotid occlusion, carotid thrombosis, cor pulmonale, embolus lower extremity, endocarditis, heart block, increased capillary fragility, intracranial aneurysm, nodal tachycardia, QT interval shortened, retinal vein thrombosis, ST elevated, T inverted, vascular headache, vasculitis
Digestive system	
Frequent	Nausea, diarrhea, anorexia, gastrointestinal disorder
Infrequent	Gastroenteritis, tooth disorder, periodontal abscess, colitis, gastritis, liver function tests abnormal, increased salivation, thirst, nausea and vomiting, rectal disorder, gingivitis, dysphagia, stomatitis, mouth ulceration, cholelithiasis, rectal hemorrhage, gastrointestinal hemorrhage, glossitis, tooth caries, abnormal stools, cholecystitis, melena, oral moniliasis, esophagitis, tongue disorder, cheilitis, tongue edema
Rare	Eructation, pancreatitis, stomach ulcer, ulcerative stomatitis, esophageal stenosis, fecal incontinence, gum hemorrhage, intestinal obstruction, enteritis, peptic ulcer, enterocolitis, gum hyperplasia, hepatomegaly, liver fatty deposit, tenesmus, biliary pain, fecal impaction, jaundice, periodontitis, ulcerative colitis, aphthous stomatitis, cholestatic jaundice, gastrointestinal carcinoma, hemorrhagic gastritis, hepatitis, liver tenderness,

https://doi.org/10.1017/S0317167100116956 Published online by Cambridge University Press

Body System	Adverse Events
	nausea, vomiting and diarrhea, salivary gland enlargement, stomach atony, bloody diarrhea, cardiospasm, duodenal ulcer, gamma glutamyl transpeptidase increased, hematemesis, hepatoma, intestinal perforation, intestinal stenosis, intestinal ulcer, leukoplakia of mouth, necrotizing pancreatitis, pancreas disorder, pseudomembranous colitis, sialadenitis, stomach ulcer hemorrhage, tongue discoloration
Endocrine system	
Infrequent	Diabetes mellitus, hypothyroidism
Rare	Goiter, prolactin increased, thyroid disorder, gonadotropic follicle stim hormone increase, hyperthyroidism, thyroiditis, adrenal insufficiency, parathyroid disorder, thyroid carcinoma, thyroid neoplasia, virilism
Hemic and lymphatic	
Infrequent	Anemia, leukopenia, thrombocytopenia, lymphadenopathy, hypochromic anemia, leukocytosis, eosinophilia
Rare	Lymphocytosis, petechia, iron deficiency anemia, cyanosis, lymphedema, polycythemia, lymphoma like reaction, megaloblastic anemia, splenomegaly, purpura, thrombocythemia, thrombocytopenic purpura, chronic leukemia, coagulation disorder, erythrocytes abnormal, leukemoid reaction, lymphangitis, macrocytic anemia, pancytopenia, prothrombin decreased, rupture of spleen, sedimentation rate increased
Metabolic and nutritional	
Infrequent	Hyperglycemia, SGPT increased, hypoglycemia, hypokalemia, hypercholesteremia, SGOT increased, weight loss, hyperlipemia, amylase increased, hyperuricemia, alkaline phosphatase increased, creatinine increased, hyponatremia, gout, dehydration, BUN increased, healing abnormal
Rare	Hypercalcemia, hyperkalemia, hypocalcemia, bilirubinemia, alcohol intolerance, hypoglycemic reaction, ketosis, calcium disorder, hypochloremia, hypomagnesemia, hypoproteinemia, NPN increased, uremia, acidosis, avitaminosis, enzymatic abnormality, gamma globulins increased, hypernatremia, hypophosphatemia, lactic acidosis, obesity
Musculoskeletal system	
Frequent	Arthralgia, myalgia, arthritis, leg cramps, myasthenia
Infrequent	Tendon disorder, arthrosis, joint disorder, bone disorder, tenosynovitis, bursitis, tendinous contracture, osteoporosis, tendon rupture, bone pain
Rare	Rheumatoid arthritis, osteomyelitis, rhabdomyolysis, myopathy, muscle atrophy, myositis, pyogenic arthritis, bone neoplasm, musculoskeletal congenital anomaly, pathological fracture
Nervous system	
Frequent	Insomnia, anxiety, libido decreased, depersonalization, hypertonia, neuropathy
Infrequent	Reflexes decreased, sleep disorder, abnormal dreams, hostility, hallucinations, hyperkinesia, personality disorder, dysarthria, hyperesthesia, hypokinesia, circumoral paresthesia, libido increased, neuralgia, vestibular disorder, aphasia, movement disorder, hyperalgesia, apathy, hypotonia, convulsion, facial paralysis, psychosis
Rare	Drug dependence, neuritis, paranoid reaction, CNS depression, CNS neoplasia, manic reaction, neurosis, extrapyramidal syndrome, meningitis, hemiplegia, reflexes increased, akathisia, delirium, paralysis, withdrawal syndrome, brain edema, CNS stimulation, dyskinesia, encephalopathy, foot drop, grand mal convulsion, hypalgesia, peripheral neuritis, psychotic depression, addiction, arachnoiditis, cerebellar syndrome, cogwheel rigidity, dementia, dystonia, Guillain-Barre syndrome, intracranial hemorrhage, multiple sclerosis, myelitis, schizophrenic reaction, subarachnoid hemorrhage, torticollis
Respiratory system	
Frequent	Sinusitis, rhinitis, dyspnea, cough increased, pneumonia, lung disorder
Infrequent	Asthma, epistaxis, laryngitis, voice alteration, respiratory disorder, sputum increased
Rare	Apnea, emphysema, aspiration pneumonia, hyperventilation, lung edema, pleural disorder, atelectasis, hemoptysis, hiccup, hypoxia, laryngismus, lung fibrosis, pleural effusion, lung function decreased, pulmonary hypertension, yawn, bronchiectasis, bronchiolitis, carcinoma of lung, hypoventilation, laryngeal neoplasia, nasal septum disorder, pneumothorax
Skin and appendages	
Infrequent	Pruritus, sweating, skin disorder, acne, dry skin, alopecia, skin ulcer, herpes simplex, urticaria, nail disorder, eczema, herpes zoster, skin benign neoplasm, fungal dermatitis, maculopapular rash, vesiculobullous rash, skin carcinoma, furunculosis, skin discoloration, skin hypertrophy, psoriasis, seborrhea, hirsutism
Rare	Skin nodule, angioedema, cutaneous moniliasis, skin atrophy, exfoliative dermatitis, pustular rash, ichthyosis, skin melanoma, subcutaneous nodule, sweating decreased, hair disorder, lichenoid dermatitis, melanosis, miliaria, purpuric rash, skin necrosis, Stevens Johnson syndrome
Special sense	
Frequent	Eye disorder, conjunctivitis, otitis media
Infrequent	Retinal disorder, tinnitus, eye pain, cataract specified, dry eyes, taste perversion, ear pain, lacrimation disorder, ear disorder, deafness, eye hemorrhage, photophobia, glaucoma, vitreous disorder, corneal lesion, otitis externa, refraction disorder, blepharitis, retinal edema, taste loss, abnormality of accommodation
Rare	Hyperacusis, keratitis, mydriasis, parosmia, ptosis, retinal hemorrhage, color blindness, retinal depigmentation, retinal detachment, corneal opacity, corneal ulcer, iritis, night blindness, optic atrophy, retinal degeneration, cataract NOS, scleritis, strabismus, anisocoria, blindness, exophthalmos, keratoconjunctivitis, ophthalmoplegia, papilledema
Urogenital system	
Frequent	Anorgasmia
Infrequent	Urinary frequency, urinary incontinence, cystitis, abnormal ejaculation, urination impaired, dysuria, metrorrhagia, hematuria, vaginal moniliasis, prostatic disorder, vaginitis, dysmenorrhea, urinary urgency, kidney calculus, breast pain, menstrual disorder, amenorrhea, menorrhagia, kidney function abnormal, nephritis, urine abnormality, vaginal hemorrhage, urinary retention, urinary tract disorder, leukorrhea, breast neoplasm, menopause, oliguria, polyuria, albuminuria, pyuria
Rare	Breast carcinoma, penis disorder, papanicolau smear suspicious, fibrocystic breast, prostatic carcinoma, uterine fibroids enlarged, acute kidney failure, creatinine clearance decreased, nephrosis, nocturia, polycystic kidney, bladder carcinoma, breast enlargement, cervicitis, cervix disorder, female lactation, glycosuria, gynecomastia, hypomenorrhea, kidney pain, mastitis, pyelonephritis, kidney failure, breast abscess, epididymitis, orchitis, prostate neoplasia, prostatic specific antigen increase, salpingitis, urogenital disorder, urolithiasis, uterine disorder, vulvovaginal disorder, balanitis, bladder calculus, calcium crystalluria, cervix neoplasm, dyspareunia, endometrial carcinoma, endometrial disorder, glomerulitis, hydronephrosis, ovarian cancer, unintended pregnancy, urethral pain, urethritis, urogenital anomaly, urogenital neoplasia, uterine hemorrhage

