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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_{0-24} 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_{0-24} 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

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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
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)

		Pregabalin (mg/day)			
Body System Preferred Term	Placebo (n = 398) %	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

		Pregabalin (mg/day)			
Adverse Event Preferred Term	Placebo (n = 459) %	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

		Pregabalin (mg/day)			
Adverse Event Preferred Term	Placebo (n = 398) %	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**).

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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, 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.

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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 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	$C_{max,ss}$ (µg/mL)	t_{max} (hr)	$C_{min,ss}$ (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

$C_{max,ss}$: Steady-state peak plasma concentration.
t_{max}: Time of peak plasma concentration at steady state.
$C_{min,ss}$: 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.

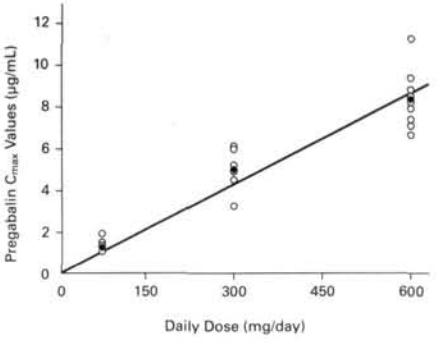
a Percent coefficient of variation

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 (O) 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.

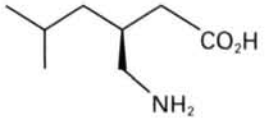
DOSAGE FORMS, COMPOSITION AND PACKAGING

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, June 2005. **2.** Data on file, Pfizer Canada Inc., study 1008-196. **3.** 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;115:254-263.

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ALTACE® ramipril

PHARMACOLOGIC CLASSIFICATION:
Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY
ALTACE (ramipril) is an angiotensin converting enzyme (ACE) inhibitor.

Following oral administration, ALTACE is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

INDICATIONS AND CLINICAL USE: *Essential Hypertension.* ALTACE (ramipril) is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics. ALTACE should normally be used in patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. The safety and efficacy of ALTACE in renovascular hypertension have not been established and therefore, its use in this condition is not recommended. The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

Treatment Following Acute Myocardial Infarction
ALTACE is indicated following acute myocardial infarction in clinically stable patients with signs of left ventricular dysfunction to improve survival and reduce hospitalizations for heart failure. Sufficient experience in the treatment of patients with severe (NYHA class IV) heart failure immediately after myocardial infarction is not yet available. (See WARNINGS – Hypotension.)

MANAGEMENT OF PATIENTS AT INCREASED RISK OF CARDIOVASCULAR EVENTS: ALTACE may be used to reduce the risk of myocardial infarction, stroke or cardiovascular death in patients over 55 years of age who are at high risk of cardiovascular events because of a history of coronary artery disease, stroke, peripheral artery disease, or diabetes that is accompanied by at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, low high density lipoprotein levels, cigarette smoking, or documented microalbuminuria. The incidence of the primary outcome (composite of myocardial infarction, stroke and death from cardiovascular causes) was reduced from 17.8% in the placebo-treated group to 14.0% in the ramipril-treated group.

GENERAL: In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS). **When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy, and INFORMATION FOR THE PATIENT).**

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: *Angioedema:* Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered. *In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ALTACE (see ADVERSE REACTIONS – Treatment Following Acute Myocardial Infarction, DOSAGE AND ADMINISTRATION – Treatment Following Acute Myocardial Infarction).*

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease. Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: *As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of ALTACE should include appropriate assessment of renal function. ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.*

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Concomitant Diuretic Therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reducing initial dose. Agents increasing serum potassium: Use potassium sparing diuretics with caution and monitor frequently. Agents causing renin release: ALTACE antihypertensive effect increased. Lithium: Lithium levels may be increased. Administer lithium with caution and monitor levels frequently. Antacids: The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. Digoxin: No change in ramipril, ramiprilat or digoxin serum levels. Warfarin: The co-administration of ALTACE with warfarin did not alter the anticoagulant effects. Acenocoumarol: No significant changes. Non-steroidal anti-inflammatory agents (NSAID): The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (*e.g. indomethacin*).

ADVERSE REACTIONS: *Essential Hypertension.* Serious adverse events occurring in North American placebo-controlled clinical trials with ramipril monotherapy in hypertension (*n*=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ramipril patients (*n*=1,244), angioedema occurred in patients treated with ramipril and a diuretic (0.1%). The most frequent adverse events occurring in these trials with ALTACE monotherapy in hypertensive patients (*n*=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%). In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (*n*=972) have required discontinuation because of cough.

Treatment Following Acute Myocardial Infarction
Adverse events (except laboratory abnormalities) in a controlled clinical trial of post-AMI patients with clinical signs of heart failure considered possibly/probably related to ALTACE and occurring in more than 1% of stabilized patients (n=1,004) were: hypotension (10.7%); increased cough (7.6%); dizziness/vertigo (5.6%); nausea/vomiting (3.8%); angina pectoris (2.9%); postural hypotension (2.2%); syncope (2.1%); heart failure (2.0); severe/resistant heart failure (2.0%); myocardial infarction (1.7%); vomiting (1.6%); headache (1.2%); abnormal kidney function (1.2%); abnormal chest pain (1.1%); diarrhea (1.1%). Isolated cases of death have been reported with the use of ramipril that appear to be related to hypotension (including first dose effects), but many of these are difficult to differentiate from progression of underlying disease (see WARNINGS – Hypotension). Discontinuation of therapy due to adverse reactions was required in 368/1,004 post-AMI patients taking ramipril (36.7%), compared to 401/982 patients receiving placebo (40.8%).

Clinical Laboratory Test Findings: increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

DOSAGE AND ADMINISTRATION

Essential Hypertension: Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg of ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/1.73 m^2 (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg of ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73 m^2) the maximum total daily dose of 2.5 mg of ALTACE should not be exceeded.

Treatment Following Acute Myocardial Infarction:
Initiation of therapy requires consideration of concomitant medication and baseline blood pressure and should be instituted under close medical supervision, usually in a hospital, three to ten days following an acute myocardial infarction in haemodynamically stable patients with clinical signs of heart failure. The recommended initial dosage of ALTACE is 2.5 mg given twice a day (b.i.d.), one in the morning and one in the evening. If tolerated, and depending on the patient's response, dosage may be increased by doubling at intervals of one to three days. The maximum daily dose of ALTACE should not exceed 5 mg twice daily (b.i.d). After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If a patient becomes hypotensive at this dosage, it is recommended that the dosage be lowered to 1.25 mg b.i.d. following effective management of the hypotension. (see WARNINGS – Hypotension).

Patients who have been fluid or salt depleted, or treated with diuretics are at an increased risk of hypotension (see WARNINGS – Hypotension). An excessive fall in blood pressure may occur particularly in the following: after the initial dose of ALTACE; after every first increase of dose of ALTACE; after the first dose of a concomitant diuretic and/or when increasing the dose of the concomitant diuretic. If appropriate, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension (see PRECAUTIONS – Drug Interactions). Consideration should be given to reducing the initial dose to 1.25 mg of ALTACE in these patients.

Use in Renal Impairment: in patients with impaired renal function (creatinine clearance of 20-50 mL/min/1.73 m^2 body surface area), the initial recommended dosage is generally 1.25 mg of ALTACE once daily. This dosage may be increased with caution up to 1.25 mg of ALTACE twice daily, depending upon clinical response and tolerability.

Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and severe renal failure. (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Renal Impairment).

Use in Hepatic Impairment: Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and hepatic dysfunction. Dose reduction and careful monitoring of these patients is required (see ACTIONS AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Patients with Impaired Liver Function).

Management of Patients at Increased Risk of Cardiovascular Events: Recommended initial dose: 2.5 mg of ALTACE once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and – after another three weeks – to increase it to 10 mg. Usual maintenance dose: 10 mg of ALTACE daily (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS). Dosage recommendations for special risk groups such as patients with renal or hepatic impairment, or at an increased risk of hypotension (fluid or salt depletion, treated with diuretics) are to be followed as previously described (see WARNINGS and PRECAUTIONS).

DOSAGE FORM

a) Composition
ALTACE (ramipril) capsules 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg contain the medicinal ingredient ramipril in quantities of 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg respectively. The qualitative formulation for all potencies of ALTACE is: ramipril, pre-gelatinized starch NF (as filler, gliding agent and disintegration agent) and empty gelatin capsules. Empty gelatin capsules for all potencies of ALTACE are composed of gelatin NF and coloring agents specific to each potency (see below).

POTENCY	CAP	BODY
1.25 mg	Yellow iron oxide Titanium dioxide	Titanium dioxide
2.5 mg	Yellow iron oxide FD & C red no. 3 Titanium dioxide	Titanium dioxide
5.0 mg	FD & C blue no. 2 FD & C red no. 3 Titanium dioxide	Titanium dioxide
10.0 mg	FD & C blue no. 2 FD & C red no. 3 Black iron oxide Titanium dioxide	Titanium dioxide

b) Stability and storage recommendations
Store ALTACE (ramipril) in original container at room temperature, below 25°C and not beyond the date indicated on the container.

AVAILABILITY: No. 4 hard gelatin capsules:
- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5.0 mg (white/red);
- 10.0 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules. Bottles of 100 capsules and 500 capsules also available.

Product monograph available upon request.

References:
1. ALTACE Product Monograph. **2.** The Heart Outcomes Prevention Evaluation Study Investigators (HOPE) Trial. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342(3):145-53.

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See page A-15

BRIEF PRESCRIBING INFORMATION
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Reminyl®

galantamine hydrobromide tablets
4 mg, 8 mg, 12 mg galantamine base

Reminyl® ER

galantamine hydrobromide extended release capsules
8 mg, 16 mg, 24 mg galantamine base

Cholinesterase Inhibitor

INDICATIONS AND CLINICAL USE REMINYL (galantamine hydrobromide) and REMINYL ER are indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL and REMINYL ER have not been studied in controlled clinical trials for longer than 6 months. *REMINYL and REMINYL ER should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.* **Geriatrics (≥ 85 years of age):** There is limited safety information for REMINYL and REMINYL ER in this patient population (see **WARNINGS AND PRECAUTIONS**). **Pediatrics:** No data are available in children. Therefore, the use of REMINYL and REMINYL ER are not recommended in children under 18 years of age.

