AUSTRALIAN PRODUCT INFORMATION

RELPAX®

(eletriptan hydrobromide) tablets

1 NAME OF THE MEDICINE

Eletriptan hydrobromide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RELPAX 40 mg tablets contain eletriptan hydrobromide equivalent to 40 mg eletriptan.

RELPAX 80 mg tablets contain eletriptan hydrobromide equivalent to 80 mg eletriptan.

Excipients with known effect: contains sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

RELPAX 40 mg tablets are orange, standard round convex, film-coated tablets debossed with "REP 40" on one side and "VLE" on the other.

RELPAX 80 mg tablets are orange, standard round convex, film-coated tablets debossed with "REP 80" on one side and "VLE" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Acute treatment of migraine headache with or without aura.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults (18-65 years of age)

In controlled clinical trials, single doses of 20 mg, 40 mg and 80 mg were effective for the acute treatment of migraine in adults. A greater proportion of patients had a response following a 40 mg or 80 mg dose than following a 20 mg dose. The recommended initial dose is 40 mg. The maximum single dose is 80 mg.

If the initial dose is ineffective, controlled clinical trials have not shown a benefit of a second dose to treat the same attack. However, if the headache returns following initial improvement, there is evidence to suggest that a repeat dose may be beneficial. If a second dose is required, it should not be taken within 2 hours of the initial dose.

The maximum daily dose should not exceed 160 mg.

Method of administration

Oral 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.

Dosage adjustment

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 5.2 PHARMACOKINETIC PROPERTIES).

Renal Impairment

There is no specific study to demonstrate the clinical safety of RELPAX in renally impaired patients. Pharmacokinetic study of a single 80 mg dose showed a two-fold increase of T_{max} in patients with severe renal impairment when compared to normal subjects, although other parameters were not affected. In some subjects with renal impairment, an elevation in blood pressure was observed. A dose of greater than 40 mg should be administered with caution (see 5.2 PHARMACOKINETIC PROPERTIES and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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. As effects on blood pressure may be more marked in elderly patients than in younger adults, doses higher than 40 mg should be used with caution.

Use in children (below 17 years of age)

Although the pharmacokinetics is similar to those seen in healthy adults (see 5.2 PHARMACOKINETIC PROPERTIES), efficacy of eletriptan has not been proven below 17 years of age. Therefore, the use of RELPAX is not recommended in children below 17 years of age.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of the preparation.

Severe hepatic impairment.

Other contraindications based on the pharmacodynamic properties of 5-HT_1 receptor agonists:

Patients with uncontrolled hypertension.

Patients with confirmed coronary heart disease, including ischaemic heart disease (angina pectoris, previous myocardial infarction or confirmed silent ischaemia).

Patients with coronary artery vasospasm, 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 4.5 INTERACTIONS WITH OTHER MEDICINE AND OTHER FORMS OF INTERACTIONS).

Concomitant administration of other 5-HT_1 receptor agonists.

Within 48 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, erythromycin, clarithromycin, amprenavir, ritonavir, indinavir, saquinavir, nelfinavir and nefazodone.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other 5-HT_1 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.

5-HT_1 receptor agonists including 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 4.3 Contraindications).

Eletriptan has not been systematically evaluated for use in patients with heart failure. As with other 5-HT_1 receptor agonists, use in these patients is not recommended.

The effect of eletriptan on the systemic, pulmonary and coronary circulation was examined in patients undergoing diagnostic coronary arteriography. Coronary artery diameter decreased by a mean of 3%, 15 minutes after the end of intravenous infusion of eletriptan (50 microgram/kg). Nevertheless, caution is advised when administering RELPAX to patients at risk of myocardial ischaemia.

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. In a small sample, open, parallel group, clinical pharmacology study, a single oral 80 mg dose was administered to normal (n=6) subjects and to subjects with severe (n=5), moderate (n=5) and mild (n=6) degrees of renal impairment. The maximum increase from baseline in subjects with renal impairment ranged from 14 to 17 mmHg for systolic blood pressure or 14 to 21 mmHg for diastolic blood pressure and was greater than that observed in the normal subjects (3 to 4 mmHg). This was not statistically significant for systolic BP (p=0.11) but was statistically significant for diastolic BP (p=0.011).

