

# Tune In to Sleep Problems in ADHD Patients

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**NEW YORK**—Insomnia is a real and pressing concern for children with attention-deficit hyperactivity disorder and their families, Judith A. Owens, M.D., said at a psychopharmacology update sponsored by the American Academy of Child and Adolescent Psychiatry.

“At least 60% of the kids in our ADHD clinic have significant problems with sleep

that really impact their quality of life,” said Dr. Owens of the department of pediatrics at Brown University, and director of the pediatric sleep disorders clinic, Hasbro Children’s Hospital, Providence, R.I.

The problem is multifaceted and bidirectional. Insufficient or fragmented sleep can lead to excessive daytime sleepiness, which in turn can result in ADHD-like symptoms. The medications, such as psychostimulants used to control ADHD themselves, can affect sleep onset and con-

tinuity. Methylphenidate, for example, has been shown to delay sleep onset by 30 minutes, Dr. Owens said.

Other psychotropic medications can affect sleep architecture, altering percentages of rapid eye movement (REM) and slow wave sleep, and can interfere with the neurochemicals responsible for regulation of sleep and wakefulness.

Comorbid conditions may further complicate the situation, with bedtime resistance seen in oppositional defiant

disorder, insomnia and early awakening in depression, and night waking in anxiety disorders.

A subset of children with ADHD may have a primary sleep dysfunction involving homeostatic dysregulation, she said.

“But no sleep medications are approved for use in the pediatric population, which some of us have been trying to change,” she said. This has proved difficult, at least in part because of the perception that insomnia in ADHD children is largely a parent-driven complaint. “It has been very difficult to convince the Food and Drug Administration that there is a need for these,” Dr. Owens said.

The lack of approved drugs leaves clinicians relying on drugs that are less than effective and those that may have problematic side effects and questionable long-term safety.

**‘At least 60% of the kids in our ADHD clinic have significant problems with sleep that really impact their quality of life.’**

Preliminary data from a recent survey of 1,271 practicing members of the American Academy of Child and Adolescent Psychiatry suggest that 51% use insomnia medications in more than half of their ADHD patients, she said.

On the list of drugs used, clonidine (Catapres) topped the list, with 86%, followed by antihistamines, at 67%.

The central  $\alpha_2$ -agonist clonidine has various effects on sleep architecture, including slowing sleep-onset latency, increasing slow-wave sleep, and decreasing REM sleep, she said. Its side effects include hypotension, bradycardia, anticholinergic effects, and dysphoria. It can interact with CNS depressants and stimulants, and tolerance often develops.

“I don’t have a lot of arguments to suggest that other things are much better, but I do think there are some problems with this drug,” Dr. Owens said. Interestingly, recent reports have identified a 10-fold increase in overdoses seen in emergency rooms, she said.

Antihistamines generally are viewed as benign by parents and physicians, and they are used quite often in cases when sleep-onset latency problems are less severe. “But they’re not terribly effective,” she said.

Trazodone (Desyrel) is also used, though it tends to cause morning hangover. Benzodiazepines are little used in children, nor are zolpidem (Ambien) and zaleplon (Sonata), although the latter appear to be safe and well tolerated in adults and have little effect on sleep architecture.

“We worry about sleep architecture in children because if slow-wave sleep is suppressed, it can alter their production of growth hormone,” she said.

Melatonin is being evaluated as a possible sleep aid for children, but much more information is needed before this dietary supplement can be recommended. ■

**References:** 1. Sandrini G, Färkkilä M, Burgess G, Forster E, Haughe S, for the Eletriptan Steering Committee. Eletriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. *Neurology*. 2002;59:1210-1217. 2. Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache*. 2003;43:214-222.