CONTRAINDICATIONS REMINYL and REMINYL ER are contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

WARNINGS AND PRECAUTIONS Carcinogenesis and Mutagenesis See ***Product Monograph Part II:*** **TOXICOLOGY- Carcinogenicity, Mutagenicity** for discussion on animal data. **Cardiovascular** Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL and REMINYL ER 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. In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, but was rarely severe and rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [5/273]). A 6-week cardiovascular safety clinical trial (GAL-USA-16; n= 139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular caution is warranted during titration where the majority of pauses occurred in the above study. **Metabolism** Cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored. **Gastrointestinal** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with galantamine, patients with symptomatic peptic ulceration were excluded. Clinical studies of galantamine have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS**). Galantamine, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see **ADVERSE REACTIONS**); with nausea and vomiting being more prevalent in women and patients with lower body weight and correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation. **Genitourinary** Although not observed in clinical trials of galantamine, cholinomimetics may cause bladder outflow obstruction. **Neurologic** Seizures: In placebo-controlled trials with galantamine, cases of seizure were reported, there was no increase in incidence compared with placebo. Although cholinomimetics are believed to have some potential to cause seizures, seizure activity may also be a manifestation of Alzheimer's disease. The risk/benefit of REMINYL and REMINYL ER treatment for patients with a history of seizure disorder must therefore be carefully evaluated. REMINYL and REMINYL ER have not been studied in patients with moderately severe or severe Alzheimer's disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of REMINYL and REMINYL ER in these patient populations are unknown. **Peri-Operative Considerations** Anesthesia: Galantamine, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. **Respiratory** Like other cholinomimetic drugs, REMINYL and REMINYL ER should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease. **Special Populations Hepatic Impairment:** There is limited information on the pharmacokinetics of galantamine in hepatically impaired patients. It is therefore recommended that dose escalation with REMINYL or REMINYL ER in Alzheimer's disease patients with hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see **DOSAGE AND ADMINISTRATION, Special Populations**). Since no data are available on the use of REMINYL or REMINYL ER in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL and REMINYL ER are not recommended for this population. **Renal Impairment:** There is limited information on the pharmacokinetics of galantamine in renally impaired patients. It is therefore recommended that dose escalation with REMINYL or REMINYL ER in Alzheimer's disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) be undertaken with caution and under conditions of close monitoring for adverse effects (see **DOSAGE AND ADMINISTRATION, Special Populations**). Since no data are available on the use of REMINYL or REMINYL ER in patients with a creatinine clearance of less than 9 mL/min, REMINYL and REMINYL ER are not recommended for this population. **Geriatrics (≥85 years of age):** In controlled clinical studies, the number of patients aged 85 years or over who received REMINYL at therapeutic doses of 16 or 24 mg/day was 123. Of these patients, 70 received the maximum recommended dose of 24 mg/day. There is limited safety information for REMINYL in this patient population. Since cholinomimetics as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of REMINYL and REMINYL ER in elderly patients with low body weight, especially in those ≥85 years o.d. Use in Elderly Patients with Serious Comorbid Disease There is limited information on the safety of galantamine treatment in patients with mild to moderate Alzheimer's disease and serious/significant comorbidity. The use of REMINYL and REMINYL ER 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. Dose escalation in this patient population should proceed with caution. **Patients with Mild Cognitive Impairment (MCI):** Mortality in Investigational Trials in MCI Two randomized, double-blind, placebo-controlled efficacy and safety studies of 2 years' duration were completed in non-demented subjects with MCI. Individuals with MCI demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's Disease. In these trials, REMINYL was not shown to be effective in patients with MCI. In the double-blind portion of these two trials, a total of 13 deaths in subjects on REMINYL (n= 1026) were recorded and 1 death in subjects on placebo (n= 1022); the reason for this difference is currently unknown. This difference in mortality has not been observed in REMINYL studies in Alzheimer's Disease. Approximately half of the REMINYL deaths appeared to have resulted from various vascular causes (myocardial infarction, stroke, and sudden death); other deaths appeared to have resulted from infection, suicide and cancer. There is no evidence of an increased risk of mortality when REMINYL is used in patients with mild to moderate Alzheimer's Disease. **Pregnant Women:** In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis. The safety of REMINYL and REMINYL ER in pregnant women has not been established. REMINYL and REMINYL ER should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus. **Nursing Women:** It is not known whether galantamine is excreted in human breast milk and therefore REMINYL and REMINYL ER should not be used in nursing mothers. **Pediatrics:** The safety and effectiveness of REMINYL and REMINYL ER in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS Clinical Trial Adverse Drug Reactions Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. A total of 2287 patients with mild to moderate Alzheimer's disease were treated with REMINYL in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days). Adverse Events Leading to Discontinuation Overall, 19% (441/2287) of patients treated with REMINYL discontinued from Phase III controlled clinical trials due to adverse events compared to 8% (68/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females. In the 4-week dose-escalation fixed dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events. Table 1.1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

Table 1.1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

	Recommended 4-week dose escalation		
Adverse Events	Placebo n=286 %	16 mg/day n=279 %	24 mg/day n=273 %
Nausea	<1	2	4
Vomiting	0	1	3
Anorexia	<1	1	<1
Dizziness	<1	2	1
Syncope	0	0	1

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used are shown in Table 1.2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose. Administration of REMINYL with food, the use of anti-emetic medication and ensuring adequate fluid intake may reduce the impact of these events.

Table 1.2: Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)

	Week 1-12			Week 13-21		
Adverse Events	Placebo n=286 %	16 mg/day n=279 %	24 mg/day n=273 %	Placebo n=259 %	16 mg/day n=243 %	24 mg/day n=241 %
Nausea	5	11	13	<1	4	6
Vomiting	<1	5	6	<1	2	6
Diarrhea	5	9	4	2	5	2
Anorexia	2	5	5	1	2	5

* Dose escalation occurred with 4 weeks per dose increment.

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%, 16 mg/day, 3%, 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%, 16 mg/day, 3%, 24 mg/day, 3%. Dose-escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs. Adverse Events Reported in Controlled Trials The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ. Table 1.3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 1.3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 1.3: Adverse events reported in at least 2% of patients with Alzheimer's disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)

Body System/ Adverse Events	Placebo (n=801) %	REMINYL* (n=1040) %
Body as a whole - general disorders		
Fatigue	3	5
Syncope	1	2
Central & peripheral nervous system disorders		
Dizziness	6	9
Headache	5	8
Tremor	2	3
Gastrointestinal system disorders		
Nausea	9	24
Vomiting	4	13
Diarrhea	7	9
Abdominal pain	4	5
Dyspepsia	2	5
Heart rate and rhythm disorders		
Bradycardia	1	2
Metabolic and nutritional disorders		
Weight decrease	2	7
Psychiatric disorders		
Anorexia	3	9
Depression	5	7
Insomnia	4	5
Somnolence	3	4
Red blood cell disorders		
Anemia	2	3
Respiratory system disorders		
Rhinitis	3	4
Urinary system disorders		
Urinary tract infection	7	8
Hematuria	2	3

* Adverse events in patients treated with 16 or 24 mg/day of REMINYL in three placebo-controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see **WARNINGS AND PRECAUTIONS**). Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL ER Adverse reactions in clinical trials of once-daily treatment with REMINYL ER extended release capsules were similar to those seen with REMINYL immediate release tablets (see Table 1.4).

Table 1.4: Adverse events reported in at least 2% of patients with Alzheimer's disease administered REMINYL or REMINYL ER and at a frequency greater than placebo

System Organ Class / Preferred Term	Placebo (n=320) %	REMINYL (n=326) %	REMINYL ER (n=319) %
Body as a whole – general disorders			
Injury	6	4	8
Edema peripheral	3	2	4
Fatigue	1	4	4
Syncope	1	1	2
Fever	1	2	1
Leg pain	1	2	<1
Central & peripheral nervous system disorders			
Dizziness	4	7	10
Headache	6	6	8
Tremor	0	1	2
Gastrointestinal system disorders			
Nausea	5	14	17
Vomiting	2	9	7
Abdominal pain	2	3	2
Dyspepsia	2	3	2
Heart rate and rhythm disorders			
Bradycardia	2	2	3
Metabolic and nutritional disorders			
Weight decrease	1	5	4
Hyperglycemia	1	2	2
Musculoskeletal system disorders			
Arthralgia	2	2	3
Skeletal pain	1	3	2
Arthritis	1	1	2
Myalgia	1	1	2
Psychiatric disorders			
Anorexia	3	7	6
Depression	3	5	6
Anxiety	3	1	4
Somnolence	2	2	3
Depression aggravated	1	2	2
Aggressive reaction	1	2	2
Nervousness	1	2	1
Respiratory system disorders			
Rhinitis	3	4	4
Pneumonia	1	2	2
Secondary terms			
Abrasion nos*	1	1	2
Skin and appendages disorders			
Rash	1	<1	3
Urinary system disorders			
Hematuria	1	1	2
Micturition frequency	1	2	1
Vision disorders			
Cataract	1	1	2

* not otherwise specified

Other Adverse Events Observed During Clinical Trials REMINYL has been administered to 3055 patients with Alzheimer's disease during clinical trials worldwide. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or routinely minor events. Events are classified by body system and listed using the following definitions: *frequent* adverse events - those occurring in at least 1/100 patients; *infrequent* adverse events - those occurring in 1/100 to 1/1000 patients; *rare* - those occurring in 1/1000 to 1/10000 patients; *very rare* - those occurring in fewer than 1/10000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. Body as a Whole - General Disorders: *Frequent:* chest pain, asthenia, fever, malaise. Cardiovascular System Disorders: *Frequent:* hypertension; *infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure, myocardial ischemia or infarction. Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia, leg cramps, tinnitus, transient ischemic attack or cerebrovascular accident. Gastrointestinal System Disorders: *Frequent:* flatulence; *infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophagea perforation Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial arrhythmias incuding atrial fibrillation and supraventricular tachycardia, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia; *Rare:* severe bradycardia. Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased, NPN increased. Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia. Psychiatric Disorders: *Infrequent:* apathy, paranoia, paranoid reaction, libido increased delirium; *Rare:* suicidal ideation, suicide attempt. Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi. **Post-Market Adverse Drug Reactions** Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with REMINYL include: Body as a Whole - General Disorders: dehydration (including rare, severe cases leading to renal insufficiency and renal failure). Central & Peripheral Nervous System Disorders: behavioural disturbances including agitation, aggression and hallucinations. Gastrointestinal: upper and lower GI bleeding. Metabolic & Nutritional Disorders: hypokalemia. Some of these adverse events may be attributable to cholinomimetic properties of REMINYL or in some cases may represent manifestations or exacerbations of the underlying disease processes common in the elderly population.

DRUG INTERACTIONS Overview Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. 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 the clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL and REMINYL ER with these drugs. **Drug-Drug Interactions** Effect of Other Drugs on the Metabolism of Galantamine Pharmacokinetic studies to assess the potential of galantamine for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done. *In vitro* CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant. *In vivo Cimetidine and Ranitidine* Galantamine was administered as a single dose of 4 mg or Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine. *Ketoconazole* Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b...d. for 8 days (n=8 males and 8 females). *Erythromycin:* Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females). *Paroxetine* Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who received galantamine together with 20 mg/day paroxetine. Effect of Galantamine on the Metabolism of Other Drugs *In vitro* Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. *In vivo Warfarin:* Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine. *Digoxin:* Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females). Nicotinic Receptor Modulation Single *in vitro* applications of galantamine dose-dependently modulate the effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted. It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors. **Drug-Food Interactions** Interactions with food have not been established. **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 REMINYL (galantamine hydrobromide) and REMINYL ER are not indicated for use in patients with mild cognitive impairment (see WARNINGS AND PRECAUTIONS, Special Populations, Patients with Mild Cognitive Impairment (MCI): Mortality in Investigational Trials in MCI). *REMINYL and REMINYL ER should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.* REMINYL tablets should be administered twice a day, preferably with morning and evening meals. REMINYL ER extended release capsules should be administered once daily in the morning, preferably with food. Patients and caregivers should be advised to ensure adequate fluid intake during treatment. **Dosing Considerations** • Concomitant Treatment: in patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered. • Special Populations: Dosage adjustments may be required for elderly patients (>65 years old) with low body weight (especially females), and patients with hepatic and/or renal impairment. • Missed Dose: The missed dose should be taken at the next scheduled dose. Doses should not be doubled. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose. **Recommended Dose and Dosage Adjustment** The dosage of REMINYL, shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients. The recommended starting dose is 8 mg/day. The dose should be increased to the initial maintenance dose of 16 mg/day after 4 weeks. If this initial maintenance dose is well tolerated, a further increase to 24 mg/day may be considered only after a minimum of 4 weeks at 16 mg/day. The abrupt withdrawal of REMINYL or REMINYL ER in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL and REMINYL ER are lost, however, when the drug is discontinued. Special Populations Dose escalation for elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution. Hepatic Impairment Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), based on pharmacokinetic modeling, dosing with REMINYL tablets should begin with 4 mg once daily in the morning, preferably with food, for at least 1 week. Then the dosage should be increased to 4 mg twice a day for at least 4 weeks. For REMINYL ER extended release capsules, based on pharmacokinetic modeling, dosing should begin with 8 mg every other day in the morning, preferably with food, for at least 1 week. Then the dosage should be increased to 8 mg once daily for at least 4 weeks. In these patients, daily doses should not exceed a total of 16 mg/day. Since no data are available on the use of REMINYL or REMINYL ER in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL and REMINYL ER are not recommended for this population (see **WARNINGS AND PRECAUTIONS**). Renal Impairment For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. Since no data are available on the use of REMINYL or REMINYL ER in patients with a creatinine clearance less than 9 mL/min, REMINYL and REMINYL ER are not recommended for this population (see **WARNINGS AND PRECAUTIONS**). In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