Comparison of Gender and Race The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race. *Peripheral Edema* Incidence of peripheral edema in controlled neuropathic pain studies was 10.4% in the pregabalin group compared with 2.9% in the placebo group. In clinical trials, these events of peripheral edema were dose-related, mostly mild to moderate in intensity and rarely led to withdrawal. Peripheral edema was not associated with cardiovascular complications such as hypertension or congestive heart failure and there was no evidence of hemodilution or changes in any laboratory parameters indicative of underlying organ dysfunction (see **WARNINGS AND PRECAUTIONS, Peripheral Edema**). *Weight Gain* In the controlled neuropathic pain studies, patients on pregabalin had a higher incidence (5.9%) of weight gain as defined by a ≥7% increase from baseline weight as compared with the placebo group (1.6%). The mean change in the pregabalin group was an increase of 1.5 kg compared with 0.2 kg in the placebo group; few patients (0.1%) withdrew due to weight gain. This weight gain was dose-related, and not associated with clinically important changes in blood pressure or cardiovascular adverse events. There was no relationship between baseline body mass index and the incidence of ≥7% weight gain in the controlled trials. Based on the results of a controlled study of reproductive function in healthy male volunteers, the ≥7% weight gain on pregabalin appeared to be reversible. In this study, there were no reports of peripheral edema (see **WARNINGS AND PRECAUTIONS, Weight Gain**). **Abnormal Hematologic and Clinical Chemistry Findings** In all controlled trials, 1.0% of patients on pregabalin and 0.5% of placebo patients had an increase in creatine kinase of >3x upper limit of normal. Renal dysfunction was generally not associated with the elevated creatine kinase in these patients. Mean changes in creatine kinase ranged from 9.6 to 26.3 U/L for pregabalin-treated patients and 4.8 U/L for the placebo patients (see **DOSAGE AND ADMINISTRATION**, Patients with Renal Impairment). Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with LYRICA (see **WARNINGS AND PRECAUTIONS**). **Post-Marketing Adverse Drug Reactions** The worldwide post-marketing experience to date with LYRICA is consistent with the clinical program. The most frequently reported adverse events from spontaneous post-marketing reports for LYRICA are shown below. There are insufficient data to support an estimate of their incidence or to establish causation. **Eye disorders:** diplopia, vision blurred, visual disturbance. There have also been rare reports of accommodation disorder, eyelid edema and eye redness (see **WARNINGS AND PRECAUTIONS, Ophthalmological Effects**). **Gastrointestinal disorders:** diarrhea, dry mouth, nausea, vomiting **General disorders and administration site conditions:** fatigue, feeling abnormal, pain **Nervous system disorders:** ataxia, coordination abnormal, dizziness, dysarthria, headache, memory impairment, paresthesia, somnolence, speech disorder, tremor (see **WARNINGS AND PRECAUTIONS, Dizziness and Somnolence**). **Psychiatric disorders:** confusional state, depression, insomnia, psychotic disorder. There have been rare reports of psychotic disorders in patients receiving pregabalin. **Renal and urinary disorders:** urinary retention **Respiratory, thoracic and mediastinal disorders:** dyspnea **Skin and subcutaneous tissue disorders:** pruritus