## RELMAX® (eletriptan hydrobromide) Tablets

### BRIEF SUMMARY OF PRESCRIBING INFORMATION

**CONTRAINDICATIONS:** RELMAX Tablets should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms, or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal’s variant angina, or other significant underlying cardiovascular disease (see WARNINGS). RELMAX Tablets should not be given to patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks (see WARNINGS). RELMAX Tablets should not be given to patients with peripheral vascular disease including (but not limited to) ischemic bowel disease (see WARNINGS). Because RELMAX Tablets may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS). RELMAX Tablets should not be administered to patients with hemiplegic or basilar migraine. RELMAX Tablets should not be used within 24 hours of treatment with another 5-HT<sub>1</sub> agonist, an ergotamine-containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide. RELMAX Tablets should not be used in patients with known hypersensitivity to eletriptan or any of its inactive ingredients. RELMAX Tablets should not be given to patients with severe hepatic impairment.

**WARNINGS:** RELMAX Tablets should only be used where a clear diagnosis of migraine has been established. CYP3A4 Inhibitors: Eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, trovafloxacin, clarithromycin, ritonavir, and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS or PRECAUTIONS sections of their labeling. In a coronary angiographic study of rapidly infused intravenous eletriptan to concentrations exceeding those achieved with 80 mg oral eletriptan in the presence of potent CYP3A4 inhibitors, a small dose-related decrease in coronary artery diameter similar to that seen with a 6 mg subcutaneous dose of sumatriptan was observed. Risk of Myocardial Ischemia and/or Infarction and Other Cardiac Events: Because of the potential of 5-HT<sub>1</sub> agonists to cause coronary vasospasm, eletriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that eletriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male 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 modest, at best. If, during the cardiovascular evaluation, the patient’s medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with coronary artery vasospasm or myocardial ischemia, eletriptan should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of eletriptan take place in the setting of a physician’s office or similar medically staffed and equipped facility unless the patient has previously received eletriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of RELMAX Tablets. In these patients with risk factors, it is recommended that patients who are intermittent long-term users of 5-HT<sub>1</sub> agonists including RELMAX Tablets, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use RELMAX Tablets. The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to eletriptan. Cardiac Events and Fatalities Associated With 5-HT<sub>1</sub> Agonists: 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 other 5-HT<sub>1</sub> agonists. Considering the extent of use of 5-HT<sub>1</sub> agonists in patients with migraine, the incidence of these events is extremely low. Premarketing experience with eletriptan among the 7,143 unique individuals who received eletriptan during pre-marketing clinical trials: In a clinical pharmacology study, in subjects undergoing diagnostic coronary angiography, a subject with a history of angina, hypertension and hypercholesterolemia, receiving intravenous eletriptan (C<sub>50</sub> of 127 ng/mL equivalent to 60 mg oral eletriptan), reported chest tightness and experienced angiographically documented coronary vasospasm with no ECG changes of ischemia. There was also one report of atrial fibrillation in a patient with a past history of atrial fibrillation. Postmarketing experience with eletriptan: There was one report of myocardial infarction and death in a patient with cardiovascular risk factors (hypertension, hyperlipidemia, strong family history of CAD) in association with inappropriate concomitant use of eletriptan and sumatriptan. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively if the case was actually caused by eletriptan or to reliably assess causation in individual cases. Cerebrovascular Events and Fatalities Associated With 5-HT<sub>1</sub> Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT<sub>1</sub> 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, and transient ischemic attack). Other Vasospasm-Related Events: 5-HT<sub>1</sub> agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT<sub>1</sub> agonists. Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT<sub>1</sub> agonists with and without a history of hypertension. In clinical pharmacology studies, oral eletriptan (at doses of 60 mg or more) was shown to cause small, transient dose-related increases in blood pressure, predominantly diastolic, consistent with its mechanism of action and with other 5-HT<sub>1</sub> agonists. The effect was more pronounced in renally impaired and elderly subjects. A single patient with hepatic cirrhosis received eletriptan 80 mg and experienced a blood pressure of 220/96 mm Hg five hours after dosing. The treatment related event persisted for seven hours. Eletriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT<sub>1</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

