

# CorCap Helps Even Without Mitral Valve Surgery

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PHILADELPHIA — Surgical placement of the CorCap cardiac support device led to significant but modest improvements in heart failure patients who did not undergo concurrent mitral valve surgery.

The moderate benefit in patients with severe heart failure who were not otherwise scheduled for heart surgery left it unclear exactly which types of patients

would benefit most from having a CorCap mesh bag surgically placed around their heart, Mariell L. Jessup, M.D., said at the annual meeting of the International Society for Heart and Lung Transplantation.

Further studies are needed to better define the best candidates for placement of the cardiac support device (CSD), said Dr. Jessup, medical director of the heart failure/transplant program at the University of Pennsylvania, Philadelphia.

Last November, at the annual scientific

sessions of the American Heart Association, researchers presented the results from a randomized, controlled study that compared the safety and efficacy of this CSD with conventional therapy in a total of 300 patients with severe heart failure. In the overall group, which included 193 patients who had concurrent mitral valve repair or replacement and 107 patients who did not undergo a mitral valve procedure, placement of the CorCap was associated with significant reductions in the

need for subsequent cardiac procedures, improved left ventricular shape and function, and improved quality of life during a median follow-up of 22 months. The study was sponsored by Acorn Cardiovascular, the company that makes the CorCap.

Dr. Jessup and the other investigators in the study are paid consultants to Acorn. On the basis of these findings, Acorn has submitted an application to the Food and Drug Administration to approve the CorCap for use in patients with advanced heart failure.

Additional analyses of the results broke the study into its two parts: the patients who also had mitral valve repair, and those who did not. Dr. Jessup presented the sub-study results for patients who did not have concurrent mitral valve treatment, the subgroup that provides “a more obvious way to test the efficacy of the cardiac support device,” she said, because the absence of additional procedures provides “the purest test of efficacy.” In this subgroup, 57 patients who were on optimal medical therapy underwent cardiac surgery to place the CSD, while a group of 50 control patients continued on optimal medical therapy only.

The effect of the cardiac support device in patients without mitral valve repair was very similar to the results seen in the entire study. In this subgroup, placement of the CorCap led to an improvement in a composite efficacy index in 35% of patients, compared with 19% who improved in the control arm, a statistically significant difference.

This composite, the primary end point for the study, included death, changes in heart failure severity, and the need for cardiac procedures such as heart transplant, placement of a ventricular assist device, or placement of a cardiac resynchronization pacemaker. In this substudy, as in the entire study group, the difference in this end point between the control and intervention arms was mostly due to differences in the need for subsequent cardiac procedures. There was no difference seen in survival.

Treatment with the CSD also led to favorable changes in left ventricular size in this subgroup, although the changes were smaller than in the patients who also had mitral valve repair.

In this subgroup, the heart surgery used to place the CSD led to an acute increase in mortality: five patients died within the first 30 days in the CorCap group, compared with no deaths in the control group. But this difference disappeared during longer follow-up. The initial surgery also led to an early surge in serious adverse events, but again these balanced out during longer follow-up, Dr. Jessup said. ■

**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.

## RELAPX<sup>®</sup> (eletriptan hydrobromide) Tablets

### BRIEF SUMMARY OF PRESCRIBING INFORMATION

**CONTRAINDICATIONS:** RELAPX 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). RELAPX 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). RELAPX Tablets should not be given to patients with peripheral vascular disease including (but not limited to) ischemic bowel disease (see WARNINGS). Because RELAPX Tablets may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS). RELAPX Tablets should not be administered to patients with hemiplegic or basilar migraine. RELAPX Tablets should not be used within 24 hours of treatment with another 5-HT<sub>1B/1D</sub> agonist, an ergotamine-containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide. RELAPX Tablets should not be used in patients with known hypersensitivity to eletriptan or any of its inactive ingredients. RELAPX Tablets should not be given to patients with severe hepatic impairment.