DRUG INTERACTIONS

Overview Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions. *Pharmacokinetic* **In Vitro Studies:** In vitro drug metabolism studies revealed that pregabalin at concentrations which were, in general, 10-fold greater than observed in Phase 2/3 clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. **In Vivo Studies:** The drug interaction data described in this section were obtained from studies involving healthy adults, patients with epilepsy, and patients with chronic pain disorders. **Carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate** In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no clinically significant pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs. **Tiagabine:** The results of a population pharmacokinetic analysis indicated that in patients with partial seizures tiagabine had no clinically significant effect on pregabalin clearance. **Gabapentin:** The pharmacokinetics of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single dose administration of 100 mg pregabalin and 300 mg gabapentin, and in 18 healthy subjects following concomitant multiple dose administration of 200 mg pregabalin q8h and 400 mg gabapentin q8h. Gabapentin pharmacokinetics following single and multiple dose administration were unaltered by pregabalin coadministration. The rate of pregabalin absorption was reduced by approximately 26% (single dose administration) and 18% (multiple dose administration) based on lower C_{max} values; however, the extent of pregabalin absorption was unaffected by gabapentin coadministration. **Oral Contraceptives:** Pregabalin coadministration (200 mg TID) had no effect on the steady state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects. **Lorazepam:** Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of lorazepam single dose pharmacokinetics and single dose administration of lorazepam (1 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin. **Oxycodone:** Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of oxycodone single dose pharmacokinetics. Single dose administration of oxycodone (10 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin. **Ethanol:** Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of ethanol single dose pharmacokinetics and single dose administration of ethanol (0.7 g/kg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin. **Diuretics, Oral Hypoglycemics, and Insulin:** A population pharmacokinetic analysis in patients with chronic pain showed no clinically significant effect on pregabalin clearance with the concomitant use of diuretics, oral hypoglycemics, and insulin. *Pharmacodynamic* Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam. **Drug-Food Interactions** The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total amount of pregabalin absorbed. Therefore, pregabalin can be taken with or without food. **Drug-Herb Interactions** LYRICA (pregabalin) has no known drug/herb interactions. **Drug-Laboratory Interactions** LYRICA (pregabalin) has no known drug/laboratory test interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations ***Patients with Impaired Renal Function*** **Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Dosage Adjustment Based on Renal Function, below).** In accordance with current clinical practice, if LYRICA (pregabalin) has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**). **Adults: Neuropathic pain associated with diabetic peripheral neuropathy** The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently. **Neuropathic pain associated with postherpetic neuralgia** The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently. **Dosage Adjustment Based on Renal Function** LYRICA is primarily eliminated by renal excretion. Therefore, the dose should be adjusted for patients with reduced renal function. Pregabalin clearance is directly proportional to creatinine clearance. Therefore, dosing adjustment should be based on creatinine clearance (CL_{Cr}), as indicated in Table 7. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{Cr}) in mL/min is needed. CL_{Cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

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

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 7).

Table 7. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CL_{Cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.
a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
b Supplementary dose is a single additional dose.

Geriatrics (>65 years): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. ***Pediatrics (<18 years of age):*** The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended. **Administration** LYRICA (pregabalin) is given orally with or without food (see **ACTION AND CLINICAL PHARMACOLOGY**).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans The highest known dose of pregabalin received in the clinical development program was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin. **Treatment or Management of Overdose** There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin. **Hemodialysis** Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action *Pharmacodynamics* LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta protein (a calcium channel subunit) of brain tissues and has analgesic, antiepileptic and anxiolytic activity. Pregabalin is known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally-related to pregabalin indicate that selective binding to the alpha$_2$-delta protein is required for analgesic, antiepileptic and anxiolytic action in animal models. In vitro, pregabalin reduces the release of several neurotransmitters, suggesting a modulatory action on calcium channel function. Pregabalin does not mimic

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GABA at $GABA_A$ or $GABA_B$ receptors, nor does it augment $GABA_A$ responses like benzodiazepines or barbiturates. In contrast to vascular calcium channel blockers, pregabalin does not alter systemic blood pressure or cardiac function. Various in vitro and in vivo results differentiate pregabalin from GABA uptake inhibitors or GABA transaminase inhibitors. In addition, pregabalin does not block sodium channels, it is not active at opiate receptors, it does not alter cyclooxygenase enzyme activity, it is not a serotonin agonist, it is not a dopamine antagonist, and it is not an inhibitor of dopamine, serotonin or noradrenaline reuptake. Pregabalin treatment reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin given intrathecally prevents pain-related behaviors and reduces pain-related behavior caused by spinally administered agents, suggesting that it acts directly on tissues of the spinal cord or brain. **Pharmacokinetics** All pharmacological actions following pregabalin administration are due to the activity of the parent compound; pregabalin is not appreciably metabolized in humans. Mean steady-state plasma pregabalin concentration-time profiles following 75, 300 and 600 mg/day given in equally divided doses every 8 hours (TID) and 600 mg/day given in equally divided doses every 12 hours (BID) are shown in Table 8. Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%).