**PRECAUTIONS: General:** As with other 5-HT<sub>1</sub> agonists, sensations of tightness, pain, pressure and heaviness have been reported after treatment with eletriptan in the precordium, throat, and jaw. Events that are localized to the chest, throat, neck and jaw have not been associated with arrhythmias or ischemic ECG changes in clinical trials; in a clinical pharmacology study of subjects undergoing diagnostic coronary angiography, one subject with a history of angina, hypertension and hypercholesterolemia, receiving intravenous eletriptan, reported chest tightness and experienced angiographically documented coronary vasospasm with no ECG changes of ischemia. Because 5-HT<sub>1</sub> agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal’s variant angina before receiving additional doses of medication, 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 the use of any 5-HT<sub>1</sub> agonist are candidates for further evaluation (see CONTRAINDICATIONS and WARNINGS). Hepatically Impaired Patients: The effects of severe hepatic impairment on eletriptan metabolism was not evaluated. Subjects with mild or moderate hepatic impairment demonstrated an increase in both AUC (34%) and half-life. The C<sub>50</sub> was increased by 18%. Eletriptan should not be used in patients with severe hepatic impairment. No dose adjustment is necessary in mild to moderate impairment. Binding to Melanin-Containing Tissues: In rats treated with a single intravenous (3 mg/kg) dose of radiolabeled eletriptan, elimination of radioactivity from the retina was prolonged, suggesting that eletriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin-rich tissues over time, this raises the possibility that eletriptan could cause toxicity in these tissues after extended use. Although no systematic monitoring of ophthalmological function was undertaken in clinical trials, and no specific recommendations for ophthalmological monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmological effects. Corneal Opacities: Transient corneal opacities were seen in dogs receiving oral eletriptan at 5 mg/kg and above. They were observed during the first week of treatment, but were not present thereafter despite continued treatment. Exposure at the no-effect dose level of 2.5 mg/kg was approximately equal to that achieved in humans at the maximum recommended daily dose. Laboratory Tests: No specific laboratory tests are recommended. Drug Interactions: Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine [DHE] or methysergide) and eletriptan within 24 hours of each other is not recommended (see CONTRAINDICATIONS). CYP3A4 Inhibitors: Eletriptan is metabolized primarily by CYP3A4 (see WARNINGS regarding use with potent CYP3A4 inhibitors). Monoamine Oxidase Inhibitors: Eletriptan is not a substrate for monoamine oxidase (MAO) enzymes, therefore there is no expectation of an interaction between eletriptan and MAO inhibitors. Propranolol: The C<sub>50</sub> and AUC of eletriptan were increased by 10 and 33% respectively in the presence of propranolol. No interactive increases in blood pressure were observed. No dosage adjustment appears to be needed for patients taking propranolol. Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT<sub>1</sub> agonists. If concomitant treatment with eletriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. Other 5-HT<sub>1</sub> agonists: Concomitant use of other 5-HT<sub>1</sub> agonists within 24 hours of RELMAX treatment is not recommended (see CONTRAINDICATIONS). Drug/Laboratory Test Interactions: RELMAX Tablets are not known to interfere with commonly employed clinical laboratory tests. Carcinogenesis: Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by administering eletriptan in the diet. In rats, the incidence of testicular interstitial cell adenomas was increased at the high dose of 75 mg/kg/day. The estimated exposure (AUC) to parent drug at that dose was approximately 6 times that achieved in humans receiving the maximum recommended daily dose (MRDD) of 80 mg, and at the no-effect dose of 15 mg/kg/day it was approximately 2 times the human exposure at the MRDD. In mice, the incidence of hepatocellular adenomas was increased at the high dose of 400 mg/kg/day. The exposure to parent drug (AUC) at that dose was approximately 18 times that achieved in humans receiving the MRDD, and the AUC at the no-effect dose of 90 mg/kg/day was approximately 7 times the human exposure at the MRDD. Mutagenesis: Eletriptan was not mutagenic in bacterial or mammalian cell assays *in vitro*, testing negative in the Ames reverse mutation test and the hypoxanthine-thymine phosphoribosyl transferase (HGPRT) mutation test in Chinese hamster ovary cells. It was not clastogenic in two *in vitro* micronucleus assays. Results were equivocal in *in vitro* human lymphocyte clastogenicity tests, in which the incidence of polyploidy was increased in the absence of metabolic activation (-S9 conditions), but not in the presence of metabolic activation. Impairment of Fertility: In a rat fertility and early embryonic development study, doses tested were 50, 100 and 200 mg/kg/day, resulting in systemic exposures to parent drug in rats, based on AUC, that were 4, 8 and 16 times MRDD, respectively, in males and 7, 14 and 28 times MRDD, respectively, in females. There was a prolongation of the estrous cycle at the 200 mg/kg/day dose due to an increase in duration of estrus, based on vaginal smears. There were also dose-related, statistically significant decreases in mean numbers of corpora lutea per dam at