OVERDOSAGE Symptoms Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the forth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day, inadvertently ingested 160 mg and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours. **Treatment** Galantamine has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL or REMINYL ER should be administered and the patient should be monitored. As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for galantamine overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether galantamine and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals include hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

DOSAGE FORMS REMINYL (galantamine hydrobromide, expressed as galantamine base) is available as film-coated tablets in the following strengths: 4 mg galantamine as off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "64" on the other side; 8 mg galantamine as pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "68" on the other side; 12 mg galantamine as orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "612" on the other side. REMINYL ER (galantamine hydrobromide) extended release capsules contain white to off-white pellets. The following strengths are available: 8 mg galantamine as white opaque capsules imprinted with "8"; 16 mg galantamine as pink opaque capsules imprinted with "16"; 24 mg galantamine as caramel opaque capsules imprinted with "624".

Product Monograph available upon request.

JANSSEN-ORTHO

Janssen Orthe Inc. Toronto Ontario M3C 1L9
Last revised April 2005

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See OBC

***LIPITOR* (atorvastatin calcium) 10 mg, 20 mg, 40 mg and 80 mg tablets**

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

Please refer to the Product Monograph for complete ACTIONS AND CLINICAL PHARMACOLOGY information.

INDICATIONS AND CLINICAL USE

Hypercholesterolemia

LIPITOR (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet (at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet), for the reduction of elevated total cholesterol (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

Primary hypercholesterolemia (Type IIa); Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern; Dysbetalipoproteinemia (Type III); Hypertriglyceridemia (Type IV); Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available; an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are still present:

a. LDL-C remains ≥4.9 mmol/L (190 mg/dL) or
b. LDL-C remains ≥4.1 mmol/L (160 mg/dL) and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the pediatric patient

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb dyslipidemia). In pooled data from 24 controlled clinical trials, LIPITOR raised HDL-C levels 5%-7% in primary hypercholesterolemic (Type IIa) patients and 10%-15% in mixed (Type IIb) dyslipidemic patients.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), *LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased* high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25-56%) and LDL-C levels (23-40%). LIPITOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels >11 mmol/L), i.e., Types I and V.

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open-label study in patients with homozygous familial hypercholesterolemia (FH), LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = total-C - [(0.37 x (TG) + HDL-C)]
LDL-C (mg/dL) = total-C - [(0.2 x (TG) + HDL-C)]

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e., >2.2 mmol/L (200 mg/dL) or >5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with LIPITOR.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis *(see* **WARNINGS – Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia [elevated triglycerides, small dense LDL particles and low HDL-cholesterol], insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).

(For the treatment of specific dyslipidemias, refer to the Report of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias or to the *US NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults* [Adult Treatment Panel III], under **REFERENCES**).

When drugs are prescribed, attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibres) should always be maintained and reinforced.

Prevention of Cardiovascular Disease

LIPITOR is indicated to reduce the risk of myocardial infarction in adult hypertensive patients without clinically evident coronary heart disease, but with at least 3 additional risk factors for coronary heart disease such as: age ≥55 years, male sex, smoking, type 2 diabetes, left ventricular hypertrophy, other specified abnormalities on ECG, microalbuminuria or proteinuria, ratio of plasma total cholesterol to HDL-C ≥6 or premature family history of coronary heart disease.

LIPITOR is also indicated to reduce the risk of myocardial infarction and stroke in adult patients with type 2 diabetes mellitus and hypertension without clinically evident coronary heart disease, but with other risk factors such as age ≥55 years, retinopathy, albuminuria or smoking.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see **WARNINGS**).

Pregnancy and nursing women: Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see **PRECAUTIONS – Use in Pregnancy, Use in Nursing Mothers**).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme (see **WARNINGS – Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions, Cytochrome P-450-mediated Interactions**).

Muscle Effects

Effects on skeletal muscle such as myalgia, myopathy and very rarely, rhabdomyolysis have been reported in patients treated with LIPITOR. **Very rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported with LIPITOR and other HMG-CoA reductase inhibitors.**

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to >10 times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. LIPITOR therapy should be discontinued if markedly elevated CK levels are measured or myopathy is diagnosed or suspected.

Predisposing Factors for Myopathy/Rhabdomyolysis: LIPITOR, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis. Such factors include:

Personal or family history of hereditary muscular disorders; Previous history of muscle toxicity with another HMG-CoA reductase inhibitor; Concomitant use of a fibrate or niacin; Hypothyroidism; Alcohol abuse; Excessive physical exercise; Age >70 years; Renal impairment; Hepatic impairment; Diabetes with hepatic fatty change; Surgery and trauma; Frailty; Situations where an increase in plasma levels of active ingredient may occur.

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of *myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as sepsis,* severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders and uncontrolled seizures).

LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As *there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic* studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see **PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**).

Hepatic Effects

In clinical trials, persistent increases in serum transaminases >3 times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to >3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR, as well as other HMG-CoA reductase inhibitors, should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the *drug should be discontinued.*

PRECAUTIONS

General

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see **INDICATIONS AND CLINICAL USE**). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure.

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy.

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see **CONTRAINDICATIONS**).

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Use in Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see **CONTRAINDICATIONS**).

Pediatric Use

Safety and effectiveness of LIPITOR in patients 10-17 years of age (N=140) with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had a safety and tolerability profile generally similar to that of placebo. Doses >20 mg have not been *studied in this patient population.*

LIPITOR had no effect on growth or sexual maturation in boys and in girls. The effects on menstrual cycle were not assessed [see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** for **Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)**].

Adolescent females should be counselled on appropriate contraceptive methods while on LIPITOR therapy (see **CONTRAINDICATIONS; PRECAUTIONS – Use in Pregnancy**). LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.

Doses of LIPITOR up to 80 mg/day for 1 year have been evaluated in 8 pediatric patients with homozygous familial hypercholesterolemia.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially.

Elderly patients may be more susceptible to myopathy (see **WARNINGS – Muscle Effects – Predisposing Factors for Myopathy/Rhabdomyolysis**).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see **WARNINGS – Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**). Refer also to **DOSAGE AND ADMINISTRATION**.

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Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see **PRECAUTIONS – Geriatric Use, Renal Insufficiency; Patients with Severe Hypercholesterolemia**).

Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid-lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see **WARNINGS – Muscle Effects**). Therefore, combined drug therapy should be approached with caution.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone. However, the combination drug therapy was less effective in lowering triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients.

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (nicotinic acid): Although there is limited experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with drugs in this class, including atorvastatin, is increased with concurrent administration (see **WARNINGS – Muscle Effects**).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily. Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state.

(quinapril): In a randomized, open-label study in healthy subjects, steady-state quinapril dosing (80 mg QD) did not significantly affect the pharmacokinetic profile of atorvastatin tablets (10 mg QD).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive containing 1 mg norethindrone and 35 µg ethinyl estradiol increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or the LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e., erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e., itraconazole, ketoconazole), protease inhibitors, or the antidepressant nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR. Caution should thus be exercised with concomitant use of these agents (see **WARNINGS – Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS – Renal Insufficiency, Endocrine Function; DOSAGE AND ADMINISTRATION**).

Terfenadine: In healthy subjects, coadministration of maximum doses of atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g., pre-existing prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see **WARNINGS – Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION**).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme (cytochrome P-450) system. LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin by approximately 40% and 80%, respectively (see **WARNINGS – Muscle Effects**).

Protease Inhibitors (nelfinavir mesylate): In healthy adults, coadministration of nelfinavir mesylate (1250 mg BID), a known CYP 3A4 inhibitor, and atorvastatin (10 mg QD) resulted in increased plasma concentrations of atorvastatin. AUC and C_{max} of atorvastatin were increased by 74% and 122% respectively.

Patients with Severe Hypercholesterolemia

Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors** (see **WARNINGS – Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions; DOSAGE AND ADMINISTRATION**).

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and creatine kinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related include constipation, diarrhea, dyspepsia, flatulence, nausea, headache, pain, myalgia and asthenia.

The following additional adverse events were reported in clinical trials (not all have been associated with a causal relationship to LIPITOR therapy): muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia and hypoglycemia.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=187, where 140 patients received LIPITOR), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was similar to that of placebo. The adverse events reported in ≥1% of patients were abdominal pain, depression and headache (see **PRECAUTIONS – Pediatric Use**).

Laboratory Changes and Adverse Events

The criteria for clinically significant laboratory changes were >3 X the upper limit of normal (ULN) for liver enzymes, and >5 X ULN for creatine kinase. A total of 8 unique subjects met one or more of these criteria during the double-blind phase. Hence, the incidence of patients who experienced abnormally high enzymatic levels (AST/ALT and creatine kinase) was >4% (8/187).

Five atorvastatin and one placebo subjects had increases in CK >5 X ULN during the double-blind phase; two of the five atorvastatin-treated subjects had increases in CK >10 X ULN. Two subjects had clinically significant increases in ALT.

Post-Market Adverse Drug Reaction: The following adverse events have also been reported during post-marketing experience with LIPITOR, regardless of causality assessment: Very rare reports: severe myopathy with or without rhabdomyolysis (see **WARNINGS – Muscle Effects; PRECAUTIONS – Renal Insufficiency, Pharmacokinetic Interaction Studies and Potential Drug Interactions**). Isolated reports: Gynecomastia, thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) and fatigue. These may have no causal relationship to atorvastatin.

Abnormal Hematologic and Clinical Chemistry Findings

Ophthalmologic observations: see **PRECAUTIONS**.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with LIPITOR, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

The recommended starting dose of LIPITOR is 10 or 20 mg once daily, depending on the patient's LDL-C reduction required (see Tables 1 and 2). Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of 2 to 4 weeks. The maximum dose is 80 mg/day.

TABLE 1. Dose-Response in Patients With Mild-to-Moderate Hypercholesterolemia (Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

[a] Results are pooled from 2 dose-response studies
[b] Mean baseline values

The dosage of LIPITOR should be individualized according to the baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the recommended target lipid values at the lowest dose needed to achieve the LDL-C target (see Recommendations for the Management of Dyslipidemia and the Prevention of Cardiovascular Disease [Canada], summarized below in Table 2, and/or the Third Report of the US National Cholesterol Education Program [NCEP Adult Treatment Panel III]), and the patient's response. Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

TABLE 2. Canadian Recommendations for the Target Lipid Values Based on Level of Risk

Risk Category	Target Levels		
	LDL-C level (mmol/L)		Total-C/HDL-C ratio
High[†] (10-year risk of CAD ≥20%, or a history of diabetes mellitus[††] or any atherosclerotic disease)	<2.5	**and**	<4.0
Moderate (10-year risk 11%-19%)	<3.5	**and**	<5.0
Low[†††] (10-year risk ≤10%)	<4.5	**and**	<6.0

Note: LDL-C = low-density lipoprotein cholesterol.