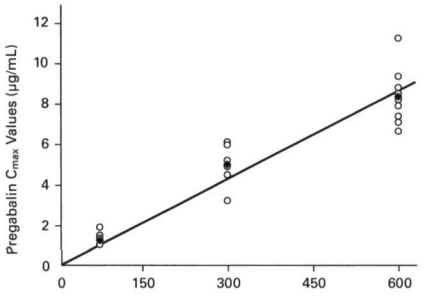
Table 8. Pregabalin Mean (CV%[a]) Steady-State Pharmacokinetic Parameter Values in Healthy Volunteers

Dose (mg)	Regimen	Daily Dose (mg/day)	n	C_{maxss} (µg/mL)	t_{max} (hr)	C_{minss} (µg/mL)	$AUC_{(0-t)}$ (µg•hr/mL)	$t_{1/2}$ (hr)	$C_{L/F}$ (mL/min)
25	TID[b]	75	8	1.39	0.9	0.45	6.7	5.9	64.1
				-19.5	-34.2	-25	-18.3	-17.3	-16.1
100	TID	300	6	5.03	0.8	1.94	25.2	6.3	68.9
				-21.3	-31	-33.6	-23	-19.6	-20.9
200	TID	600	11	8.52	0.9	3.28	41.7	6.3	81
				-14.8	-22.2	-29.2	-12.8	-13.6	-11.7
300	BID[c]	600	8	9.07	1.4	2.6	59	6.7	85.1
				-10.5	-57.1	-15.5	-6.4	-16.2	-6.4

C_{maxss}: Steady-state peak plasma concentration.
t_{max}: Time of peak plasma concentration at steady state.
C_{minss}: Steady-state trough plasma concentration
$AUC_{(0-t)}$: Area under the plasma concentration-time curve during one dosing interval at steady state
$t_{1/2}$: Elimination half-life
$C_{L/F}$: Oral clearance
a: Percent coefficient of variation
b: Total daily dose given in equally divided doses every 8 hours
c: Total daily dose given in equally divided doses every 12 hours

Absorption: Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1.5 hours following both single- and multiple-dose administration. Pregabalin oral bioavailability is ≥90% and is independent of dose. C_{max} (Figure 1) and AUC values increase proportionally following single- and multiple-dose administration. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple dose pharmacokinetics are predictable from single-dose data.

Figure 1. Individual and Mean Steady-State Pregabalin C_{max} Values Following 75, 300 and 600 mg/day Given in Equally Divided Doses TID (q8h) to Healthy Volunteers[a]



a: Solid line is the regression line going through the origin; individual (○) and mean (◆) values.

Distribution: In preclinical studies, pregabalin has been shown to readily cross the blood brain barrier in mice, rats and monkeys. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood-brain barrier. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is not bound to plasma proteins. At clinically efficacious doses of 150 and 600 mg/day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6.0 µg/mL, respectively. **Metabolism:** Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits or monkeys. **Excretion:** Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean $t_{1/2}$ is 6.3 hours. Pregabalin elimination is proportional to creatinine clearance. Pregabalin clearance is reduced in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). **Special Populations and Conditions** Pregabalin undergoes negligible metabolism, is not bound to plasma proteins and is eliminated predominately as unchanged drug by renal excretion. Clinically important differences in pregabalin pharmacokinetics due to race and gender have not been observed and are not anticipated. **Pediatrics:** Pharmacokinetics of pregabalin have not been studied in paediatric patients. **Geriatrics:** Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Gender:** A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar between genders when adjusted for gender-related differences in creatinine clearance. **Race:** A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar among Caucasians, Blacks and Hispanics. **Renal Insufficiency:** Because renal elimination is the major elimination pathway, dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 15°C-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

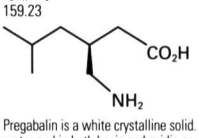
Each capsule of LYRICA (pregabalin) contains 25, 50, 75, 150 or 300 mg pregabalin, lactose monohydrate, maize starch and talc. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid, which may not be present. The markings on the capsules are in black ink, which contains shellac, black iron oxide, propylene glycol, potassium hydroxide and water.

Capsules are packaged in HDPE bottles containing 60 capsules, and PVC/aluminum blisters.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: pregabalin
Chemical name: (S)-3-(aminomethyl)-5-methylhexanoic acid
Molecular formula: $C_8H_{17}NO_2$
Molecular mass: 159.23
Structural formula:



Physicochemical properties: Pregabalin is a white crystalline solid. It is soluble in water and in both basic and acidic aqueous solutions.

Product Monograph available upon request.

Last revised: June 3, 2005.

References: 1. LYRICA Product Monograph, Pfizer Canada Inc., June 2005. **2.** Freynhagen R *et al.* Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005; 115:254-63. **3.** Data on file, Pfizer Canada Inc., study 1008-96. **4.** van Seventer R *et al.* Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Clin Med Res Opin* 2006; 22(2):375-84.

https://doi.org/10.1017/S0317167100116956 Published online by Cambridge University Press

CALENDAR OF EVENTS

February 29 and March 1, 2008
Mont Tremblant, Quebec, Canada
Canadian Radiosurgery Society (CaRS) 2008 Meeting
Details can be found at www.CaRS2008.ca

March 7-9, 2008
Miami, Florida, USA
2008 Miami Headache Symposium
For more information individuals can contact (856) 423-0043 or fax: (856) 423-0082, or e-mail: ahsmtgs@talley.com or access our web-site at www.ahsnet.org.

