

DATA SHEET

RELPAX[®]

Eletriptan hydrobromide

20 mg, 40mg, and 80 mg tablets

Presentation

RELPAX film-coated round tablets containing eletriptan hydrobromide equivalent to 20, 40 or 80 mg eletriptan are supplied for oral administration. 20 mg tablets are orange, round, film-coated tablets, with "Pfizer" on one side and "REP20," on the other side. 40 mg tablets are orange, round, film-coated tablets, with "Pfizer" on one side and "REP40" on the other side. 80 mg tablets are orange, round, film-coated tablets, with "Pfizer" on one side and "REP80" on the other side.

Each RELPAX tablet contains the following inactive ingredients: cellulose-microcrystalline, lactose, croscarmellose sodium, magnesium stearate, titanium dioxide CI 77891, hypromellose, glycerol triacetate and sunset yellow FCF CI 15985.

Uses

Actions

Eletriptan is a potent and selective agonist at the vascular 5-HT_{1B} and neuronal 5-HT_{1D} receptors. Eletriptan also exhibits high affinity for the 5-HT_{1F} receptor which may contribute to its activity against migraine.

The human 5-HT_{1B} receptor mediates constriction of intracranial blood vessels. Dilation of these vessels is thought to be one of the underlying mechanisms of migraine.

The human 5-HT_{1D} receptor is predominantly located presynaptically on the peripheral synapses of the trigeminal nerve. Recent studies have also located both the 5-HT_{1B} and 5-HT_{1F} receptors to the human trigeminal ganglia. Inhibition of the release of neuropeptides via activation of these receptors may contribute to the efficacy of eletriptan.

Eletriptan has modest affinity for recombinant human 5-HT_{1A}, 5-HT_{2B}, 5-HT_{1E} and 5-HT₇ receptors. It has no significant affinity for or pharmacological activity at a range of other receptors (beta-adrenoceptors, adenosine A1, dopamine [D1 and D2], muscarinic and opioid receptors) and calcium channel dihydropyridine binding sites.

In animal studies eletriptan shows greater selectivity for the carotid as opposed to the coronary and femoral vascular beds compared to sumatriptan. Furthermore, eletriptan has been shown to inhibit neurogenic inflammation in the dura mater of animals. Both the ability of eletriptan to constrict intracranial blood vessels and its inhibitory action on neurogenic inflammation may contribute to its anti-migraine efficacy in man.

Further Information on Clinical Trials

RELPAx rapidly relieved migraine headache and its associated symptoms in six randomised, double blind, placebo controlled studies involving 5,362 patients aged 17 to 78. All six studies used 40 mg and 80 mg doses. Two of these studies included a 20 mg dose.

In all six studies, randomised patients treated their headaches as outpatients. Patients treated in these six studies were predominantly female (85%) and Caucasian (94%) with a mean age of 39.8 years. Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 4 hours after dosing. Associated symptoms such as nausea, vomiting, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post dose. A second dose of RELPAx Tablets or other medication was allowed 2 to 24 hours after the initial treatment for both persistent and recurrent headaches. The incidence and time to use of these additional treatments were also recorded. In all studies, the effect of RELPAx was compared to placebo in the treatment of a single migraine attack. Four of the six studies assessed 3 attacks.

In all six studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving RELPAx Tablets at all doses compared to those who received placebo. The two-hour response rates from these controlled clinical studies are summarised in Table 1 and Figure 1.