[†] Apolipoprotein B can be used as an alternative measurement, particularly for follow-up of patients treated with statins. An optimal level of apolipoprotein B in a patient at high risk is <0.9 g/L, in a patient at moderate risk <1.05 g/L and in a patient at low risk <1.2 g/L.
[††] Includes patients with chronic kidney disease and those undergoing long-term dialysis.
[†††] In the 'very low' risk stratum, treatment may be deferred if the 10-year estimate of cardiovascular disease is <5% and the LDL-C level is <5.0 mmol/L.

Severe Dyslipidemias

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see **WARNINGS – Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS – Pharmacokinetic Interaction Studies and Potential Drug Interactions**).

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

In this population, the recommended starting dose of LIPITOR is 10 mg/day; the maximum recommended dose is 20 mg/day (doses >20 mg/day have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines; **INDICATIONS AND CLINICAL USE**). Adjustments should be made at intervals of 4 weeks or more.

NCEP (National Cholesterol Education Program) Pediatric Panel Guidelines: Classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mmol/L [mg/dL])	LDL-C (mmol/L [mg/dL])
Acceptable	<4.4 [170]	<2.8 [110]
Borderline	4.4-5.1 [170-199]	2.8-3.3 [110-129]
High	≥5.2 [200]	≥3.4 [130]

Concomitant Therapy

See **PRECAUTIONS – Drug/Laboratory Test Interactions**.

Dosage in Patients With Renal Insufficiency

See **PRECAUTIONS**.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

1. Friedewald WT, *et al. Clin Chem* 1972;18(6):489-502.

For a copy of the Product Monograph or full Prescribing Information, please contact:

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See page A-11

Brief Prescribing Information

BETASERON®

Interferon beta-1b

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

Description: BETASERON® (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon $beta_{ser17}$. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta, and gamma. Interferon beta-1b, interferon alpha, and interferon gamma have overlapping yet distinct biologic activities. The activities of interferon beta are species-restricted and, therefore, the most pertinent pharmacological information on BETASERON (interferon beta-1b) is derived from studies of human cells in culture and *in vivo*.

Biologic Activities: Interferon beta-1b has been shown to possess both antiviral and immunomodulatory activities. The mechanisms by which BETASERON exerts its actions in multiple sclerosis (MS) are not clearly understood. However, it is known that the biologic response-modifying properties of interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of interferon beta-1b to these receptors induces the expression of a number of interferon-induced gene products (e.g., 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of interferon beta-1b. A number of these interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1b.

INDICATIONS AND CLINICAL USE

BETASERON (interferon beta-1b) is indicated for:

- the reduction of the frequency of clinical exacerbations in ambulatory patients with relapsing-remitting multiple sclerosis. Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery.
- the slowing of progression in disability and the reduction of the frequency of clinical exacerbations in patients with secondary-progressive multiple sclerosis.

The safety and efficacy of BETASERON in primary progressive MS have not been evaluated.

CONTRAINDICATIONS

BETASERON (interferon beta-1b) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin Human USP, or any other component of the formulation.

WARNINGS

The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.

In the RR-MS clinical trial, one suicide and four attempted suicides were observed among 372 study patients during a 3-year period. All five patients received BETASERON (interferon beta-1b) (three in the 0.05 mg [1.6 MIU] group and two in the 0.25 mg [8.0 MIU] group). There were no attempted suicides in patients on study who did not receive BETASERON. In the SP-MS study there were 5 suicide attempts in the placebo group and 3 in the BETASERON group including one patient in each group who committed suicide. Depression and suicide have been reported to occur in patients receiving interferon alpha, a related compound. Patients treated with BETASERON should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

PRECAUTIONS

General: Rare cases of cardiomyopathy have been reported. If this occurs, and a relationship to BETASERON (interferon beta-1b) is suspected, treatment should be discontinued.

Rare cases of thyroid dysfunction (hyper- as well as hypothyroidism) associated with the use of BETASERON have been reported.

Symptoms of flu syndrome observed with BETASERON therapy may prove stressful to patients with severe cardiac conditions. Patients with cardiac disease such as angina, congestive heart failure or arrhythmia should be monitored closely for worsening of their clinical conditions.

Information to be Provided to the Patient: Patients should be instructed in injection techniques to assure the safe self-administration of BETASERON. (See below and the **BETASERON® INFORMATION FOR THE PATIENT** section.)

Instruction on Self-Injection Technique and Procedures: It is recommended that the first injection be administered by, or under the direct supervision of, a physician. Appropriate instructions for reconstitution of BETASERON and self-injection, using aseptic techniques, should be given to the patient. A careful review of the **BETASERON® INFORMATION FOR THE PATIENT** section is also recommended.

Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. Information on how to acquire a puncture-resistant container for disposal of used needles and syringes should be given to the patient along with instructions for safe disposal of full containers.

Overall, 80% of patients in the two controlled clinical trials reported injection site reactions at one or more times during therapy. Post-marketing experience has been consistent with this finding, with infrequent reports of injection site necrosis.

The onset of injection site necrosis usually appears early in therapy with most cases reported to have occurred in the first two to three months of therapy. The number of sites where necrosis has been observed was variable.

Rarely, the area of necrosis has extended to subcutaneous fat or fascia. Response to treatment of injection site necrosis with antibiotics and/or steroids has been variable. In some of these patients elective debridement and, less frequently, skin grafting took place to facilitate healing which could take from three to six months.

Some patients experienced healing of necrotic skin lesions while BETASERON therapy continued. In other cases new necrotic lesions developed even after therapy was discontinued.

The nature and severity of all reported reactions should be carefully assessed. Patient understanding and use of aseptic self-injection technique and procedures should be periodically reevaluated.

Flu-like symptoms are not uncommon following initiation of therapy with BETASERON. In the controlled MS clinical trials, acetaminophen was permitted for relief of fever or myalgia.

Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

Awareness of Adverse Reactions: Patients should be advised about the common adverse events associated with the use of BETASERON,particularly, injection site reactions and the flu-like symptom complex (see **ADVERSE REACTIONS).**

Patients should be cautioned to report depression or suicidal ideation (see **WARNINGS**).

Patients should be advised about the abortifacient potential of BETASERON (see **PRECAUTIONS, Use in Pregnancy**).

Laboratory Tests: The following laboratory tests are recommended prior to initiating BETASERON therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating BETASERON therapy. In the controlled MS trials, patients were monitored every 3 months. The study protocol stipulated that BETASERON therapy be discontinued in the event the absolute neutrophil count fell below 750/mm^3. When the absolute neutrophil count had returned to a value greater than 750/mm^3, therapy could be restarted at a 50% reduced dose. No patients were withdrawn or dose-reduced for neutropenia or lymphopenia.

Similarly, if AST/ALT (SGOT/SGPT) levels exceeded 10 times the upper limit of normal, or if the serum bilirubin exceeded 5 times the upper limit of normal, therapy was discontinued. In each instance during the controlled MS trial, hepatic enzyme abnormalities returned to normal following discontinuation of therapy. When measurements had decreased to below these levels, therapy could be restarted at a 50% dose reduction, if clinically appropriate. Dose was reduced in two patients due to increased liver enzymes; one continued on treatment and one was ultimately withdrawn.

Drug Interactions: Interactions between BETASERON and other drugs have not been evaluated. Although studies designed to examine drug interactions have not been done, it was noted that BETASERON patients (n=180) have received corticosteroid or ACTH treatment of relapses for periods of up to 28 days.

BETASERON administered in three cancer patients over a dose range of 0.025 mg (0.8 MIU) to 2.2 mg (71 MIU) led to a dose-dependent inhibition of antipyrine elimination. The effect of alternate-day administration of 0.25 mg (8 MIU) BETASERON on drug metabolism in MS patients is unknown.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when BETASERON is administered in combination with agents that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance.

Impairment of Fertility: Studies in female rhesus monkeys with normal menstrual cycles, at doses up to 0.33 mg (10.7 MIU)/kg/day (equivalent to 32 times the recommended human dose based on body surface area comparison) showed no apparent adverse effects on the menstrual cycle or on associated hormonal profiles (progesterone and estradiol) when administered over 3 consecutive menstrual cycles. The extrapolability of animal doses to human doses is not known. Effects of BETASERON on women with normal menstrual cycles are not known.

Use in Pregnancy: BETASERON was not teratogenic at doses up to 0.42 mg (13.3 MIU)/kg/day in rhesus monkeys, but demonstrated dose-related abortifacient activity when administered at doses ranging from 0.028 mg (0.89 MIU)/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 MIU)/kg/day (40 times the recommended human dose based on body surface area comparison). The extrapolability of animal doses to human doses is not known. Lower doses were not studied in monkeys.Spontaneous abortions while on treatment were reported in 4 patients who participated in the BETASERON RR-MS clinical trial, whereas there was one induced abortion in each of the placebo and BETASERON groups in the SP-MS trial. BETASERON given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if teratogenic effects exist in humans. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should take reliable contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking BETASERON, the patient should discontinue therapy. It is not known if interferons alter the efficacy of oral contraceptives.

Nursing Mothers: It is not known whether BETASERON is excreted in human milk. Given that many drugs are excreted in human milk, there is a potential for serious adverse reactions in nursing infants, therefore a decision should be made whether to discontinue nursing or discontinue BETASERON treatment.

Pediatric Use: Safety and efficacy in children under 18 years of age have not been established.

Dependence Liability: No evidence or experience suggests that abuse or dependence occurs with BETASERON therapy; however, the risk of dependence has not been systematically evaluated.

ADVERSE REACTIONS

The following adverse events were observed in placebo-controlled clinical studies of BETASERON (interferon beta-1b), at the recommended dose of 0.25 mg (8 MIU), in patients with relapsing-remitting MS (n=124) and secondary-progressive MS (n=360):

1. Relapsing-remitting MS: Injection site reactions (85%) and injection site necrosis (5%) occurred after administration of BETASERON. Inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated ($p<0.05$) with the 0.25 mg (8 MIU) BETASERON-treated group,compared to placebo. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7days per year. Three patients withdrew from the 0.25 mg (8 MIU) BETASERON-treated group for injection site pain.

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 MIU) BETASERON. A patient was defined as having a flu-like symptom complex if flu-like syndrome or at least two of the following symptoms were concurrently reported: fever, chills, myalgia, malaise or sweating. Only myalgia, fever, and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 60% of patients experiencing the event during the first 3 months of treatment compared to 10% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3.5 days and the median duration per patient was 7.5 days per year.

Laboratory abnormalities included:

- lymphocyte count < 1500/mm^3 (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm^3 (18%) (no patients had absolute neutrophil counts < 500/mm^3),
- WBC < 3000/mm^3 (16%), and
- total bilirubin > 2.5 times baseline value (6%).