March 25-26, 2008
Washington, DC, USA
Tregs and Th17 Cells in Autoimmunity
Call for Abstracts by February 25, 2008.
For information or to register, please visit www.biosymposia.org.

April 12-19, 2008
Chicago, Ill, USA
American Academy of Neurology - 60th Annual Meeting
For information go to: www.aan.com/go/am

April 18, 2008
Toronto, Ontario, Canada
SpineFESTT - Symposium Forum on Emerging Spinal Technologies
For information please go to:
http://events.cmetoronto.ca/website/index/SUR0836

April 26-May 1, 2008
Chicago, Illinois, USA
American Association of Neurological Surgeons (AANS) 2008 Annual Meeting
For more information or to register, please visit www.AANS.org or email meeting@aans.org

May 25-27, 2008
Houston, Texas, USA
Goodman Oral Board Preparation: Neurosurgery Review by Case Management
For more information or to register, please visit www.AANS.org or email epm@aans.org

June 6-9, 2008
Toronto, Ontario, Canada
Canadian College of Neuropsychopharmacology (CCNP) Annual Conference
For more information contact Ms. Rachelle Anderson at (780) 407-6543 (Tel) or (780) 407-6672 (Fax) or email rmena@ualberta.ca. Visit our website www.ccnp.ca.

June 15-19, 2008
Melbourne, Australia
2008 Organization for Human Brain Mapping Meeting
Please visit www.hbm2008.com for more information.

June 17-20, 2008
Victoria, British Columbia, Canada
43rd Annual Congress of the Canadian Neurological Sciences Federation
For more information go to: www.cnsfederation.org or contact the secretariat office at (403) 229-9544.

September 5-6, 2008
Toronto, Ontario, Canada
9th Annual Interventional Neuroradiology Symposium
For more information contact the Office of Continuing Education and Professional Development, E-mail: help-MIM0804@cmetoronto.ca or go to our website: www.cme.utoronto.ca

September 17-20, 2008
Montreal, Quebec, Canada
World Congress on Treatment and Research in Multiple Sclerosis
Please visit www.msmontreal for more information on program, registration and abstract submission.

October 23-26, 2008
Athens, Greece
Controversies in Neurology (CONy)
For additional information regarding CONy, please visit our website: www.comtecmed.com/cony

November 9-11, 2008
Houston, Texas, USA
Goodman Oral Board Preparation: Neurosurgery Review by Case Management
For more information or to register, please visit www.AANS.org or email epm@aans.org

January 16-18, 2009
Orlando, Florida, USA
AAN Annual Meeting
For information go to: www.aan.com/fall07

April 15-18, 2009
Rotterdam, The Netherlands
9th European Skull Base Society Meeting
For more information please visit our website: www.esbs2009.eu

June 9 - 12, 2009
Halifax, Nova Scotia, Canada
44th Annual Congress of the Canadian Neurological Sciences Federation
For more information go to: www.cnsfederation.org or contact the secretariat office at (403) 229-9544.

August 30-September 4, 2009
Boston, Massachusetts, USA
XIV Congress of the World Federation of Neurosurgical Societies (WFNS)
For more information or to register, please visit www.AANS.org/wfns2009 or email wfns2009@aans.org

https://doi.org/10.1017/S0317167100116956 Published online by Cambridge University Press

Once-a-day
℞ **Aricept®**
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rapidly disintegrating tablets

PHARMACOLOGIC CLASSIFICATION Cholinesterase Inhibitor **INDICATIONS AND CLINICAL USE** **ARICEPT** (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. Efficacy of **ARICEPT** in patients with mild-to-moderate Alzheimer's disease was established in two 24-week and one 54-week placebo-controlled trials. **ARICEPT** tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. **CONTRAINDICATIONS** **ARICEPT** (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS AND PRECAUTIONS** ***Cardiovascular:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials in Alzheimer's disease, most patients with serious *cardiovascular conditions were excluded. Patients such as those with controlled hypertension (DBP<95 mmHg), right bundle branch blockage* and pacemakers were included. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes have been reported in association with the use of **ARICEPT.** It is recommended that **ARICEPT** should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes. ***Gastrointestinal:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), including high doses of acetylsalicylic acid (ASA), should be monitored for symptoms of active or occult gastrointestinal bleeding. Clinical studies of **ARICEPT** have shown no increase relative to placebo in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS** section). **ARICEPT,** as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with Alzheimer's disease, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks, and have resolved during continued use of **ARICEPT** (see **ADVERSE REACTIONS** section). Treatment with the 5 mg/day dose for 4–6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance. ***Genitourinary:*** Although not observed in clinical trials of **ARICEPT,** cholinomimetics may cause bladder outflow obstruction. ***Hepatic:*** There is limited information regarding the pharmacokinetics of **ARICEPT** in hepatically impaired Alzheimer's disease patients. Close monitoring for adverse effects in patients with hepatic disease being treated with **ARICEPT** is therefore recommended. ***Neurologic:*** **Seizures:** Some cases of seizures have been reported with the use of **ARICEPT** in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of Alzheimer's disease. The risk/benefit of **ARICEPT** treatment for patients with a history of seizure disorder must therefore be carefully evaluated. **ARICEPT** has not been studied in patients with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patients are unknown. ***Peri-Operative Considerations:*** **Anesthesia: ARICEPT,** as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Renal:*** There is limited information regarding the pharmacokinetics of **ARICEPT** in renally impaired Alzheimer disease patients. Close monitoring for adverse effects in patients with renal disease being treated with **ARICEPT** is therefore recommended. ***Respiratory:*** Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **ARICEPT** has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients. ***Special Populations:*** **Pregnant and Nursing Women:** The safety of **ARICEPT** during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant. Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of **ARICEPT. Pediatrics:** There are no adequate and well-controlled trials to document the safety and efficacy of **ARICEPT** in any illness occurring in children. Therefore, **ARICEPT** is not recommended for use in children. **Geriatrics (≥85 years of age):** In controlled clinical studies with 5 and 10 mg of **ARICEPT,** 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of **ARICEPT** in low body-weight elderly patients, especially in those ≥85 years old. **Use in Elderly Patients with Comorbid Disease:** There is limited safety information for **ARICEPT** in patients with mild-to-moderate Alzheimer's disease and significant comorbidity. The use of **ARICEPT** in Alzheimer's disease patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of **ARICEPT** doses above 5 mg in this patient population. **ADVERSE REACTIONS** **Adverse Drug Reaction Overview:** ***Alzheimer's Disease:*** A total of 747 patients with mild-to-moderate Alzheimer's disease were treated in controlled clinical studies with **ARICEPT** (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 132 days (range 1–356 days). ***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 the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day **ARICEPT** 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
Number of Patients Randomized	**355**	**350**	**315**
Events / % 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 duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day. An open label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common adverse events were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a 1-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day. See Table 2 for a comparison of the most common adverse events following 1- and 6-week initial treatment periods with 5 mg/day **ARICEPT.**