Co- administration of eletriptan with other drugs having serotonergic activity, such as SNRIs and SSRIs, should be undertaken with caution due to reports of the development of serotonin syndrome in isolated cases of concomitant use of a triptan with other serotonergic drugs (see 4.5 INTERACTIONS WITH OTHER MEDICINE AND OTHER FORMS OF INTERACTIONS).

Excessive use of any anti-migraine medicinal product can lead to daily chronic headaches. Overuse of all triptans has been reported primarily in patients with chronic daily headache.

Use in Hepatic Impairment [if required]

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 5.2 PHARMACOKINETIC PROPERTIES).

Use in Renal Impairment [if required]

There is no specific study to demonstrate the clinical safety of RELPAX in renally impaired patients. Pharmacokinetic study of a single 80 mg dose showed a two-fold increase of T_{max} in patients with severe renal impairment when compared to normal subjects, although other parameters were not affected. In some subjects with renal impairment, an elevation in blood pressure was observed. A dose of greater than 40 mg should be administered with caution (see 5.2 PHARMACOKINETIC PROPERTIES and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in the Elderly

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. As effects on blood pressure may be more marked in elderly patients than in younger adults, doses higher than 40 mg should be used with caution.

Paediatric Use

Although the pharmacokinetics is similar to those seen in healthy adults (see 5.2 PHARMACOKINETIC PROPERTIES), efficacy of eletriptan has not been proven below 17 years of age. Therefore, the use of RELPAX is not recommended in children below 17 years of age.

Effects on Laboratory Tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other drugs on eletriptan

There is no evidence that concomitant use of migraine prophylactic medications (e.g. beta-blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, methysergide and flunarizine) has any effect on the efficacy or undesired effects of eletriptan.

In clinical studies with propranolol, the exposure of eletriptan was increased by 33% (AUC). This effect is not considered clinically significant as there was no associated increase in blood pressure or adverse events compared to administering eletriptan alone.

In clinical studies with oral Cafergot (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 or methysergide) 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.

CYP3A4 Inhibitors:

In vitro studies have shown that RELPAX is metabolized by the CYP3A4 enzyme. An *in vivo* clinical study demonstrated a 2.7-fold increase in C_{max} and a 5.9-fold increase in the AUC of eletriptan when combined with ketoconazole. The half-life increased from 5 hours to 8 hours and the T_{max} increased from 2.8 hours to 5.4 hours. Another clinical study demonstrated a 2-fold increase in C_{max} and a 4-fold increase in AUC when erythromycin was co-administered with eletriptan. Both are selective and potent inhibitors of CYP3A4. (see 5.2 PHARMACOKINETIC PROPERTIES). Therefore, eletriptan should not be used within 48 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, amprenavir, ritonavir, indinavir, saquinavir, nelfinavir and nefazodone (see 4.3 CONTRAINDICATIONS).

Concomitant use of the herbal remedy St John's Wort (Hypericum perforatum) in patients receiving triptans should be avoided since there is a possibility of serotonergic potentiation.

Population pharmacokinetic analysis of clinical studies have shown that the following drugs: beta-blockers, tricyclic antidepressants, selective serotonin re-uptake inhibitors, estrogen based hormone replacement therapy, estrogen containing oral contraceptives and calcium channel blockers, have no effect on the pharmacokinetic properties of eletriptan.

Eletriptan is not a substrate for monoamine oxidase (MAO). Therefore, there is no expectation of an interaction between eletriptan and MAO inhibitors.

The effect of eletriptan on other drugs

In-vitro human liver microsome studies suggest that eletriptan has little potential to inhibit CYP1A2, 2C9, 2E1 and 3A4 at concentrations up to 100 mcM. Eletriptan does have a small effect on CYP2D6 with an IC50 of approximately 41 mcM. The average C_{max} of eletriptan following a single oral dose of 80 mg was 0.5 mcM. There is no *in vitro* or *in vivo* evidence that clinical doses (and associated concentrations) of eletriptan will

induce drug metabolising enzymes. Therefore, eletriptan is unlikely to cause clinically important drug interactions mediated by these enzymes.

Co-administration of 5-HT agonists, including eletriptan, with drugs having serotonergic activity, such as SSRIs and SNRIs, may increase the risk of serotonin syndrome. If concomitant treatment with eletriptan and a serotonergic active drug is clinically warranted, caution is advised. Careful observation of the patient is warranted particularly during treatment initiation or dose increase of either drug.