Three patients were withdrawn from treatment with 0.25 mg (8 MIU) BETASERON for abnormal liver enzymes including one following dose reduction (see **PRECAUTIONS, Laboratory Tests).**

Twenty-one (28%) of the 76 females of childbearing age treated at 0.25 mg (8 MIU) BETASERON and 10 (13%) of the 76 females of childbearing age treated with placebo reported menstrual disorders. All reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

Mental disorders such as depression, anxiety, emotional lability, depersonalization, suicide attempts and confusion were observed in this study. Two patients withdrew for confusion. One suicide and four attempted suicides were also reported. It is not known whether these symptoms may be related to the underlying neurological basis of MS, to BETASERON treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be monitored closely and cessation of therapy should be considered.

Additional common clinical and laboratory adverse events associated with the use of BETASERON are listed in the following paragraphs. These events occurred at an incidence of 5% or more in the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to 3 years in the controlled trial, and at an incidence that was at least twice that observed in the 123 placebo patients. Common adverse clinical and laboratory events associated with the use of BETASERON were:

- injection site reaction (85%),
- lymphocyte count < 1500/mm^3 (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm^3 (18%),
- menstrual disorder (17%),
- WBC < 3000/mm^3 (16%),
- palpitation (8%),
- dyspnea (8%),
- cystitis (8%),
- hypertension (7%),
- breast pain (7%),
- tachycardia (6%),
- gastrointestinal disorders (6%),
- total bilirubin > 2.5 times baseline value (6%),
- somnolence (6%),
- laryngitis (6%),
- pelvic pain (6%),
- menorrhagia (6%),
- injection site necrosis (5%), and
- peripheral vascular disorders (5%).

A total of 277 MS patients have been treated with BETASERON in doses ranging from 0.025 mg (0.8 MIU) to 0.5 mg (16 MIU). During the first 3 years of treatment, withdrawals due to clinical adverse events or laboratory abnormalities not mentioned above included:

- fatigue (2%, 6 patients),
- cardiac arrhythmia (< 1%, 1 patient),
- allergic urticarial skin reaction to injections (< 1%, 1 patient),
- headache (< 1%, 1 patient),
- unspecified adverse events (< 1%, 1 patient), and
- "felt sick" (< 1%, 1 patient).

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to 3 years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been re-classified using the standard COSTART glossary to reduce the total number of terms employed in Table 1. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

Table 1: Adverse Events and Laboratory Abnormalities

Adverse Event	Placebo n=123	0.25 mg (8 MIU) n=124
Body as a Whole		
Injection site reaction*	37%	85%
Headache	77%	84%
Fever*	41%	59%
Flu-like symptom complex*	56%	76%
Pain	48%	52%
Asthenia*	35%	49%
Chills*	19%	46%
Abdominal pain	24%	32%
Malaise*	3%	15%
Generalized edema	6%	8%
Pelvic pain	3%	6%
Injection site necrosis*	0%	5%
Cyst	2%	4%
Necrosis	0%	2%
Suicide attempt	0%	2%
Cardiovascular System		
Migraine	7%	12%
Palpitation*	2%	8%
Hypertension	2%	7%
Tachycardia	3%	6%
Peripheral vascular disorder	2%	5%
Hemorrhage	1%	3%
Digestive System		
Diarrhea	29%	35%
Constipation	18%	24%
Vomiting	19%	21%
Gastrointestinal disorder	3%	6%
Endocrine System		
Goiter	0%	2%
Hemic and Lymphatic System		
Lymphocytes < 1500/mm^3	67%	82%
ANC < 1500/mm^3*	6%	18%
WBC < 3000/mm^3*	5%	16%
Lymphadenopathy	11%	14%
Metabolic and Nutritional Disorders		
ALT (SGPT) > 5 times baseline*	6%	19%
Glucose < 55 mg/dL	13%	15%
Total bilirubin > 2.5 times baseline	2%	6%
Urine protein > 1+	3%	5%
AST (SGOT) > 5 times baseline*	0%	4%
Weight gain	0%	4%
Weight loss	2%	4%
Musculoskeletal System		
Myalgia*	28%	44%
Myasthenia	10%	13%

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Nervous System		
Dizziness	28%	35%
Hypertonia	24%	26%
Depression	24%	25%
Anxiety	13%	15%
Nervousness	5%	8%
Somnolence	3%	6%
Confusion	2%	4%
Speech disorder	1%	3%
Convulsion	0%	2%
Hyperkinesia	0%	2%
Amnesia	0%	2%
Respiratory System		
Sinusitis	26%	36%
Dyspnea*	2%	8%
Laryngitis	2%	6%
Skin and Appendages		
Sweating*	11%	23%
Alopecia	2%	4%
Special Senses		
Conjunctivitis	10%	12%
Abnormal vision	4%	7%
Urogenital System		
Dysmenorrhea	11%	18%
Menstrual disorder*	8%	17%
Metrorrhagia	8%	15%
Cystitis	4%	8%
Breast pain	3%	7%
Menorrhagia	3%	6%
Urinary urgency	2%	4%
Fibrocystic breast	1%	3%
Breast neoplasm	0%	2%
Cardiovascular System		
Vasodilatation	4%	6%
Peripheral vascular disorder	5%	5%
Chest pain	4%	5%
Migraine	3%	4%
Hypotension	4%	2%
Hypertension*	2%	4%
Palpitation	3%	2%
Syncope	3%	2%
Hemorrhage	2%	2%
Tachycardia	1%	2%
Digestive System		
Nausea	13%	13%
Constipation	12%	12%
Diarrhea	10%	7%
Gastroenteritis	5%	6%
Vomiting	6%	4%
Dysphagia	5%	4%
Gastrointestinal disorder	5%	4%
Tooth disorder	4%	4%
Dyspepsia	4%	4%
Anorexia	2%	4%
Fecal incontinence	3%	2%
Liver function test abnormal	1%	3%
Gastritis	2%	2%
Flatulence	1%	3%
Sore throat	1%	2%
Colitis	2%	0%
Gastrointestinal pain	0%	2%
Gingivitis	0%	2%
Hemic and Lymphatic System		
Leukopenia*	5%	10%
Anemia	5%	2%
Ecchymosis	2%	1%
Lymphadenopathy	1%	3%
Injection Site		
Injection site reaction*	10%	46%
Injection site inflammation*	4%	48%
Injection site pain	5%	9%
Injection site necrosis*	0%	5%
Injection site hemorrhage	2%	2%
Metabolic and Nutritional Disorders		
Peripheral edema	7%	7%
Weight loss	3%	2%
SGPT increased	2%	2%
Hypercholesteremia	2%	1%
Musculoskeletal System		
Myasthenia	40%	39%
Arthralgia	20%	20%
Myalgia*	9%	23%
Bone fracture (not spontaneous)	5%	3%
Muscle cramps	3%	3%
Spontaneous bone fracture	3%	3%
Arthritis	1%	2%
Joint disorder	1%	2%
Nervous System		
Headache	41%	47%
Neuropathy	41%	38%
Paresthesia	39%	35%
Hypertonia*	31%	41%
Abnormal gait	34%	34%
Depression	31%	27%
Ataxia	23%	19%
Dizziness	14%	14%
Incoordination	13%	11%
Insomnia	8%	12%
Vertigo	12%	8%
Emotional lability	11%	8%
Paralysis	10%	8%
Somnolence	8%	8%
Tremor	9%	6%
Sweating increased	6%	6%
Neuralgia	7%	5%
Movement disorder	6%	5%
Sleep disorder	5%	6%
Anxiety	5%	6%
Hypesthesia	4%	6%
Nervousness	3%	4%
Speech disorder	5%	2%
Dysarthria	4%	2%
Spastic paralysis	1%	3%
Convulsion	2%	2%
Hyperesthesia	2%	2%
Amnesia	3%	1%
Dry mouth	2%	1%
Hemiplegia	2%	1%
Thinking abnormal	2%	1%
Myoclonus	2%	0%
Respiratory System		
Rhinitis	32%	28%
Pharyngitis	20%	16%
Bronchitis	12%	9%
Cough increased	10%	5%
Sinusitis	6%	6%
Pneumonia	5%	5%
Dyspnea	2%	3%
Upper respiratory tract infection	2%	3%
Asthma	2%	1%
Voice alteration	2%	1%
Skin and Appendages		
Rash*	12%	20%
Pruritus	6%	6%
Skin disorder	4%	4%
Eczema	4%	2%
Herpes simplex	2%	3%
Alopecia	2%	2%
Acne	2%	2%
Dry skin	3%	1%
Subcutaneous hematoma	3%	1%
Breast pain	2%	1%
Herpes zoster	2%	1%
Seborrhea	2%	1%
Special Senses		
Abnormal vision	15%	11%
Amblyopia	10%	7%
Diplopia	9%	7%
Eye pain	5%	4%
Otitis media	3%	2%
Conjunctivitis	3%	2%
Eye disorder	2%	3%
Deafness	3%	1%
Optic neuritis	2%	2%
Ear disorder	2%	1%
Tinnitus	2%	1%
Urogenital System		
Urinary tract infection	25%	22%
Urinary incontinence	15%	8%
Urinary tract disorder	10%	7%
Cystitis	9%	7%
Urinary urgency	7%	8%
Menstrual disorder	13%	9%
Increased urinary frequency	5%	6%
Metrorrhagia	6%	12%
Urinary retention	6%	4%
Vaginitis	4%	3%
Amenorrhea	4%	3%
Dysuria	2%	2%
Impotence	4%	7%
Menopause	4%	2%
Menorrhagia	4%	2%
Nocturia	1%	2%
Vaginal moniliasis	2%	2%
Kidney pain	2%	0%
Pyelonephritis	0%	2%
Prostatic disorder	1%	2%

* significantly associated with BETASERON treatment ($p<0.05$)

It should be noted that the figures cited in Table 1 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. The cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

2. Secondary-progressive MS: The incidence of adverse events that occurred in at least 2% of patients treated with 8 MIU BETASERON or placebo for up to three years, orwhere an adverse event was reported at a frequency at least 2% higher with BETASERON than that observed for placebo-treated patients in the secondary-progressive study, is presented in Table 2. Adverse events significantly associated with BETASERON compared to placebo ($p<0.05$) are also indicated in Table 2.

Table 2: Incidence of Adverse Events ≥ 2% or > 2% Difference (BETASERON vs. Placebo) in the Secondary Progressive MS Study

Adverse Event	Placebo n=358	0.25 mg (8 MIU) n=360
Body as a Whole		
Asthenia	58%	63%
Flu syndrome*	40%	61%
Pain	25%	31%
Fever*	13%	40%
Back pain	24%	26%
Accidental injury	17%	14%
Chills*	7%	23%
Pain in Extremity	12%	14%
Infection	11%	13%
Abdominal pain*	6%	11%
Malaise	5%	8%
Neck pain	6%	5%
Abscess*	2%	4%
Laboratory test abnormal	1%	3%
Allergic reaction	3%	2%
Chills and fever*	0%	3%
Thorax pain	2%	1%

*significantly associated with BETASERON treatment ($p<0.05$)

Seventy-four (74) patients discontinued treatment due to adverse events (23 on placebo and 51 on BETASERON). Injection site reactions were significantly associated with early termination of treatment in the BETASERON group compared to placebo ($p<0.05$). The highest frequency of adverse events leading to discontinuation involved the nervous system, of which depression (7 on placebo and 11 on BETASERON) was the most common.

Significantly more patients on active therapy (14.4% vs. 4.7% on placebo) had elevated ALT (SGPT) values (>5 times baseline value). Elevations were also observed in AST (SGOT) and gamma-GT values in the BETASERON group throughout the study. In the BETASERON group, most ALT (SGPT) abnormalities resolved spontaneously with continued treatment whereas some resolved upon dose reduction or temporary discontinuation of treatment.