**WARNINGS:** RELAPX 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, troleanomycin, clarithromycin, ritonavir, and nelfinavir. Eletriptan should not be used within 72 hours of 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>1B/1D</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 satisfactory clinical evidence that the patient is reasonably free of cardiac symptoms. Consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of RELAPX Tablets. In these patients with risk factors, it is recommended that patients who are intermittent long-term users of 5-HT<sub>1B/1D</sub> agonists including RELAPX Tablets, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use RELAPX 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>1B/1D</sub> Agonists: Serious adverse cardiac events, including acute myocardial infarction and sudden cardiac death, have been reported with the use of 5-HT<sub>1B/1D</sub> agonists. Because cardiac events can occur in the absence of clinical symptoms, consideration should be given to 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>1B/1D</sub> Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT<sub>1B/1D</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 cerebrovascular events (e.g., stroke, hemorrhage, and transient ischemic attack). Other Vasospasm-Related Events: 5-HT<sub>1B/1D</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>1B/1D</sub> agonists. Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasion in patients receiving 5-HT<sub>1B/1D</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>1B/1D</sub> agonists. The effect was more pronounced in dialyzed 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>1B/1D</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

**PRECAUTIONS:** General: As with other 5-HT<sub>1B/1D</sub> agonists, sensations of tightness, pain, pressure and heaviness have been reported after treatment with eletriptan in the precordium, throat, and jaw, and 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>1B/1D</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>1B/1D</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>max</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 ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic 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>max</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>1B/1D</sub> agonists. If concomitant treatment with eletriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. Other 5-HT<sub>1B/1D</sub> agonists: Concomitant use of other 5-HT<sub>1B/1D</sub> agonists within 24 hours of RELAPX treatment is not recommended (see CONTRAINDICATIONS). Drug/Laboratory Test Interactions: RELAPX 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* mouse 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 fused sternebrae 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 RELAPX is administered to nursing women. Pediatric Use: Safety and effectiveness of RELAPX Tablets in pediatric patients have not been established; therefore, RELAPX is not recommended for use in patients under 18 years of age. The efficacy of RELAPX 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>1B/1D</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 RELAPX in short-term placebo-controlled trials, the most common adverse events reported with treatment with RELAPX 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 of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Only adverse events that were more frequent in a RELAPX treatment group compared to the placebo group with an incidence greater than or equal to 2% are included in Table 1.

TABLE 1. Adverse Experience Incidence in Placebo-Controlled Migraine Clinical Trials: Events Reported by ≥ 2% Patients Treated with RELAPX and More Than Placebo

Adverse Event Type	Placebo (n=988)	RELAPX 20 mg (n=431)	RELAPX 40 mg (n=1774)	RELAPX 80 mg (n=1932)
<b>ATYPICAL SENSATIONS</b>				
Paresthesia	2%	3%	3%	4%
Flushing/feeling of warmth	2%	2%	2%	2%
<b>PAIN AND PRESSURE SENSATIONS</b>				
Headache	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%

RELAPX 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 when up to 2 doses of RELAPX 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 RELAPX 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 RELAPX Tablets in the 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 RELAPX. 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 1/1000 patients and rare adverse events are those occurring in fewer than 1/1000 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, hiccups, hives, 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. Hemic 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 vertigo, hyperesthesia 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, catatonic reaction, dementia, diplopia, dystonia, hallucinations, hemiplegia, hyperalgesia, hypokinesia, hysteria, manic reaction, neuropathy, neurosis, oculogyric crisis, paralysis, psychotic depression, sleep disorder and twitching. Respiratory: Frequent were pharyngitis. Infrequent were asthma, dyspnea, respiratory disorder, respiratory tract infection, rhinitis, voice alteration and yawn. Rare were bronchitis, choking sensation, cough increased, epistaxis, hiccups, hyperventilation, laryngitis, sinusitis and sputum increased. Skin and Appendages: Frequent was sweating. Infrequent were pruritus, rash and skin disorder. Rare were alopecia, dry skin, eczema, exfoliative 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 RELAPX has not been assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received RELAPX in clinical trials or their extensions. The 5-HT<sub>1B/1D</sub> agonists, as a class, have not been associated with drug abuse.

**OVERDOSEAGE:** 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 III trials. Based on the pharmacology of the 5-HT<sub>1B/1D</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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