	Placebo	RELPAx 20 mg	RELPAx 40 mg	RELPAx 80 mg	sumatriptan 25 mg	sumatriptan 50 mg	sumatriptan 100 mg	Cafergot®
Study 1	23.8% (n=126)	54.3%* (n=129)	65.0%* (n=117)	77.1%* ³ (n=118)	NA	NA	54.8 (n=115)	NA
Study 2	19.0% (n=232)	NA	61.6%* (n=430)	64.6%* (n=446)	NA	NA	NA	NA
Study 3	21.7% (n=276)	47.3%* (n=273)	61.9%* (n=281)	58.6%* (n=290)	NA	NA	NA	NA
Study 4	39.5% (n=86)	NA	62.3%* (n=175)	70.0%* ^{1,2} (n=170)	52.6% (n=171)	56.0% (n=175)	NA	NA
Study 5	20.6% (n=102)	NA	53.9%* ⁴ (n=206)	67.9%* ⁴ (n=209)	NA	NA	NA	33.0% (n=197)
Study 6	31.3% (n=80)	NA	63.9%* ^{2,3} (n=169)	66.9%* ^{2,3} (n=160)	NA	50.0% (n=176)	53.1% (n=160)	NA

* stat sig vs placebo

¹ stat sig vs sumatriptan 25mg

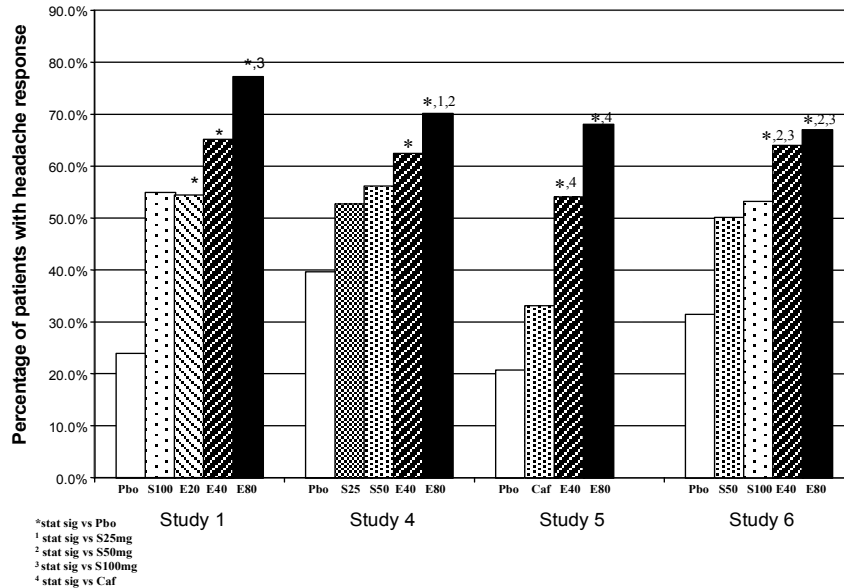
² stat sig vs sumatriptan 50mg

³ stat sig vs sumatriptan 100mg

⁴ stat sig vs Cafergot®

NA - Not Applicable

Figure 1: Percentage of Patients with Headache Response 2 Hours Following Treatment in Comparative Studies



In controlled clinical trials, patients treated with RELPAX had significantly higher response rates as early as 30 minutes following oral dosing compared to those on placebo.

Comparisons of drug performance based upon results obtained in different clinical trials may not always be reliable. Because studies are generally conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may therefore be expected to vary considerably from study to study. However, the eletriptan clinical development program was designed to minimise these potential effects. The cumulative headache response up to 4 hours following treatment is depicted in Figure 2.