Lymphopenia ($<1500/mm^3$) was observed in 90.9% of BETASERON patients compared to 74.3% of placebo patients and neutropenia ($<1400/mm^3$) was noted in 18.0% BETASERON and 5.1% placebo patients.

DOSAGE AND ADMINISTRATION FOR SUBCUTANEOUS USE ONLY

BETASERON (interferon beta-1b) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of multiple sclerosis.

The recommended dose of BETASERON for both relapsing-remitting and secondary-progressive MS patients is 0.25 mg (8 MIU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose in relapsing-remitting MS patients are presented above (see **ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials**).

In the secondary-progressive MS study, patients initiated treatment with half the dose (4 MIU s.c. every other day) for a period of 2 weeks prior to escalating to the recommended dose of 8 MIU (s.c. every other day).

Efficacy of treatment for longer than 2 years has not been substantially demonstrated in relapsing-remitting multiple sclerosis. For secondary-progressive multiple sclerosis, safety and efficacy data beyond 3 years are not available.

To reconstitute lyophilized BETASERON for injection, use a sterile syringe and needle to inject 1.2 mL of the diluent supplied, Sodium Chloride, 0.54% Solution, into the BETASERON vial. Gently swirl the vial of BETASERON to dissolve the drug completely; do not shake. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with accompanying diluent, each mL of solution contains 0.25 mg (8 MIU) interferon beta-1b, 13 mg Albumin Human USP and 13 mg Mannitol USP.

Withdraw 1 mL of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge ½-inch needle and inject the solution subcutaneously. Sites for self-injection include abdomen, buttocks and thighs. A vial is suitable for single use only; unused portions should be discarded (See **BETASERON® [Interferon beta-1b] INFORMATION FOR THE PATIENT** section for **SELF-INJECTION PROCEDURE**.)

AVAILABILITY OF DOSAGE FORMS

BETASERON (interferon beta-1b) is presented in single-use vials of lyophilized powder containing 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg Albumin Human USP, and 15 mg Mannitol, USP. BETASERON is supplied in cartons containing 15 vials of medication and 15 vials of diluent (2 mL of Sodium Chloride 0.54% solution, per vial).

Product Monograph available upon request.
B10204E5

REFERENCES:

1. Data on file. Berlex Canada Inc., 1999.
2. Product Monograph of PrBETASERON® (interferon beta-1b). Berlex Canada, June 1999.
3. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomised controlled trial. Neurology 1995; 45:1227-1285.

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See pages A-7, A-13

Amerge®

1 & 2.5 mg Tablets

Therapeutic Classification: Migraine Therapy

Pharmacological Classification: 5-HT_1 Receptor Agonist

Indications and Clinical Use: AMERGE (naratriptan hydrochloride) Tablets are indicated for the acute treatment of migraine attacks with or without aura. AMERGE Tablets are not for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

Contraindications: AMERGE (naratriptan hydrochloride) Tablets are contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular disease (e.g., atherosclerotic disease, congenital heart disease) should not receive AMERGE. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).

Because AMERGE can give rise to increases in blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS). Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because AMERGE may also cause coronary vasospasm and these effects may be additive, the use of AMERGE within 24 hours before or after treatment with other 5-HT_1 receptor agonists, or ergotamine-containing drugs or their derivatives (e.g., dihydroergotamine, methysergide) is contraindicated. AMERGE is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine. AMERGE Tablets are contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min) (see DOSAGE AND ADMINISTRATION).

AMERGE Tablets are contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) (see DOSAGE AND ADMINISTRATION).

AMERGE Tablets are contraindicated in patients with hypersensitivity to naratriptan or any component of the formulation.

Warnings:

AMERGE (naratriptan hydrochloride) should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: AMERGE has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of another 5-HT_1 agonist. AMERGE should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). **It is strongly recommended that AMERGE not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, AMERGE should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD who are considered to have a satisfactory cardiovascular evaluation, the first dose of AMERGE should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following AMERGE administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.**

Intermittent long-term users of AMERGE who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment.

If symptoms consistent with angina occur after the use of AMERGE, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to AMERGE (naratriptan hydrochloride).

Cardiac Events and Fatalities Associated With 5-HT_1 Agonists: AMERGE can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience With AMERGE Tablets: Among approximately 3500 patients with migraine who participated in premarketing clinical trials of AMERGE Tablets, four patients treated with single oral doses of AMERGE ranging from 1 to 10 mg experienced asymptomatic ischemic ECG changes with at least one, who took 7.5 mg, likely due to coronary vasospasm.

Cerebrovascular Events and Fatalities With 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA).

Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, naratriptan at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

Migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving subcutaneous naratriptan 1.5 mg in the absence of a migraine attack. Naratriptan was associated with a reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperemic myocardial blood flow (~10%). The relevance of these findings to the use of recommended oral doses of naratriptan is not known.

Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as AMERGE. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, AMERGE should not be used in patients having a history of hypersensitivity to sumatriptan or chemically-related 5-HT_1 receptor agonists. As AMERGE contains a sulphonamide component, there is a theoretical risk of hypersensitivity reactions in patients with known hypersensitivity to sulphonamides.

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of another 5-HT_1 agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

Increases in Blood Pressure: Elevations in blood pressure have been reported following use of AMERGE. At the recommended oral doses, the elevations are generally small (population average maximum increases of <5 mmHg systolic and <3 mmHg diastolic at the 2.5 mg dose). The effects may be more pronounced in the elderly and hypertensive patients. In a pharmacodynamic study conducted in normotensive patients (n=12) and in hypertensive patients controlled by antihypertensive treatment (n=12), the pressor effects of AMERGE were greater in hypertensive patients (weighted mean increases in systolic and diastolic blood pressure of 6 and 4 mmHg in hypertensive subjects versus 3 and 2 mmHg in normotensive patients receiving two 2.5 mg doses separated by a 2 hour time interval). Two hypertensive patients experienced three events of chest discomfort while receiving naratriptan. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. AMERGE is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS).

Precautions: Cardiovascular: Discomfort in the chest, neck, throat, and jaw (including pain, pressure, heaviness, tightness) has been reported after administration of AMERGE (naratriptan hydrochloride). Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following AMERGE should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS).

Neurologic Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of AMERGE.

Seizures: Caution should be observed if AMERGE is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.

Renal or Hepatic Impairment: AMERGE Tablets should be administered with caution to patients with impaired renal or hepatic function (see ACTIONS AND CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Psychomotor Impairment: In a study of psychomotor function in healthy volunteers, single oral 5 and 10 mg doses of AMERGE were associated with sedation and decreased alertness. Although these doses are higher than those recommended for the treatment of migraine, patients should be cautioned that drowsiness may occur following treatment with AMERGE. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.

Drug Interactions: The limited metabolism of AMERGE and the wide range of cytochrome P450 isoenzymes involved, as determined by *in vitro* studies, suggest that significant drug interactions with AMERGE are unlikely. AMERGE did not inhibit monoamine oxidase enzymes (MAO-A or MAO-B) *in vitro*. The possibility of pharmacodynamic *in vivo* interactions between AMERGE and monoamine oxidase inhibitors has not been investigated.

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of AMERGE administration (see CONTRAINDICATIONS).

Other 5-HT_1 Agonists: The administration of AMERGE with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated.

Other Serotonergic Drugs: Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT_1 agonists. If concomitant treatment with AMERGE and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, monoamine oxidase inhibitor, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

Hormonal contraceptives: In a population pharmacokinetic study in migraine patients, hormonal contraceptive use was associated with a 32% decrease in naratriptan clearance.

Tobacco: In a population pharmacokinetic study in migraine patients, tobacco use was associated with a 29% increase in naratriptan clearance.

Alcohol and Food: Clinical studies did not reveal any pharmacokinetic interaction when naratriptan was administered together with alcohol or food.

Use in Pregnancy: The safety of AMERGE for use during human pregnancy has not been established. AMERGE Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To monitor fetal outcomes of pregnant women exposed to AMERGE, Glaxo Wellcome Inc. maintains a Naratriptan Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

Use in Nursing Mothers: AMERGE and/or its metabolites are distributed into the milk of lactating rats (at 2 hours post oral gavage dosing, levels in milk were 3.5 times higher than maternal plasma levels). Therefore, caution should be exercised when considering the administration of AMERGE Tablets to nursing women.

Use in Pediatrics: Safety and effectiveness of AMERGE Tablets have not been studied in children under 12 years of age. Use of the drug in this age group is, therefore, not recommended.

Adolescents: The efficacy of AMERGE Tablets at single doses of 0.25, 1.0 and 2.5 mg was not demonstrated to be greater than placebo in adolescents (12-17 years). Therefore, the use of the drug in adolescents is not recommended.

Use in the Elderly: The safety and effectiveness of AMERGE has not been adequately studied in individuals over 65 years of age. AMERGE Tablets are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in elderly patients who have reduced renal function. In addition, elderly patients are more likely to have decreased hepatic function; they are at higher risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical studies of AMERGE Tablets did not include patients over 65 years of age. Its use in this age group is, therefore, not recommended.

Drug/Laboratory Test Interactions: AMERGE Tablets are not known to interfere with commonly employed clinical laboratory tests.

Dependence Liability: In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, subjective responses typically associated with many drugs of abuse were produced with less intensity during treatment with AMERGE (1-5 mg) than with codeine (30 to 90 mg). Long term studies (12 months) in migraine patients using AMERGE Tablets revealed no evidence of increased drug utilization.

Melanin Binding: In pigmented rats treated with a single oral dose (10 mg/kg) of radiolabelled naratriptan, radioactivity was detected in the eyes at 3 months post-administration, a finding which suggests that the drug or its metabolites may bind to the melanin of the eye. The possible clinical significance of this finding is unknown. No systematic monitoring of ophthalmologic function was undertaken in clinical trials. Prescribers should consider the possibility of long-term ophthalmologic effects due to accumulation of naratriptan in melanin-rich tissues.

Adverse Reactions: Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Experience in Controlled Clinical Trials with AMERGE

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, AMERGE (naratriptan hydrochloride) has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety: The safety and efficacy of the 1 and 2.5 mg doses of AMERGE were investigated in four placebo-controlled clinical trials in adult migraine patients. Two of these trials were of parallel group design and involved the treatment of a single migraine attack. A third study was of crossover design and involved the treatment of one migraine attack per dose group. The fourth study was a parallel group trial in which patients treated up to 3 migraine attacks. In all studies, patients who achieved headache relief at 240 minutes post-dose, but experienced a worsening of severity between 4 and 24 hours post-dosing, were permitted to take a second dose of double-blind medication identical to the first.

The overall incidence of adverse events following doses of 1 mg or 2.5 mg AMERGE (one or two doses) were similar to placebo (28.5% and 30.2% versus 28.9% with placebo). AMERGE Tablets were generally well tolerated and most adverse reactions were mild, transient and self-limiting. The most common adverse events to occur at a higher rate than in the corresponding placebo group were malaise/fatigue (2.4% versus 0.8% with placebo) and neck/throat/jaw sensations (2.1% versus 0.3% with placebo). Table 3 lists the most common adverse events that occurred in the four large placebo-controlled clinical trials. Only events that occurred at a frequency of 1% or more in the AMERGE Tablets 2.5 mg or 1 mg group and were more frequent in that group than in the placebo group are included in Table 3. From this table, it appears that many of these adverse events are dose related.