Table 2. Comparison of Rates of Adverse Events in Patients Treated with 10 mg/day after 1 and 6 Weeks of Initial Treatment with 5 mg/day

	No Initial treatment	1-Week Initial treatment with 5 mg/day		6-Week Initial treatment with 5 mg/day
Adverse Event	**Placebo (n=315)**	**5 mg/day (n=311)**	**10 mg/day (n=315)**	**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%

Clinical Trial Adverse Drug Reactions: 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 behaviour and the kinds of patients treated may differ. Table 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT** and for which the rate of occurrence was greater for **ARICEPT** 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 and at a Higher Frequency than Placebo-Treated Patients

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

Long-Term Safety: Patients were exposed to **ARICEPT** in 2 open-label extension studies (n=885) of over 2 years. In 1 of the studies, 763 patients who previously completed 1 of 2 placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following 1 and 2 years of treatment, 76% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative Weeks 48 and 108). ***Postmarket Adverse Drug Reactions:*** Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction, that are not listed above, and for which 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. **Vascular dementia:** The initial safety profile from controlled clinical trials in Vascular dementia patients indicates that the rate of occurrence of adverse events overall was higher in Vascular dementia patients (91%) than in Alzheimer's disease patients (75%), however this was seen in both **ARICEPT**-treated subjects, and placebo-treated subjects, and may relate to the greater number of comorbid medical conditions in the Vascular dementia population. A comparison of the Alzheimer's disease and Vascular dementia studies shows that the type of **ARICEPT**-associated adverse events was similar in the 2 patient populations. A total of 827 patients with Vascular dementia were treated in controlled clinical studies with **ARICEPT.** Of these patients, 639 (77%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 152 days (range 1–428 days). In controlled clinical trials in Vascular dementia patients, the rates of discontinuation due to adverse events were 10.6 % for **ARICEPT** 5 mg and 19% for **ARICEPT** 10 mg compared to 9.9% for placebo. The most common adverse event leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, was nausea. Other less common events leading to discontinuation include cerebrovascular accident, confusion, dizziness, diarrhea and vomiting. The most common serious adverse events were cerebrovascular accident (3.4%) and pneumonia (1.6%). The most common adverse events were infection (14.4%), diarrhea (13.9%), accidental injury (13.0%) and nausea (11.3%). Most adverse events were judged by the investigator to be mild to moderate in intensity and not related to study medication. **DRUG INTERACTIONS** **Concomitant Use with Other Drugs:** ***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. ***Use with Other Psychoactive Drugs:*** Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants. There is thus limited information concerning the interaction of **ARICEPT** with these drugs. **Drug-Drug Interactions** Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects evaluated the potential of **ARICEPT** for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done. ***Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed in vitro between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil 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 donepezil to human albumin was not affected by furosemide, digoxin and warfarin. ***Effect of ARICEPT on the Metabolism of Other Drugs:*** In vitro studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50-130 µM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 5 mg/day for 7 days had no clinically significant effect on the pharmacokinetics *of ketoconazole. No other clinical trials have been conducted to investigate the effect of* **ARICEPT** *on the clearance of drugs metabolized* by CYP 3A4 (eg, cisapride, terfenadine) or by CYP 2D6 (eg, imipramine). It is not known whether **ARICEPT** has any potential for enzyme induction. ***Effect of Other Drugs on the Metabolism of ARICEPT:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/day **ARICEPT** together with 200 mg/day ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30%-36%. Inducers of CYP 2D6 and CYP 3A4 (eg, phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of **ARICEPT.** Pharmacokinetic studies demonstrated that the metabolism of **ARICEPT** is not significantly affected by concurrent administration of digoxin or cimetidine. **Drug-Food Interactions:** Food does not have an influence on the rate and extent of donepezil hydrochloride absorption. **Drug-Herb Interactions:** Interactions with herbal products have not been established. **Drug-Laboratory Interactions:** Interactions with laboratory tests have not been established. **DOSAGE AND ADMINISTRATION** **Dosing considerations:** **ARICEPT** (donepezil hydrochloride) or **ARICEPT RDT** should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. **Recommended Dose and Dosage Adjustment:** ***Adults:*** The recommended initial dose of **ARICEPT** or **ARICEPT RDT** is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** section) and to allow plasma levels to reach steady state. Based on clinical judgement, the 10 mg daily dose may be considered following 4–6 weeks of treatment at 5 mg/day. The maximum recommended dose is 10 mg taken once daily. Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. ***Special Populations:*** Adverse events are more common in individuals of low body weight, in patients ≥85 years old and in females. It is recommended that **ARICEPT** be used with caution in these patient populations. In elderly women of low body weight, the dose should not exceed 5 mg/day. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision. **ARICEPT** should be taken once daily in the morning or evening. It may be taken with or without food. **Administration: ARICEPT** tablets should be swallowed whole with water. **ARICEPT RDT** should be placed on the tongue and allowed to disintegrate before swallowing with water. **AVAILABILITY OF DOSAGE FORMS** **ARICEPT** is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT** is available in high-density polyethylene (HDPE) bottles of 30 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets). **ARICEPT RDT** is supplied as uncoated rapidly disintegrating tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT RDT** is available in blister strips boxed as 28 tablets. **STORAGE AND STABILITY:** **ARICEPT RDT** should not be removed from blisters until immediately prior to administration.