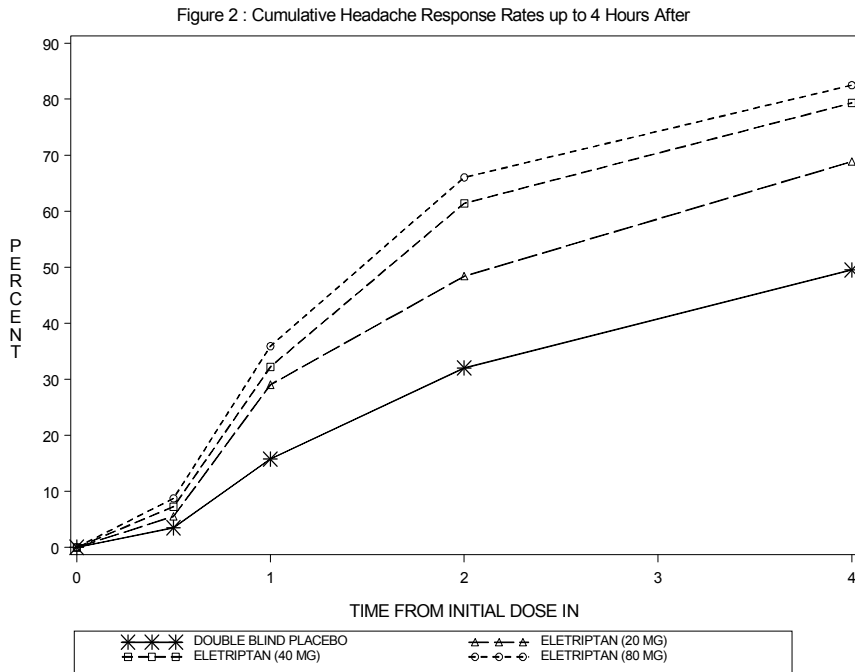
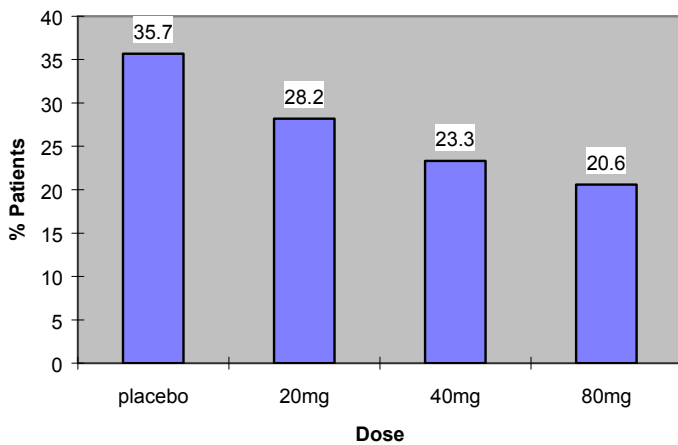


Figure 2 shows the cumulative headache response rate following treatment with RELPAX.

RELPA was shown to be significantly superior to placebo in reducing the incidence of photophobia, phonophobia, vomiting, nausea and functional impairment associated with migraine. Patients who responded to eletriptan had low rates of recurrence that decreased in a dose related manner (see Figure 3).

Figure 3: Headache Recurrence Rate Within 24 Hours



In a combined analysis of similarly designed, controlled clinical trials, a second RELPA dose of the same strength has been shown to be effective in treating those patients who initially responded but whose headaches recurred within 24 hours.

RELPAx is effective regardless of baseline severity of headache, duration of attack, race, sex or age of the patient, concomitant use of oestrogen replacement therapy/oral contraceptives or frequently used migraine prophylactic drugs (e.g., beta-blockers).

RELPAx was also shown to be effective in treating migraines that occur between one day before and four days after the onset of menses. A clear dose-response relationship for RELPAx has been demonstrated in controlled clinical trials.

Pharmacokinetics

Absorption

Eletriptan is rapidly and well absorbed across the gastrointestinal tract (at least 81%) after oral administration. Absolute oral bioavailability across males and females is approximately 50%. The mean T_{max} occurs approximately 1.5 hours after oral dosing. Linear pharmacokinetics were demonstrated over the clinical dose range (20-80 mg).

The AUC and C_{max} of eletriptan were increased by approximately 20-30% following oral administration with a high fat meal. As with other 5HT₁ receptor agonists the rate and extent of eletriptan's absorption following oral administration is reduced (AUC by 30%, T_{max} increased to 2.8 hours) during a migraine attack.

Following repeated doses (20 mg three times daily) for 5 - 7 days, the pharmacokinetics of eletriptan remain linear and accumulation was predictable. On multiple dosing of larger doses (40mg three times daily and 80mg twice daily), the drug accumulation over 7 days was greater than predicted (approximately 40%).