Table 3: Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients With Migraine*

	Placebo	AMERGE 1 mg	AMERGE 2.5 mg
Number of Patients	922	1024	1016
Number of Migraine Attacks Treated	1059	1387	1368
Symptoms of Potentially			
Cardiac Origin			
• neck/throat/jaw sensations*	0.3%	1.7%	2.1%
• chest sensations*	1.1%	0.8%	1.2%
• upper limb sensations*	0.3%	0.5%	1.4%
Neurology			
• dizziness	1.5%	1.0%	2.2%
• drowsiness/sleepiness	0.8%	0.9%	1.7%
• paresthesia	0.8%	1.6%	1.5%
• head/face sensations*	0.5%	0.5%	1.3%
• headache	0.2%	0.4%	1.0%
Gastrointestinal			
• nausea	6.2%	5.9%	6.3%
• hyposalivation	0.3%	0.5%	1.0%
Non-Site Specific			
• malaise & fatigue	0.8%	1.6%	2.4%

*The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.

Dosage and Administration: AMERGE (naratriptan hydrochloride) Tablets are recommended only for the acute treatment of migraine attacks. AMERGE should not be used prophylactically.

Adults: The minimal effective single adult dose of AMERGE Tablets is 1 mg. The maximum recommended single dose is 2.5 mg.

In three of the four studies, optimal rates of headache relief were achieved with a 2.5 mg dose. As patients may vary in their dose-responsiveness, the choice of dose should be made on an individual basis, weighing the possible benefit of the 2.5 mg dose with the potential for a greater risk of adverse events.

If the migraine headache returns, or if a patient has a partial response, the initial dose may be repeated once after 4 hours, for a maximum dose of 5 mg in a 24 hour period. The safety of treating, on average, more than four headaches in a 30 day period has not been established.

AMERGE Tablets should be swallowed whole with fluids. AMERGE tablets should be taken as early as possible after the onset of a migraine headache, but are effective if taken at a later stage.

If a patient does not respond to the first dose of AMERGE Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of benefit.

Renal disease/functional impairment causes prolongation of the half-life of orally administered AMERGE. Consequently, if treatment is deemed advisable in the presence of renal impairment, a maximum single dose of 1 mg should be administered. No more than a total of 2 mg should be taken in any 24 hour period. Repeated dosing in renally impaired patients has not been evaluated. Administration of AMERGE tablets in patients with severe renal impairment (creatinine clearance <15 mL/min) is contraindicated (see CONTRAINDICATIONS).

Hepatic disease/functional impairment causes prolongation of the half-life of orally administered AMERGE. Consequently, if treatment is deemed advisable in the presence of hepatic impairment, a maximum single dose of 1 mg should be administered. No more than a total of 2 mg should be taken in any 24 hour period. Administration of AMERGE Tablets in patients with severe hepatic impairment (Child-Pugh grade C) is contraindicated (see CONTRAINDICATIONS).

Hypertension: AMERGE should not be used in patients with uncontrolled or severe hypertension. Patients with mild to moderate controlled hypertension should be treated cautiously at the lowest effective dose.

Composition: AMERGE 2.5 mg Tablets contain 2.5 mg of naratriptan (base) as the hydrochloride salt and the following non-medicinal ingredients: croscarmellose sodium; hydroxypropyl methylcellulose; indigo carmine aluminium lake (FD&C Blue No. 2); iron oxide yellow; lactose; magnesium stearate; microcrystalline cellulose; titanium dioxide; and triacetin.

AMERGE 1 mg Tablets contain 1 mg of naratriptan (base) as the hydrochloride salt and the following non-medicinal ingredients: croscarmellose sodium; hydroxypropyl methylcellulose; lactose; magnesium stearate; microcrystalline cellulose; titanium dioxide; and triacetin.

Stability and Storage Recommendations: AMERGE Tablets should be stored below 30°C.

Availability of Dosage Forms: AMERGE Tablets 2.5 mg are green film-coated, D-shaped tablets embossed GXCE5 on one side, available in blister packs of 2 or 6 tablets (4 blister packs inserted into a carton), or bottles of 60 tablets.

AMERGE Tablets 1 mg are white film-coated, D-shaped tablets embossed GXCE3 on one side, available in blister packs of 2 tablets (4 blister packs inserted into a carton), or bottles of 60 tablets.

Full product monograph is available upon request.

GlaxoSmithKline

GlaxoSmithKline Inc.
7333 Mississauga Road North, Mississauga, Ontario L5N 6L4

ℵCESAMET® nabilone

0.5 mg and 1 mg Capsules (Nabilone)

ACTION

ℵCESAMET® (nabilone) is a synthetic cannabinoid with antiemetic properties which have been found to be of value in the management of some patients with nausea and vomiting associated with cancer chemotherapy. It also has sedative and psychotropic effects.

After oral administration, comparable peak plasma levels of nabilone and of its carbinol metabolite were attained within 2 hours. The combined plasma concentrations of nabilone and of its carbinol metabolite accounted for, at most, 10 to 20% of the total radiocarbon concentration in plasma. The plasma half-life of nabilone was approximately 2 hours, while that of the total radiocarbon was of the order of 35 hours.

Of the two major possible metabolic pathways, stereo-specific enzymatic reduction and direct enzymatic oxidation, the latter appears to be the more important in man.

The drug and its metabolites are eliminated mainly in the feces (approximately 65%) and to a lesser extent in the urine (approximately 20%). The major excretory pathway is the biliary system.

INDICATIONS

ℵCESAMET® (nabilone) is indicated in adults for the management of severe nausea and vomiting associated with cancer chemotherapy.

CONTRAINDICATIONS

ℵCESAMET® (nabilone) is contraindicated in patients with known sensitivity to marijuana or other cannabinoid agents, and in those with a history of psychotic reactions.

WARNINGS

ℵCESAMET® (nabilone) should be used with extreme caution in patients with severe liver dysfunction and in those with a history of non-psychotic emotional disorders.

ℵCESAMET® should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances.

ℵCESAMET® should not be used during pregnancy, in nursing mothers, or pediatric patients since its safety under these conditions has not been established.

PRECAUTIONS

Since ℵCESAMET® (nabilone) will often impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car and operating machinery, the patient should be warned accordingly and should not be permitted to drive or engage in dangerous tasks until the effects of nabilone are no longer present.

Adverse psychotropic reactions can persist for 48 to 72 hours following cessation of treatment.

Since ℵCESAMET® elevates supine and standing heart rates and causes postural hypotension, it should be used with caution in the elderly and in patients with hypertension or heart disease.

Drug Interactions: Potential interactions between ℵCESAMET®, and diazepam; sodium secobarbital; alcohol; or codeine, were evaluated. The depressant effects of the combinations were additive. Psychomotor function was particularly impaired with concurrent use of diazepam.

Pediatric Use: The safety and efficacy in children under the age of 18 has not been established. Therefore the use of ℵCESAMET® in this patient population is not recommended.

ADVERSE REACTIONS

The most frequently observed adverse reactions to nabilone and their incidences reported in the course of clinical trials were as follows: drowsiness (66.0%), vertigo (58.8%), psychological high (38.8%), dry mouth (21.6%), depression (14.0%), ataxia (12.8%), blurred vision (12.8%), sensation disturbance (12.4%), anorexia (7.6%), asthenia (7.6%), headache (7.2%), orthostatic hypotension (5.2%), euphoria (4.0%) and hallucinations (2.0%).

The following adverse reactions were observed in less than 1% of the patients who were administered nabilone in the course of the clinical trials: tachycardia, tremors, syncope, nightmares, distortion in the perception of time, confusion, dissociation, dysphoria, psychotic reactions and seizures.

Spontaneously Reported Adverse Reactions: The following adverse reactions listed in order of decreasing frequency by body system have been reported since ℵCESAMET® has been marketed. All events are listed regardless of causality assessment.

Blood and Hematopoetic: Leukopenia

Cardiovascular: Hypotension and tachycardia

Eye and Ear: Visual disturbances

Gastrointestinal: Dry mouth, nausea, vomiting, and constipation

Nervous System: Hallucinations, CNS depression, CNS stimulation, ataxia, stupor, vertigo, convulsion, and circumoral paresthesia

Psychiatric: Somnolence, confusion, euphoria, depression, dysphoria, depersonalization, anxiety, psychosis, and emotional lability

Miscellaneous and Ill-Defined Conditions: Dizziness, headache, insomnia, abnormal thinking, chest pain, lack of effect, and face edema

SYMPTOMS AND TREATMENT OF OVERDOSE

Signs and Symptoms: Signs and symptoms which might be expected to occur are psychotic episodes including hallucinations, anxiety reactions, respiratory depression and coma (experience with cases of overdosage of more than 10 mg/day has not yet been reported).

Treatment: Overdosage may be considered to have occurred, even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

If psychotic episodes occur, the patient should be managed conservatively, if possible. For moderate psychotic episodes and anxiety reactions, verbal support and comforting may be sufficient. In more severe cases, antipsychotic drugs may be useful; however, the utility of antipsychotic drugs in cannabinoid psychosis has not been systematically evaluated. Support for their use is drawn from limited experience using antipsychotic agents to manage cannabis overdoses. Because of the potential for drug-drug interactions (eg, additive CNS depressant effects due to nabilone and chlorpromazine), such patients should be closely monitored.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

The use of forced diuresis, peritoneal dialysis, hemodialysis, charcoal hemoperfusion, or cholestyramine has not been reported. In the presence of normal renal function, most of a dose of nabilone is eliminated through the biliary system.

Treatment for respiratory depression and comatose state consists in symptomatic and supportive therapy. Particular attention should be paid to the occurrence of hypothermia. If the patient becomes hypotensive, consider fluids, inotropes, and/or vasopressors.

DOSAGE AND ADMINISTRATION

Adults:

The usual dosage of ℵCESAMET® (nabilone) is 1 mg or 2 mg twice a day. The first dose should be given the night before initiating administration of chemotherapeutic medication. The second dose is usually administered 1 to 3 hours before chemotherapy. If required, administration of ℵCESAMET® can be continued up to 24 hours after the chemotherapeutic agent is given. The maximum recommended daily dose is 6 mg in divided doses.

ℵCESAMET® is available in a 0.5 mg strength for dose adjustment within the therapeutic range. Dose adjustment may be required for the purposes of response and tolerance in individual patients. Overdosage may occur even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

ℵCESAMET® contains nabilone in a capsule dosage form and is intended only for oral administration.

STRUCTURAL FORMULA AND CHEMISTRY

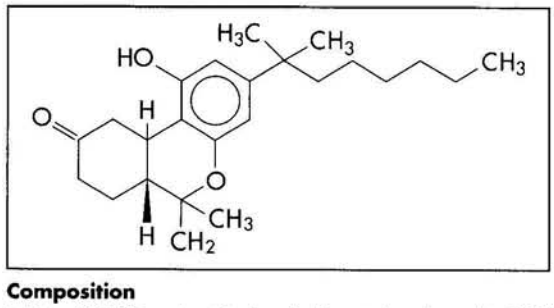
Molecular Formula: $C_{24}H_{36}O_3$

Molecular Weight: 372

U.S.A.N: Nabilone

Chemical Name: trans(±)-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo(b,d),pyran-9-one.

Description: White crystalline powder



Composition

Each 1 mg ℵCESAMET® capsule contains 1 mg of nabilone, starch, povidone, gelatin, FD&C blue #2 (indigo carmine), red iron oxide and titanium dioxide.

Each 0.5 mg ℵCESAMET® capsule contains: 0.5 mg of nabilone, starch, povidone, gelatin, titanium dioxyde, D&C red # 33, D&C yellow # 10, FD&C red # 40.