Drug Abuse and Potential

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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. Systemic exposure at this dose, based on free plasma AUC values, was approximately three times that in humans at the maximum recommended dose.

Use in Pregnancy – Pregnancy Category B1

The safety of eletriptan in pregnant women has not been established. In teratogenicity studies, rats and rabbits given oral doses up to 100 mg/kg/day, resulted in systemic exposure more than ten times higher than in humans at the maximum recommended dose. Although there is no evidence of teratogenicity at this dose level, decreased fetal weights, increased incidence of minor vertebral alterations and delays in ossification were seen in rats at 100 mg/kg/day, and decreases in fetal weight were seen in rabbits at 50 and 100 mg/kg/day. Administration of RELPAX should be considered only if the expected benefit to the mother is greater than any possible risk to the fetus.

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. Nevertheless, 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Migraine may cause drowsiness in some patients. Dizziness and drowsiness have also been reported in some patients receiving RELPAX. Therefore caution is recommended in patients performing skilled tasks, (e.g. driving or operating machinery) during the migraine attack and following administration of RELPAX.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Although not reported in pre-marketing clinical trials with RELPAX, serious cardiac events, including some that have been fatal, have occurred following the use of other 5-HT_1 agonists. Events reported have included coronary artery vasospasm, transient myocardial ischaemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Incidence in controlled clinical trials

Among 4,597 patients who treated their first attack with RELPAX in short-term, placebo controlled trials, the adverse events reported in at least 5% of patients and at a rate twice that of placebo were asthenia and dizziness. In order to generate a rigorous record of all adverse events in outpatient trials (n=4,781), patients were required to report all adverse events in a diary as they occurred.

In short-term placebo controlled trials, patients withdrew for reasons related to treatment emergent adverse events at a rate of 1.8% on eletriptan and 0.9% on placebo. Since patients treated only one to three headaches in the controlled clinical trials, the opportunity for discontinuation of therapy in response to adverse events was limited.

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 1544 patients discontinued treatment due to adverse events.

RELPAX is generally well tolerated. Across all doses, most adverse reactions were mild and transient and resolved spontaneously without additional treatment. The incidence of adverse events in controlled clinical trials was not affected by sex, age, or race of the patients, or use of SSRIs, beta blockers, calcium channel blockers, tricyclic antidepressants, and estrogen replacement therapy/oral contraceptives. 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 took only one dose.

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, those frequency estimates may not apply, as the conditions of use, reporting behaviour, and the kinds of patients treated may differ. Only adverse events that were more frequent in a RELPAX treatment group compared to the placebo group with an incidence greater than 2% are included in Table 1.

Table 1: Adverse Experience Incidence in Placebo-Controlled Migraine Clinical Trials:
Events Reported by ≥ 2% Patients Treated with RELPAX

Adverse Event Type	Placebo (n=988)	RELPAX 20 mg (n=431)	RELPAX 40 mg (n=1774)	RELPAX 80 mg (n=1932)
ATYPICAL SENSATIONS				
Paraesthesia	1.5%	3.0%	3.0%	3.9%
PAIN AND PRESSURE SENSATIONS				
Chest – tightness/pain/pressure	0.8%	0.9%	2.3%	4.3%
Abdominal – pain/discomfort/stomach pain/cramps/pressure	0.9%	1.2%	2.1%	1.9%
DIGESTIVE				
Dry mouth	2.2%	2.1%	3.2%	3.5%
Dyspepsia	0.6%	1.2%	1.7%	2.0%
Dysphagia throat tightness/difficulty swallowing	0.2%	0.7%	1.9%	2.5%
Nausea	4.8%	4.2%	5.4%	8.0%
Vomiting	4.4%	1.2%	1.7%	2.3%
NEUROLOGICAL				
Dizziness	3.0%	3.2%	5.8%	7.3%
Somnolence	3.5%	3.0%	5.7%	7.1%
Headache	2.7%	3.5%	3.3%	4.2%
OTHER				
Asthenia	2.6%	4.4%	5.2%	9.5%
Vasodilatation	2.0%	1.9%	2.3%	2.5%

Other events observed in association with the administration of RELPAX 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 RELPAX 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=6,419) exposed to RELPAX. 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: Asthenia, chest symptoms (pain, tightness and pressure), chills and pain. Infrequent: face oedema and malaise. Rare: abdomen enlarged, abscess, accidental injury, allergic reaction, fever, flu syndrome, halitosis, hernia, hypothermia, lab test abnormal, moniliasis, rheumatoid arthritis and shock.