Distribution

The volume of distribution of eletriptan following intravenous administration is 138L indicating distribution into the tissues. Eletriptan is only moderately protein bound (approximately 85%).

Metabolism

In-vitro studies indicate that eletriptan is primarily metabolised by cytochrome P-450 enzyme CYP3A4. This finding is substantiated by increased plasma concentrations of eletriptan following co-administration with erythromycin, a known selective and potent CYP3A4 inhibitor. *In-vitro* studies also indicate a small involvement of CYP2D6 although clinical studies indicate there is no clinically relevant effect of CYP2D6 polymorphism on the pharmacokinetics of eletriptan.

Two major circulating metabolites have been identified as significantly contributing to plasma radioactivity following administration of ¹⁴C-labelled eletriptan. The metabolite formed by N-deoxidation has demonstrated no activity in animal models *in vitro*. The metabolite formed by N-demethylation has been demonstrated to have similar activity to eletriptan in animal models *in vitro*. A third area of radioactivity in plasma has not been formally identified, but is most likely to be a mixture of hydroxylated metabolites which have also been observed excreted in urine and faeces.

The plasma concentrations of the N-demethylated active metabolite are only 10-20% of that of the parent drug and so it would not be expected to contribute to the therapeutic action of eletriptan.

Elimination

Mean total plasma clearance (CL) of eletriptan following intravenous administration is 36 L/h with a resultant plasma half-life of approximately 4 hours. The mean renal clearance (CL_R) following oral administration is approximately 3.9 L/h. Non-renal clearance accounts for approximately 90% of the total clearance indicating that eletriptan is eliminated primarily by metabolism.

Pharmacokinetics in Special Patient Groups

Sex

A meta analysis across clinical pharmacology studies and a population pharmacokinetic analysis of clinical trial data indicate that sex does not have any clinically significant influence on plasma concentrations of eletriptan.

Elderly (over 65 years of age)

The pharmacokinetics of eletriptan are generally unaffected by age. Though not statistically significant, there is a small reduction (16%) in clearance (CL) associated with a statistically significant increased half life (from approximately 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). An analysis of the safety database did not show evidence of an age effect on the incidence of adverse events.

Adolescents (12-17 years of age)

The pharmacokinetics of eletriptan (40 mg and 80 mg) in adolescent migraine patients dosed between attacks were similar to those seen in healthy adults.

Children (7-11 years of age)

The clearance of eletriptan is unchanged in children relative to adolescents. However the volume of distribution is lower in children resulting in higher plasma levels than would be predicted following the same dose in adults.

Hepatic Insufficiency

Subjects with hepatic impairment (Child-Pugh A and B) demonstrated a statistically significant increase in both AUC (34%) and half life. There was a small increase in C_{max} (18%). This small change in exposure is not considered clinically relevant.

Renal Insufficiency

Subjects with mild (creatinine clearance 61-89 mL/min), moderate (creatinine clearance 31-60 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment did not have any statistically significant alterations in the C_{max}, AUC, T_{1/2} or plasma protein binding of eletriptan. In renally impaired subjects, eletriptan increased blood pressure to a larger degree than in matched healthy subjects.

Indications

Acute treatment of migraine headache, with or without aura.

Dosage and Administration

RELPAx tablets should be taken as early as possible after the onset of migraine headache but they are also effective if taken at a later stage.

RELPAx tablets should not be used prophylactically.

The tablets should be swallowed whole with water.

Adults (18-65 years of age)

The recommended initial dose is 40 mg.

If headache returns within 24 hours

If after an initial response migraine headache recurs within 24 hours, an additional dose of the same strength of RELPAx has been shown to be effective in treating the recurrence. If a second dose is required, it should not be taken within 2 hours of the initial dose.