Product Monograph available upon request.

References:

1. Seltzer B *et al.* Efficacy of donepezil in early-stage Alzheimer disease. *Arch Neurol* 2004;61:1852-1856.
2. Rogers SL *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136-145.

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https://doi.org/10.1017/S0317167100116956 Published online by Cambridge University Press

University of Toronto - University Health Network/Mount Sinai Hospital

NEUROMUSCULAR NEUROLOGIST - Clinical Scientist

The Division of Neurology, Department of Medicine at The University Health Network/Mount Sinai Hospital (UHN/MSH) at the University of Toronto is seeking a clinician scientist with a focus in neuromuscular diseases.

The applicant must hold certification from the Royal College of Physicians and Surgeons of Canada in Neurology or be eligible for certification. The successful candidate will have fellowship training in neuromuscular disorders, including both clinical and electrodiagnositc techniques for the evaluation of peripheral neuromuscular disorders and central spinal motor control. Ideally, he or she will have experience in carrying out clinical trials in neuromuscular disorders, will have established expertise in both clinical care and teaching in neurology and will join a multidisciplinary academic neuromuscular clinic. He or she will be able to create and sustain an independent research program in the area of neuromuscular disorders and/or spinal physiology and will be expected to collaborate and interact with scientists at the University of Toronto and UHN/MSH who are pursuing molecular genetic, molecular biological, cell biological, neurophysiologic and neuroimaging research in this area, specifically in the field of spinal cord research.

The successful candidate will participate in all aspects of the UHN/MSH Neuroscience Program. He or she will be expected to participate in other clinical and research aspects of the Program of the UHN/MSH and the University of Toronto. Academic appointment in the Division of Neurology, University of Toronto and salary will be commensurate with training and experience.

The University of Toronto is strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, Aboriginal persons, persons with disabilities, members of sexual minority groups, and others who may contribute to further diversification of ideas. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority.

Please send curriculum vitae and letter of application to:

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University of Toronto - University Health Network/Mount Sinai Hospital

NEUROMUSCULAR NEUROLOGIST - Clinical Teacher

The Division of Neurology, Department of Medicine at The University Health Network/Mount Sinai Hospital (UHN/MSH) at the University of Toronto is seeking a clinician scientist with a focus in neuromuscular diseases.

The Division of Neurology, Department of Medicine at The University Health Network/Mount Sinai Hospital (UHN/MSH) at the University of Toronto is seeking a clinician teacher with a focus in neuromuscular diseases.

The applicant must hold certification from the Royal College of Physicians and Surgeons of Canada in Neurology or be eligible for certification. The successful candidate will have fellowship training in neuromuscular disorders, including both clinical and electrodiagnositc techniques for the evaluation of peripheral neuromuscular disorders. Ideally, he or she will have established expertise in both clinical care and teaching in neurology and will join a multidisciplinary academic neuromuscular clinic. He or she will demonstrate expertise in teaching by completing the Masters Teacher program at the University of Toronto, or equivalent credentials. He or she will be expected to collaborate and interact with other teachers at the University of Toronto and UHN/MSH to maintain the excellence of the teaching program at the University of Toronto.

The successful candidate will participate in all aspects of the UHN/MSH Neuroscience Program. He or she will be expected to participate in other clinical and research aspects of the Program of the UHN/MSH and the University of Toronto. Academic appointment in the Division of Neurology, University of Toronto and salary will be commensurate with training and experience.

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Please send curriculum vitae and letter of application to:

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https://doi.org/10.1017/S0317167100116956 Published online by Cambridge University Press

Congress of the Canadian Neurological Sciences Federation – Chairs: Michael Tymianski, Michael Hill

CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

Tuesday, June 17/08

7:15 – 8:30	Residents' Breakfast	
8:30 - 5:00	ALS	**David Cameron, Chair**
8:00 - 5:00	Neurobiology Review Course	**Peter Smith, Chair**
8:30 - 5:00	Child Neurology Day	**Juliette Hukin, Asuri Prasad, Chairs**
12:00 - 1:30	Lunch	
6:00 - 8:00	Epilepsy Video Session	**Richard McLachlan, Chair**
6:00 - 8:00	Movement Disorders	**Mandar Jog, Chair**

