

Radiotherapy Precisely Targets Acoustic Neuromas

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DENVER — Use of fractionated stereotactic radiotherapy provides excellent local control of acoustic neuroma with lower rates of facial sensory and motor nerve damage than neurosurgery, Stephanie E. Combs, M.D., said at the annual meeting of the American Society for Therapeutic Radiology and Oncology.

Applying radiotherapy on a fractionat-

ed schedule allows delivery of higher doses to the tumor while avoiding the morbidity in normal tissues that occurs with single-dose radiosurgery, said Dr. Combs of the University of Heidelberg, Germany.

She presented a prospective uncontrolled study of 108 patients regularly followed for a median of 48.5 months after undergoing linear accelerator-based fractionated stereotactic radiotherapy (FSRT) for acoustic neuroma. The tumor was associated with neurofibromatosis in 13 pa-

tients. Of the 108 patients, 85 had not undergone any treatment prior to FSRT; the remainder underwent FSRT as a salvage procedure for tumor recurrence or progression after neurologic resection.

Actuarial local tumor control after FSRT was 94.3% at 3 years and 93% at 5 years, regardless of tumor size, the presence of neurofibromatosis, or patient age.

Of patients with serviceable hearing prior to FSRT, 94% demonstrated preservation of useful hearing at 5 years. Of the

18 patients who had facial nerve dysfunction prior to FSRT, all but 3 developed the problem secondary to neurosurgery. The rate of new-onset facial nerve dysfunction after FSRT was 2.3%; affected patients had neurofibromatosis and large volumes of irradiated tissue.

Moderate irreversible radiation-induced damage to the trigeminal nerve developed in 3.4% of patients. No new severe damage to the nerve developed as a result of FSRT, she said. ■

LYRICA® (PREGABALIN) CAPSULES

BRIEF SUMMARY: For full prescribing information, see package insert.

INDICATIONS AND USAGE

LYRICA is indicated for management of

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

LYRICA is indicated as adjunctive therapy for adult patients with partial onset seizures.

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

Withdrawal of Antiepileptic Drugs (AEDs) As with all AEDs, pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued this should be done gradually over a minimum of 1 week. **Tumorigenic Potential** In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. 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 patients >12 years of age, new or worsening pre-existing tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

Dizziness and Somnolence Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (see **PRECAUTIONS-Information for Patients**). In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients. **Ophthalmological Effects** In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision). 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. Although the 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 should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions (See **PRECAUTIONS-Information for Patients**). **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 1 week rather than discontinued abruptly. **Weight Gain** Pregabalin treatment caused 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. 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 **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}). **Peripheral Edema** Pregabalin treatment caused edema, primarily described as peripheral edema. In short-term trials 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. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema. Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA 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, 4% (35/859) 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. **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 10³/µL, compared to 11 x 10³/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 10³/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 B300 mg/day. This mean change difference was not associated with an increased risk of PR increase B25% 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. Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories. **Information for Patients** Patients should be counseled that LYRICA 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. 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 **PRECAUTIONS**). Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea. 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. Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. 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. 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. Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see **PRECAUTIONS, Carcinogenesis and Impairment of Fertility**). 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 **Animal Toxicology**). 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. **Drug Interactions** Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding

displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no 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 other commonly used antiepileptic drugs.

Pharmacodynamics Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with those drugs. No clinically important effects on respiration were seen (see **PRECAUTIONS, Dizziness and Somnolence and Information for Patients**). **Animal Toxicology: Dermatology** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular Lesions** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) B2 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. **Carcinogenesis, Mutagenesis, Impairment of Fertility: 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. No evidence of carcinogenicity was 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. **Mutagenesis** 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. **Impairment of Fertility** 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. **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 at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied. **Pregnancy: Pregnancy Category C** Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) B5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at B1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at B100 mg/kg and offspring survival was decreased at B250 mg/kg. The effect on offspring survival was pronounced at doses B1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at B250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effects of pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures B50 times the mean human exposure (AUC₀₋₂₄ of 123 µg•hr/mL) at the maximum recommended clinical dose of 600 mg/day. **Use in Nursing Mothers:** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for teratogenicity shown for pregabalin in animal studies, 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. **Pediatric Use** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses B50 mg/kg. The neurobehavioral changes persisted in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65 to 74 years of age, and 88 patients were 75 years of age or older. In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older. No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years. **Adverse Events Most Commonly Leading to Discontinuation in All Controlled Clinical Studies** In controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each). **Most Common Adverse Events in All Controlled Clinical Studies** In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (B5% and twice the rate of that seen in placebo). **Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy: Adverse Events Leading to Discontinuation** In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients. **Most Common Adverse Events** Table 1 lists all adverse events, regardless of causality, occurring in B1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate."

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