Cardiovascular

Frequent: palpitation, tachycardia and sensation of warmth or flushing. Infrequent: hypertension, migraine and peripheral vascular disorder. Rare: angina pectoris, arrhythmia, atrial fibrillation, A-V block, bradycardia, hypotension, syncope, vascular disorder, vasospasm and ventricular arrhythmia.

Digestive

Infrequent: abdominal pain, anorexia, constipation, diarrhoea, dry mouth, dyspepsia, eructation, oesophagitis, flatulence, gastritis, gastrointestinal disorder, glossitis, increased salivation and liver function tests abnormal, nausea. Rare: gingivitis, haematemesis, increased appetite, rectal disorder, stomatitis, tongue disorder, tongue oedema and tooth disorder.

Endocrine

Rare: goitre, thyroid adenoma and thyroiditis.

Haemic and Lymphatic

Rare: anaemia, cyanosis, leukopenia, lymphadenopathy and monocytosis.

Metabolic

Infrequent: creatinine phosphokinase increased, oedema, peripheral oedema and thirst. Rare: alkaline phosphatase increased, bilirubinaemia, weight gain and weight loss.

Musculoskeletal

Frequent: backpain, myalgia and myasthenia. Infrequent: arthralgia, arthritis, arthrosis and bone pain. Rare: bone neoplasm, joint disorder, myopathy and tenosynovitis.

Neurological

Frequent: dizziness, headache, hypertonia, hypoaesthesia, myasthenia, paraesthesia, somnolence and vertigo. Infrequent: 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: 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: pharyngitis, throat tightness. Infrequent: asthma, dyspnoea, respiratory disorder, respiratory tract infection, rhinitis, voice alteration and yawn. Rare: bronchitis, cough increased, epistaxis, hiccup, hyperventilation, sinusitis and sputum increased.

Skin and Appendages

Frequent: sweating. Infrequent: pruritus, rash and skin disorder. Rare: alopecia, dry skin, exfoliative dermatitis, maculopapular rash, psoriasis, skin discolouration, skin hypertrophy and urticaria.

Special Senses

Infrequent: abnormal vision conjunctivitis, ear pain, eye pain, lacrimation disorder, photophobia, taste perversion and tinnitus. Rare: abnormality of accommodation, dry eyes, ear disorder, otitis media, parosmia and ptosis.

Urogenital

Infrequent: impotence, polyuria, urinary frequency and urinary tract disorder. Rare: breast pain, kidney pain, leukorrhoea, menorrhagia, menstrual disorder and vaginitis.

Post-marketing experience

In post-marketing experience, the following undesirable effects have been reported:

Immune System Disorders

Allergic reaction, some of which may be serious, including angioedema.

Nervous System Disorders

Rare cases of syncope.

Cardiovascular Disorders

Hypertension.

Gastrointestinal Disorders

Vomiting, rare cases of ischaemic colitis.

Cardiac Disorders

Myocardial ischaemia or infarction, arteriospasm coronary.

Skin and Subcutaneous Tissue Disorders

Pruritus, rash and urticaria.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia)

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Eletriptan is a potent and selective 5-hydroxytryptamine $_{1B/1D}$ (5-$HT_{1B/1D}$) receptor agonist, at the vascular 5-HT_{1B} and neuronal 5-HT_{1D} receptors. Eletriptan also exhibits high affinity for the 5-HT1F 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-HT_7 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.

Clinical Trials

Further Information on Clinical Trials

The efficacy of RELPAX in the acute treatment of migraines was evaluated in eight randomised, double blind placebo controlled studies. All eight studies used 40 mg. Seven studies evaluated the 80 mg dose and two studies included a 20 mg dose. In addition, an active comparator, sumatriptan (25 mg, 50 mg, and 100 mg) was used in three of these studies.

In all eight studies, randomised patients treated their headaches as outpatients. Seven studies enrolled adults and one study enrolled adolescents (age 11 to 17). Patients treated in the seven adult studies were predominantly female (85%) and Caucasian (94%) with a mean age of 40 years (range 18 to 78 years). In all studies, 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. In the adult studies, 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 the seven adult 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 2 and Figure 1.