Wednesday, June 18/08

8:30 - 10:30	Grand Opening Plenary-Scientific & Technical Advances in the Clinical Neurosciences:	**Speakers – Garnette Sutherland, Ed Kaye, Antoine Hakim**
10:30 - 10:45	Coffee Break	
10:45 - 12:15	Chair's Select Plenary Presentations	
12:30 - 2:00	Stroke Satellite (Boehringer Ingelheim)	
12:30 - 2:00	N/Pathic Pain Satellite (Pfizer Canada)	
2:00 - 5:30	Neuroradiology	**Karl terBrugge, Chair**
2:00 - 5:30	Spine	**Eric Massicotte, Chair**
2:00 - 5:30	Cerebrovascular Surgery	**Mike Tymianski, Chair**
2:00 - 5:30	Neurocritical Care	**J. Teitelbaum, D. Jichici, Chairs**
2:00 - 5:30	Epilepsy	**M. Sadler, T. Valiente, Chairs**
2:00 - 5:30	Stroke	**A. Woolfenden, A. Penn, Chairs**
5:30+++	Exhibitors Reception	

Thursday, June 19/08

8:30 - 10:00	Plenary-CNS Neurology	**Speakers - Peter Reickmann, TBA**
8:30 - 10:00	Plenary-CNSS Neurosurgery	**Speakers – Charles Tator, J.P. Mohr**
10:00 -10:15	Coffee Break	
10:15 - 12:30	Platforms (7 simultaneous)	
12:30 - 2:00	Lunch/Exhibit Viewing/Poster Tours	
2:00 - 4:30	Platforms (7 simultaneous)	
4:30 - 5:30	Digital Poster and Exhibit Viewing	
5:30 - 7:00	Presidents' Reception	

Friday, June 20/08

8:30 - 9:30	Distinguished guest lecture	**Speaker – Dennis Choi**
9:30 - 10:15	Coffee break/Exhibit viewing	
10:15 - 12:00	Grand Rounds	**Michael Hill, Dean Johnston, Chairs**
12:00 - 1:30	Lunch / Exhibit viewing / Poster viewing	
1:30 - 5:00	Headache	**Marek Gawel, Chair**
1:30 - 5:00	What's New in Neurosurgery?	**Christopher Honey, Chair**
1:30 - 5:00	EEG	**Seyed Mirsattari, Chair**
1:30 - 5:00	Medical Legal Course	**Claude Martin, Chair**
1:30 - 5:00	Dementia	**Howard Feldman, Chair**
1:30 - 5:00	What's New in Neurology?	**Ashfaq Shuaib, Chair**
1:30 - 5:00	Neuromuscular	**Mike Nicolle, Chair**

Please Note: This schedule is tentative and subject to change.

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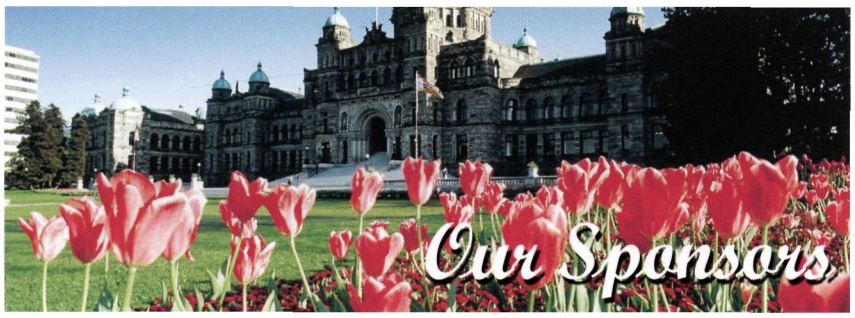

The Canadian Neurological Sciences Federation is pleased to recognize our Sponsors* for 2008. These organizations partner with CNSF to determine the causes of, and develop treatment for diseases and injuries of the nervous system, and in the care of patients with these diseases and injuries. Along with support of the Canadian Journal of Neurological Sciences and other initiatives the CNSF maintains throughout the year, these organizations graciously provide unrestricted educational grants to the Annual Congress, this year in Victoria, British Columbia; June 17th – 20, 2008.

La Fédération des sciences neurologiques du Canada est heureuse de reconnaître nos commanditaires pour l'année 2008. Ces organisations forment un partenariat avec la FSNC pour déterminer les causes des maladies et des lésions du système nerveux, pour leur trouver un traitement, et pour s'occuper des patients qui ont ces maladies et lésions. Parallèlement à l'aide financière qu'elles apportent au Journal canadien des sciences neurologiques et à d'autres initiatives que la FSNC aide tout au long de l'année, ces organisations octroient gracieusement des subventions sans condition à but éducatif au congrès annuel qui a lieu cette année à Victoria, en Colombie-Britannique, du 17 au 20 juin 2008.*

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Helping him make connections[1,2†‡]

CHOOSE ARICEPT®

ARICEPT is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. ARICEPT does not change the underlying course of the disease.

The most common adverse events with ARICEPT 10 mg/d after proper dose escalation include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia (occurring in at least 5% of patients). These events are usually mild and transient, resolving with continued ARICEPT treatment without the need for dose modification.

† In a 24-week, randomized, double-blind, placebo-controlled study of ARICEPT in 153 mild AD patients (MMSE 21-26). Patients received either ARICEPT 5 mg/d for the first 6 weeks and 10 mg/d thereafter, (n=96), or placebo (n=57). 37% of ARICEPT-treated patients experienced a 4 point ADAS-cog improvement and 10% experienced a 7 point improvement versus 16% and 7% respectively with placebo.

‡ In a 24-week, multicentre, randomized, double-blind, placebo-controlled trial, 473 patients were randomized to receive ARICEPT 5 mg/d, ARICEPT 10 mg/d or placebo. Following the 24-week, double-blind phase, all patients underwent a 6-week, single-blind placebo washout. Patients treated with either dose of ARICEPT demonstrated significantly less decline on the CIBIC-plus versus placebo (CIBIC-plus value at endpoint for ARICEPT 5 mg/d and 10 mg/d were 4.15 and 4.07 respectively versus 4.51 with placebo, p=0.0047 and p<0.0001).

Product Monograph available on request.

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For brief prescribing information see page A-17

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