all 3 doses, resulting in decreases in mean numbers of implants and viable fetuses per dam. This suggests a partial inhibition of ovulation by eletriptan. There was no effect on fertility of males and no other effect on fertility of females.

**Pregnancy: Pregnancy Category C:** In reproductive toxicity studies in rats and rabbits, oral administration of eletriptan was associated with developmental toxicity (decreased fetal and pup weights and an increased incidence of fetal structural abnormalities). Effects on fetal and pup weights were observed at doses that were, on a mg/m<sup>2</sup> basis, 6 to 12 times greater than the clinical maximum recommended daily dose (MRDD) of 80 mg. The increase in structural alterations occurred in the rat and rabbit at doses that, on a mg/m<sup>2</sup> basis, were 12 times greater than (rat) and approximately equal to (rabbit) the MRDD. When pregnant rats were administered eletriptan during the period of organogenesis at doses of 10, 30 or 100 mg/kg/day, fetal weights were decreased and the incidences of vertebral and sternal variations were increased at 100 mg/kg/day (approximately 12 times the MRDD on a mg/m<sup>2</sup> basis). The 100 mg/kg dose was also maternally toxic, as evidenced by decreased maternal body weight gain during gestation. The no-effect dose for developmental toxicity in rats exposed during organogenesis was 30 mg/kg, which is approximately 4 times the MRDD on a mg/m<sup>2</sup> basis. When doses of 5, 10 or 50 mg/kg/day were given to New Zealand White rabbits throughout organogenesis, fetal weights were decreased at 50 mg/kg, which is approximately 12 times the MRDD on a mg/m<sup>2</sup> basis. The incidences of fetal and vena cava deviations were increased in all treated groups. Maternal toxicity was not produced at any dose. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established, and the 5 mg/kg dose is approximately equal to the MRDD on a mg/m<sup>2</sup> basis. There are no adequate and well-controlled studies in pregnant women; therefore, eletriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers: Eletriptan is excreted in human breast milk. In one study of 8 women given a single dose of 80 mg, the mean total amount of eletriptan in breast milk over 24 hours in this group was approximately 0.02% of the administered dose. The ratio of eletriptan mean concentration in breast milk to plasma was 1:4, but there was great variability. The resulting eletriptan concentration-time profile was similar to that seen in the plasma over 24 hours, with very low concentrations of drug (mean 1.7 ng/mL) still present in the milk 18-24 hours post dose. The N-desmethyl active metabolite was not measured in the breast milk. Caution should be exercised when RELMAX is administered to nursing women. Pediatric Use: Safety and effectiveness of RELMAX Tablets in pediatric patients have not been established; therefore, RELMAX is not recommended for use in patients under 18 years of age. The efficacy of RELMAX Tablets (40 mg) in patients 11-17 was not established in a randomized, placebo-controlled trial of 274 adolescent migraineurs. Adverse events observed were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. Long-term safety of eletriptan was studied in 76 adolescent patients who received treatment for up to one year. A similar profile of adverse events to that of adults was observed. The long-term safety of eletriptan in pediatric patients has not been established. Geriatric Use: Eletriptan has been given to only 50 patients over the age of 65. Blood pressure was increased to a greater extent in elderly subjects than in young subjects. The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults. In clinical trials, there were no apparent differences in efficacy or the incidence of adverse events between patients under 65 years of age and those 65 and above (n=50). There is a statistically significant increase half-life (from about 4.4 hours to 5.7 hours) between elderly (65 to 93 years of age) and younger adult subjects (18 to 45 years of age).