Stability and storage Recommendations

Store at controlled room temperature at 15-30°C.

AVAILABILITY

ℵCESAMET® 1 mg capsule: each No. 2 hard gelatin capsule, opaque blue cap and white body, imprinted ICN logo on the cap and 3101 on the body, contains 1 mg of nabilone and are available in bottles of 20 capsules.

ℵCESAMET® 0.5 mg capsule: each No. 4 hard gelatin capsule, opaque red cap and white body, imprinted ICN logo on the cap and 3102 on the body, contains 0.5 mg of nabilone and are available in bottles of 50 capsules.

ℵCESAMET® (nabilone) legally is considered to be a narcotic and is subject to the controls which apply to those drugs.

References

1. Cesamet (nabilone) Product monograph. Valeant Canada Limited.

2. Grotenhermen F and Russo E. Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential. The Haworth Press, Inc. 2002: xxviii.

Product Monograph available upon request

VALEANT

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See page A-9

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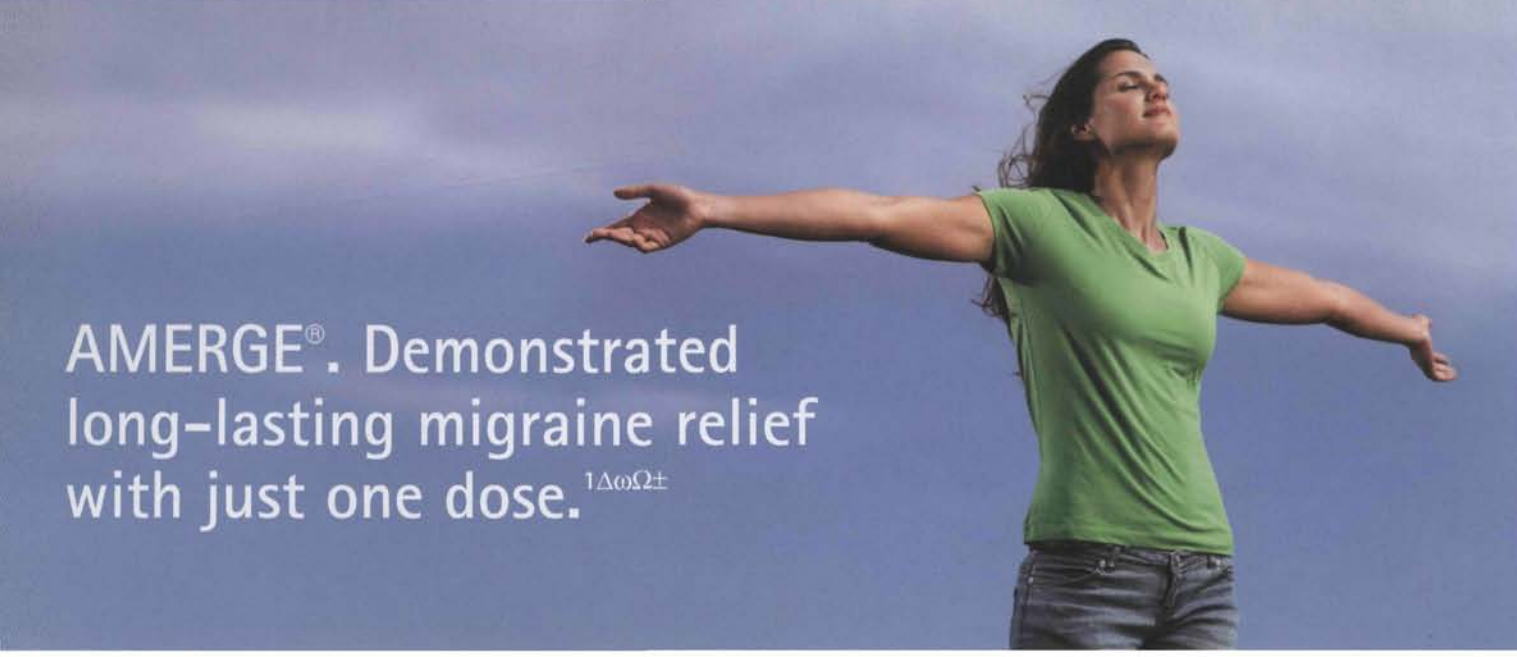
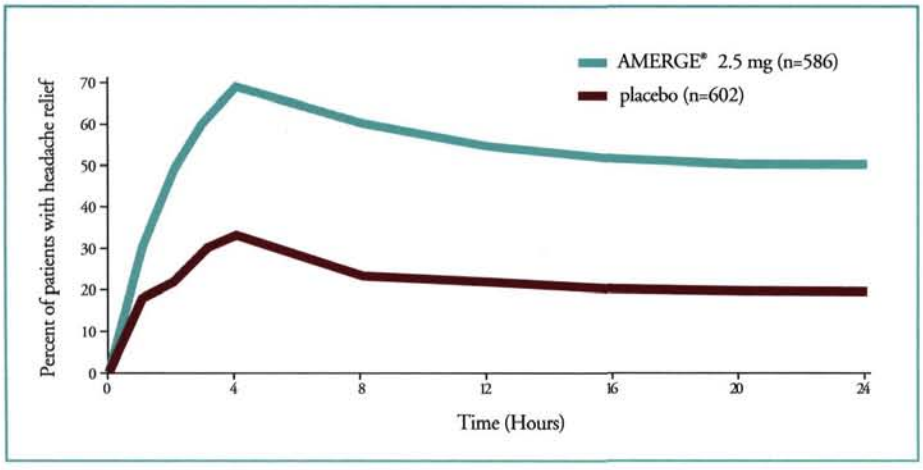


AMERGE®. Demonstrated long-lasting migraine relief with just one dose.[1ΔωΩ±]



Adapted from Mathew *et al.* Double-blind, placebo-controlled, randomized study of AMERGE® (2.5 mg, n=590) and placebo (n=606 patients)[1]

Headache relief maintained over 24 hours (in patients not requiring rescue medication or a second dose[1])

Headache relief = reduction of moderate or severe pain to mild or no pain[1]

ω Significant migraine relief beginning 60 minutes post-dose ($p<0.001$ vs placebo)[1]

Ω Among patients not using rescue medication or a second dose of study medication, headache relief was maintained for 8, 12, and 24 hours in significantly more patients ($p<0.05$ vs placebo)[1]

• Usual single adult dose: 2.5 mg daily±

±If migraine returns or if there is a partial response, initial dose may be repeated once after 4 hours (max 5 mg/day). Maximum recommended single adult dose: 2.5 mg. Total daily maximum dose: 5 mg.[2]

Minimal effective single dose: 1 mg. Dose adjustment recommended in renal and hepatic disease. Patients with mild to moderate controlled hypertension should be treated cautiously at the lowest effective dose. Use in children (<18 years) is not recommended.[2]

AMERGE® (naratriptan hydrochloride) is a selective 5-HT_1 agonist indicated for the acute treatment of migraine attacks with or without aura. AMERGE® should not be used prophylactically. AMERGE® is not indicated for the management of hemiplegic, basilar or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache.[2] The safety of treating, on average, more than four headaches in a 30 day period has not been established.[2]

AMERGE® is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias. In addition, patients with other significant underlying cardiovascular diseases should not receive AMERGE®. AMERGE® is also contraindicated in patients with uncontrolled or severe hypertension.[2]

The most common adverse events occurring at a higher rate than in the corresponding placebo group were malaise/fatigue (2.4% versus 0.8% with placebo) and neck/throat/jaw sensations (2.1% versus 0.3% with placebo).[2]

References: 1. Mathew NT *et al.* Naratriptan is effective and well tolerated in the acute treatment of migraine: results of a double-blind, placebo-controlled, crossover study. *Neurology* 1997;49:1485-1490. **2.** Product Monograph of "AMERGE" (naratriptan hydrochloride), GlaxoSmithKline Inc., May 2004.

GlaxoSmithKline

Amerge® naratriptan hydrochloride

https://doi.org/10.1017/S0317167100116336 Published online by Cambridge University Press

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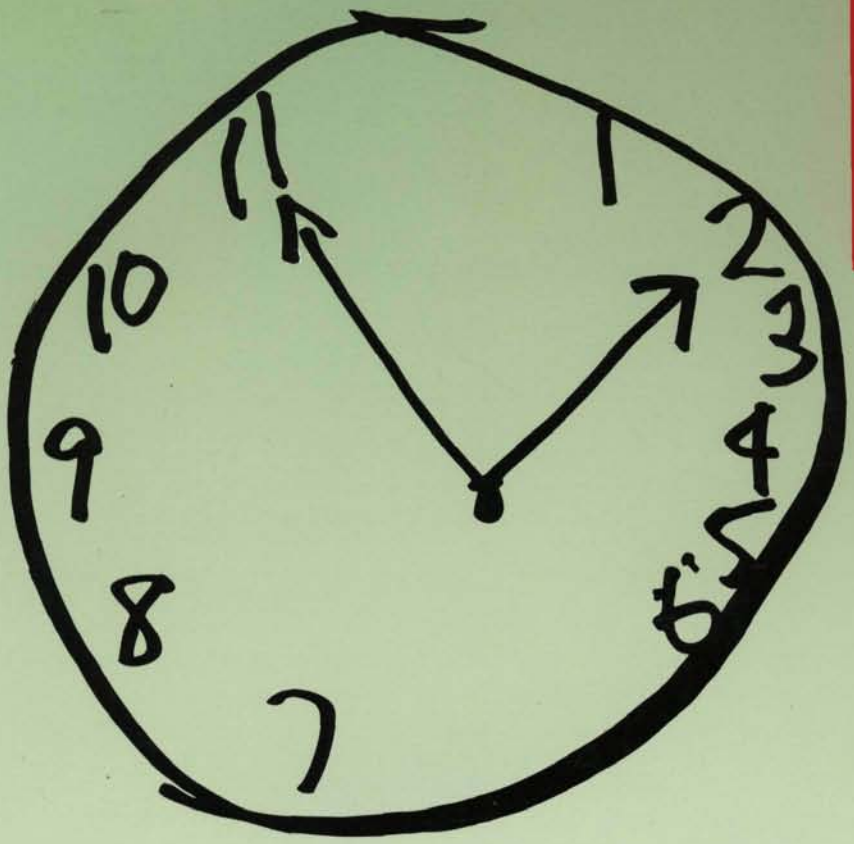

NEW
Once-a-Day
REMINYL ER

It's Time To Take Another Look at REMINYL.

REMINYL is now available in a once-a-day formulation: REMINYL ER.[1] Consider new REMINYL ER as initial treatment in AD.

REMINYL ER (galantamine hydrobromide) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL ER has not been studied in controlled clinical trials for longer than 6 months.

The most common side effects (vs. placebo) in a clinical trial were nausea (17% vs. 5%), dizziness (10% vs. 4%), injury (8% vs. 6%) and headache (8% vs. 6%). For patients who experienced adverse events, the majority occurred during the dose-escalation phase.

There is no evidence that galantamine alters the course of the underlying dementing process.

REFERENCE: 1. REMINYL* (galantamine hydrobromide tablets), REMINYL* ER (galantamine hydrobromide extended-release capsules) Product Monograph, JANSSEN-ORTHO Inc., April 8, 2005.

JANSSEN-ORTHO
19 Green Belt Drive, Toronto
Ontario, Canada M3C 1L9

R0JA050820E

Member R&D PAAB

galantamine HBr
Pr Reminyl* ER
New Once-Daily:
It may change your mind.

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