If no response is obtained

If a patient does not achieve a headache response within 2 hours of the first dose of RELPAx, a second dose should not be taken for the same attack as clinical trials have not adequately established efficacy with the second dose. Clinical trials show that the majority of patients who do not respond to the treatment of an attack will respond to the treatment of a subsequent attack.

Patients who do not obtain satisfactory efficacy with 40 mg may be effectively treated with 80 mg in a subsequent migraine attack.

The maximum daily dose should not exceed 160 mg.

Elderly (over 65 years of age)

Safety and efficacy in patients over 65 years of age have not been systematically evaluated due to a small number of such patients in clinical trials. Blood pressure effects may be more marked in this population than in younger adults (see **Warnings and Precautions**).

Adolescents (12-17 years of age)

In a clinical trial in adolescents, a high placebo response rate was observed. The efficacy of RELPAx has not been established in this population and its use is therefore not recommended in this age group. The safety profile of eletriptan was similar to that observed in adults.

Children (6-11 years of age)

The safety and efficacy of RELPAx in children have not been evaluated. Therefore the use of RELPAx is not recommended in this age group (see **Pharmacokinetics**).

Use in Hepatic and Renal Impairment

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. As RELPAx has not been studied in patients with severe hepatic impairment, it is contraindicated in these patients (see **Pharmacokinetics**).

Renal Impairment

As the blood pressure effects of RELPAX are amplified in renal impairment (see **Warnings and Precautions**), doses higher than 40 mg should be used with caution (see **Pharmacokinetics**).

Contraindications

Hypersensitivity to any component of the preparation.

Severe hepatic impairment.

As with other 5-hydroxytryptamine type 1 (5-HT₁) receptor agonists, the following contraindications are based on the pharmacodynamic properties of these drugs:

Patients with uncontrolled hypertension.

Patients with confirmed coronary heart disease, including ischaemic heart disease (angina pectoris, previous myocardial infarction or confirmed silent ischaemia), objective or subjective symptoms of ischaemic heart disease or Prinzmetal's angina.

Patients with peripheral vascular disease.

Patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Administration of ergotamine, or derivatives of ergotamine (including methysergide) within 24 hours before or after treatment with eletriptan (see **Drug Interactions**).

Concomitant administration of other 5-HT₁ receptor agonists.

Warnings and Precautions

Eletriptan use with potent CYP3A4 inhibitors, e.g. ketoconazole, itraconazole, erythromycin, clarithromycin and protease inhibitors (ritonavir, indinavir and nelfinavir), is not recommended.

As with other 5HT₁ receptor agonists, RELPAX should be used only where a clear diagnosis of migraine has been established. RELPAX is not indicated for the management of hemiplegic, ophthalmoplegic, or basilar migraine.

As with other 5HT₁ receptor agonists, RELPAX should not be given for the treatment of 'atypical' headaches, i.e. headaches which may be related to a possibly serious condition (stroke, aneurysm rupture) where cerebrovascular vasoconstriction may be harmful.

Cardiovascular evaluation prior to commencement of treatment with eletriptan is recommended for patients in whom cardiovascular disease is likely or in patients at risk of cardiovascular disease (see **Contraindications**).

Eletriptan has not been systematically evaluated for use in patients with heart failure. As with other 5-HT₁ receptor agonists, use in these patients is not recommended.

Within the clinical dose range, slight and transient increases in blood pressure have been seen with eletriptan doses of 60 mg or greater. The effect was more pronounced in renally impaired and elderly subjects. However, this has not been associated with clinical sequelae in the clinical trial program.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Carcinogenicity

There was no indication of a carcinogenic potential for humans in lifetime carcinogenicity studies, 104 weeks in duration, which were carried out in mice and rats. In mice, eletriptan was given in the diet at doses of up to 400 mg/kg/day. There was an increase in the incidence of liver adenomas in high dose males. The exposure at that dose was more than 59 times the exposure in humans receiving the recommended dose of 40 mg. In rats, the high dose of 75 mg/kg was more than 10 times the human exposure at the 40 mg dose. There was no evidence of an increase in tumours related to eletriptan administration.