**ADVERSE REACTIONS:** Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT<sub>1</sub> 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). Incidence in Controlled Clinical Trials: Among 4,597 patients who treated their first migraine headache with RELMAX in short-term placebo-controlled trials, the most common adverse events reported with treatment with RELMAX were asthenia, nausea, dizziness, and somnolence. These events appear to be dose related. In long-term open-label studies where patients were allowed to treat multiple migraine attacks for up to 1 year, 128 (8.3%) out of 1,544 patients discontinued treatment due to adverse events. Table 1 lists adverse events that occurred in the subset of 5,125 migraineurs who received eletriptan doses of 20 mg, 40 mg and 80 mg or placebo in worldwide placebo-controlled clinical trials. The events cited reflect experience gained under closely monitored conditions in clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, those frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Only adverse events that were more frequent in a RELMAX treatment group compared to the placebo group with an incidence greater than or equal to 2% are included in Table 1.

TABLE 1: Adverse Event Incidence in Placebo-Controlled Migraine Clinical Trials: Events Reported by  $\geq$  2% Patients Treated with RELMAX and More than Placebo

| Adverse Event Type  | Placebo (n=988) | RELMAX 20 mg (n=431) | RELMAX 40 mg (n=1774) | RELMAX 80 mg (n=1932) |
|---|-----------------|----------------------|-----------------------|-----------------------|
| <b>ATYPICAL SENSATIONS</b>                                |                 |                      |                       |                       |
| Paresthesia   | 2%              | 3%                   | 3%                    | 4%                    |
| Flushing/feeling of warmth                                | 2%              | 2%                   | 2%                    | 2%                    |
| <b>PAIN</b>   |                 |                      |                       |                       |
| <b>Chest – tightness/pain/pressure</b>                    | 1%              | 1%                   | 2%                    | 4%                    |
| Abdominal – pain/discomfort/ stomach pain/cramps/pressure | 1%              | 1%                   | 2%                    | 2%                    |
| <b>DIGESTIVE</b>  |                 |                      |                       |                       |
| Dry mouth   | 2%              | 2%                   | 3%                    | 4%                    |
| Dyspepsia   | 1%              | 1%                   | 2%                    | 2%                    |
| Dysphagia – throat tightness/difficulty swallowing        | 0.2%            | 1%                   | 2%                    | 2%                    |
| Nausea  | 5%              | 4%                   | 5%                    | 8%                    |
| <b>NEUROLOGICAL</b>                                       |                 |                      |                       |                       |
| Dizziness   | 3%              | 3%                   | 6%                    | 7%                    |
| Somnolence  | 4%              | 3%                   | 6%                    | 7%                    |
| Headache  | 3%              | 4%                   | 3%                    | 4%                    |
| <b>OTHER</b>  |                 |                      |                       |                       |
| Asthenia  | 3%              | 4%                   | 5%                    | 10%                   |