Mutagenicity

Bacterial and in-vivo mutagenicity tests were uniformly negative.

Impairment of Fertility

Studies of male and female rats in which eletriptan was administered prior to and during mating and up to implantation have shown no impairment of fertility at doses up to 50 mg/kg. Exposure at this dose was approximately 26 times exposure at the recommended human dose of 40 mg.

Use in Pregnancy

The safety of eletriptan in pregnant women has not been established. There is no evidence of teratogenicity in animal studies. Administration of RELPAX should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus.

Use in Lactation

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 0.02% of the dose. Therefore caution should be exercised when considering the administration of RELPAX to women who are breast-feeding. Infant exposure can be minimised by avoiding breast-feeding for 24 hours after treatment.

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. As RELPAX has not been studied in patients with severe hepatic impairment, it is contraindicated in these patients (see **Pharmacokinetics**).

Renal Impairment

As the blood pressure effects of RELPAX are amplified in renal impairment, doses higher than 40 mg should be used with caution (see **Pharmacokinetics**).

Use in Children

Children (6-11 years of age)

The safety and effectiveness of eletriptan in children have not been evaluated. Therefore the use of RELPAX is not recommended in this age group (see **Pharmacokinetics**).

Adolescents (12-17 years of age)

In a clinical trial in adolescents, a high placebo response rate was observed. The efficacy of RELPAX has not been established in this population and its use is therefore not recommended in this age group. The safety profile of eletriptan was similar to that observed in adults.

Use in the Elderly (over 65 years of age)

Safety and efficacy in patients over 65 years of age have not been systematically evaluated due to a small number of such patients in clinical trials. Blood pressure effects may be more marked in this population than in younger adults.

Adverse Effects

Eletriptan has been administered in clinical trials to more than 5000 patients. Eletriptan is generally well tolerated. Adverse reactions were usually transient and mild to moderate in nature and resolved spontaneously without additional treatment. The incidence and severity of adverse events seen in patients who took two doses of the same strength to treat a single attack were similar to these observed in patients who only took one dose.

The following adverse reactions (with an incidence $\geq 1\%$ and higher than placebo) were reported in patients treated with therapeutic doses in clinical trials:

Autonomic Nervous: Dry mouth, sweating.

Body as a Whole: Asthenia, chest symptoms (pain, tightness, pressure), pain, back pain, chills.

Cardiovascular: Sensation of warmth or flushing, palpitation, tachycardia.

Central & Peripheral Nervous System: Somnolence, dizziness, paraesthesia, hypertonia, headache, hypoesthesia, vertigo.

Gastrointestinal: Abdominal pain, nausea, throat tightness, dyspepsia.

Musculoskeletal: Myasthenia, myalgia.

Respiratory: Pharyngitis.

Some of the symptoms reported as adverse reactions may be part of the migraine attack. The common adverse events seen with eletriptan are typical of adverse events reported with 5-HT₁ agonists as a class.

Drug Interactions

Effect of Other Drugs on Eletriptan

In the pivotal clinical trials of eletriptan no evidence of interaction with beta-blockers, tricyclic antidepressants, selective serotonin re-uptake inhibitors and flunarizine was reported but data from formal clinical interaction studies with these medicinal products are not available (other than propranolol, see below)

Population pharmacokinetic analysis of clinical studies has suggested that the following medicinal products (beta-blockers, tricyclic antidepressants, selective serotonin re-uptake inhibitors, oestrogen based hormone replacement therapy, oestrogen containing oral contraceptives and calcium channel blockers) are unlikely to have an effect on the pharmacokinetic properties of eletriptan.

Eletriptan is not a substrate for MAO. There is no expectation of a pharmacokinetic interaction between eletriptan and MAO inhibitors, therefore no formal interaction study has been undertaken.

In clinical studies with propranolol (160 mg), verapamil (480 mg) and fluconazole (100 mg) the C_{max} of eletriptan was increased 1.1 fold, 2.2 fold and 1.4 fold respectively. The increase in eletriptan's AUC being 1.3 fold, 2.7 fold and 2.0 fold respectively. These effects are not considered clinically significant as there were no associated increased in blood pressure or adverse events compared to administering eletriptan alone.

In clinical studies with erythromycin (1000 mg) and ketoconazole (400 mg), specific and potent inhibitors of CYP3A4, significant increases in eletriptan C_{max} (2 and 2.7 fold) and AUC (3.6 and 5.9 fold) respectively, were observed. This increased exposure was associated with an increase in eletriptan $t_{1/2}$ from 4.6 to 7.1 hours with erythromycin and from 4.8 to 8.3 hours with ketoconazole (see **Pharmacokinetic Properties**). Therefore, eletriptan should not be used together with potent CYP3A4 inhibitors, e.g. ketoconazole, itraconazole, erythromycin, clarithromycin and protease inhibitors (ritonavir, indinavir and nelfinavir).

In clinical studies with oral caffeine/ergotamine administered 1 and 2 hours after eletriptan, minor though additive increases in blood pressure were observed which are predictable based on the pharmacology of the two drugs. Therefore, it is recommended that either ergotamine-containing or ergot-type medications (like dihydroergotamine) should not be taken within 24 hours of eletriptan dosing. Conversely, at least 24 hours should elapse after the administration of an ergotamine-containing preparation before eletriptan is given.

The effect of eletriptan on other drugs

There is no *in-vitro* or *in-vivo* evidence that clinical doses of eletriptan will inhibit or induce cytochrome P450 enzymes, including CYP3A4 drug metabolising enzymes. Therefore, it is considered that eletriptan is unlikely to cause clinically important drug interactions mediated by these enzymes.

Effects on Ability to Drive and Use of Machines

Migraine or treatment with some 5-HT₁ receptor agonists, including eletriptan, may cause drowsiness or dizziness in some patients. Therefore caution is recommended in patients performing skilled tasks, (e.g. driving or operating machinery) during the migraine attack and following administration of RELPAX.

Drug Abuse and Potential

The abuse potential of RELPAX has not been assessed in clinical trials.

Drug/Laboratory Test Interactions

RELPAX tablets are not known to interfere with commonly employed clinical laboratory tests.

Overdosage

Subjects have received single doses of 120 mg without significant adverse effects. However hypertension or other more serious cardiovascular effects could occur after overdose.

In cases of overdose, standard supportive measures should be adopted as required. The elimination half-life of eletriptan is about 4 hours, and therefore monitoring of patients and provision of general supportive therapy after overdose with eletriptan should continue for at least 20 hours or while signs and symptoms persist.

It is unknown what effect haemodialysis or peritoneal dialysis has on the serum concentrations of eletriptan.

Pharmaceutical Precautions

Store below 30°C.

Medicine Classification

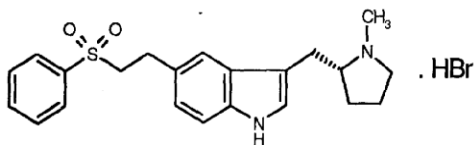
Prescription Medicine

Package Quantities

RELPAX film-coated round tablets containing eletriptan hydrobromide equivalent to 20 mg, 40 mg or 80 mg eletriptan are packaged in blister packs of 2, 4 and 6 tablets.

Further Information

RELPAX™ (eletriptan) tablets contain eletriptan hydrobromide, which is a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist. Eletriptan is chemically designated as (R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1H-indole hydrobromide, and it has the following chemical structure:



The empirical formula is C₂₂H₂₆N₂O₂S . HBr, representing a molecular weight of 463.43. Eletriptan is a white to pale coloured powder that is readily soluble in water.

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Date of Preparation

22 April 2003