RELMAX is generally well-tolerated. Across all doses, most adverse reactions were mild and transient. The frequency of adverse events in clinical trials did not increase with up to 2 doses of RELMAX were taken within 24 hours. The incidence of adverse events in controlled clinical trials was not affected by gender, age, or race of the patients. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (e.g., SSRIs, beta blockers, calcium channel blockers, tricyclic antidepressants), estrogen replacement therapy and oral contraceptives. Other Events Observed in Association With the Administration of RELMAX Tablets: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of RELMAX Tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N=4,719) exposed to RELMAX. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Frequent adverse events are those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare adverse events are those occurring in fewer than 1/1,000 patients. General: Frequent were back pain, chills and pain. Infrequent were face edema and malaise. Rare were abdomen enlarged, abscess, accidental injury, allergic reaction, fever, flu syndrome, haitosis, hernia, hypothermia, lab test abnormal, moniliasis, rheumatoid arthritis and shock. Cardiovascular: Frequent was palpitation. Infrequent were hypertension, migraine, peripheral vascular disorder and tachycardia. Rare were angina pectoris, arrhythmia, atrial fibrillation, AV block, bradycardia, hypotension, syncope, thrombophlebitis, cerebrovascular disorder, vasospasm and ventricular arrhythmia. Digestive: Infrequent were anorexia, constipation, diarrhea, eructation, esophagitis, flatulence, gastritis, gastrointestinal disorder, glossitis, increased salivation and liver function tests abnormal. Rare were gingivitis, hematemesis, increased appetite, rectal disorder, stomatitis, tongue disorder, tongue edema and tooth disorder. Endocrine: Rare were goiter, thyroid adenoma and thyroiditis. Hemie and Lymphatic: Rare were anemia, cyanosis, leukopenia, lymphadenopathy, monocytosis and purpura. Metabolic: Infrequent were creatine phosphokinase increased, edema, peripheral edema and thirst. Rare were alkaline phosphatase increased, bilirubinemia, hyperglycemia, weight gain and weight loss. Musculoskeletal: Infrequent were arthralgia, arthritis, arthrosis, bone pain, myalgia and myasthenia. Rare were bone neoplasm, joint disorder, myopathy and tenosynovitis. Neurological: Frequent were hypertension, hypesthesia and vertigo. Infrequent were abnormal dreams, agitation, anxiety, apathy, ataxia, confusion, depersonalization, depression, emotional lability, euphoria, hyperesthesia, hyperkinesia, incoordination, insomnia, nervousness, speech disorder, stupor, thinking abnormal and tremor. Rare were abnormal gait, amnesia, aphasia, catatonie reaction, dementia, diplopia, dystonia, hallucinations, hemiplegia, hyperalgesia, hypokinesia, hysteria, manic reaction, neuropathy, neurosis, oculogyric crisis, paralysis, psychotic depression, sleep disorder and twitching. Respiratory: Frequent was pharyngitis. Infrequent were asthma, dyspnea, respiratory disorder, respiratory tract infection, rhinitis, voice alteration and yawn. Rare were bronchitis, choking sensation, cough increased, epistaxis, hiccup, hyperpnea, laryngitis, sinusitis and sputum increased. Skin and Appendages: Frequent was sweating. Infrequent were pruritus, rash and skin disorder. Rare were alopecia, dry skin, eczema, eyelid dermatitis, maculopapular rash, psoriasis, skin discoloration, skin hypertrophy and urticaria. Special Senses: Infrequent was abnormal vision, conjunctivitis, ear pain, eye pain, lacrimation disorder, photophobia, taste perversion and tinnitus. Rare were abnormality of accommodation, dry eyes, ear disorder, eye hemorrhage, otitis media, parosmia and ptosis. Urogenital: Infrequent were impotence, polyuria, urinary frequency and urinary tract disorder. Rare were breast pain, kidney pain, leukorrhea, menorrhagia, menstrual disorder and vaginitis.

**DRUG ABUSE AND DEPENDENCE:** Although the abuse potential of RELMAX has not been assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received RELMAX in clinical trials or their extensions. The 5-HT<sub>1</sub> agonists, as a class, have not been associated with drug abuse.

**OVERDOSAGE:** No significant overdoses in premarketing clinical trials have been reported. Volunteers (N=21) have received single doses of 120 mg without significant adverse effects. Daily doses of 160 mg were commonly employed in Phase II trials. Based on the pharmacology of the 5-HT<sub>1</sub> agonists, hypertension or other more serious cardiovascular symptoms could occur on overdose. The elimination half-life of eletriptan is about 4 hours and therefore monitoring of patients after overdose with eletriptan should continue for at least 20 hours, or longer should symptoms or signs persist. There is no specific antidote to eletriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentration of eletriptan.

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