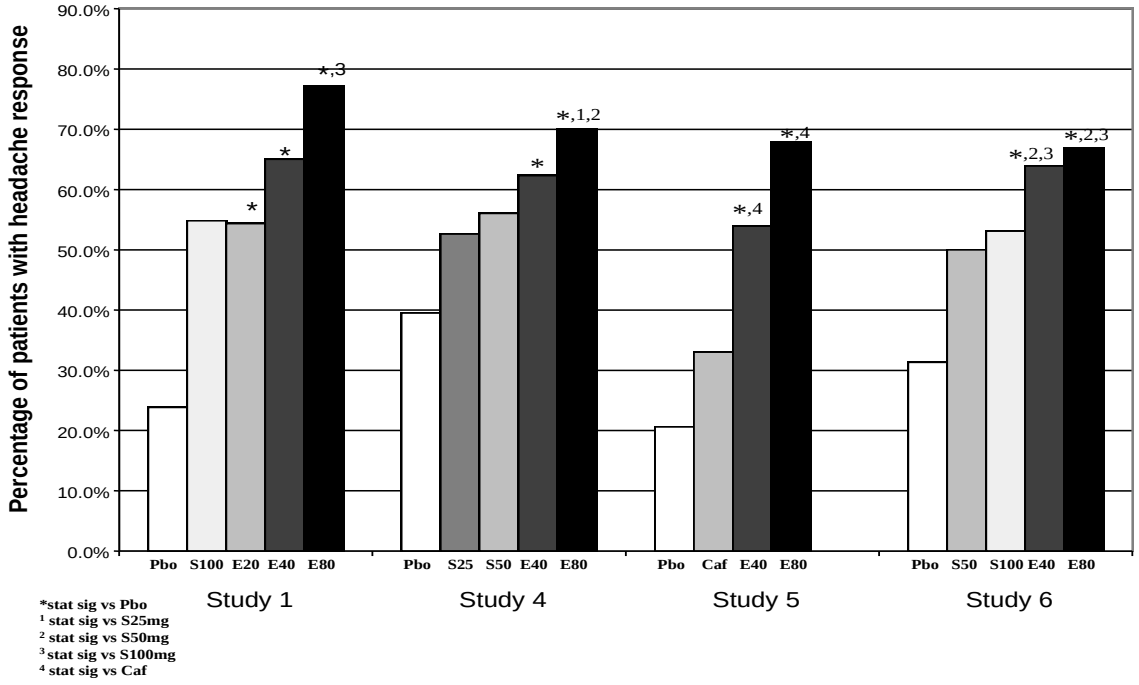
Table 2: Percentage of Patients with Headache Response (Mild or No Headache) 2 Hours Following Treatment

	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
Study 7	29.5% (n=122)	NA	57.5%* (n=169)	NA	NA	NA	NA	NA

* stat sig vs placebo
1 stat sig vs sumatriptan 25 mg
2 stat sig vs sumatriptan 50 mg
3 stat sig vs sumatriptan 100 mg
4 stat sig vs Cafergot®
NA - Not Applicable

Table 2: Percentage of Patients with Headache Response (Mild or No Headache) 2 Hours Following Treatment								
	Placebo	RELPAX 20 mg	RELPAX 40 mg	RELPAX 80 mg	sumatriptan 25 mg	sumatriptan 50 mg	sumatriptan 100 mg	Cafergot ®

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



In the three studies using an active comparator, significantly more patients receiving the 80 mg dose of RELPAX achieved a 2 hour headache response than patients receiving 25 mg, 50 mg or 100 mg sumatriptan. In one study, significantly more patients receiving 40 mg RELPAX achieved 2 hour headache response than patients receiving 50 mg or 100 mg sumatriptan while in a second study the effectiveness of 40 mg was shown to be similar to 25 mg and 50 mg sumatriptan. In a third study, the effectiveness of 20 mg and 40 mg RELPAX was shown to be similar to 100 mg sumatriptan.

In a randomised, placebo controlled trial of 274 patients aged 11 to 17, the headache response rates at 2 hours were 57% (n=138) for 40 mg, and 57% (n=129) for placebo.

The dose related increase in efficacy of eletriptan compared to sumatriptan is associated with an increased adverse event rate.

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 programme was designed to minimise these potential effects.

The cumulative headache response up to 4 hours following treatment is depicted in Figure 2.

Figure 2 : Cumulative Headache Response Rates up to 4 Hours After Dosing

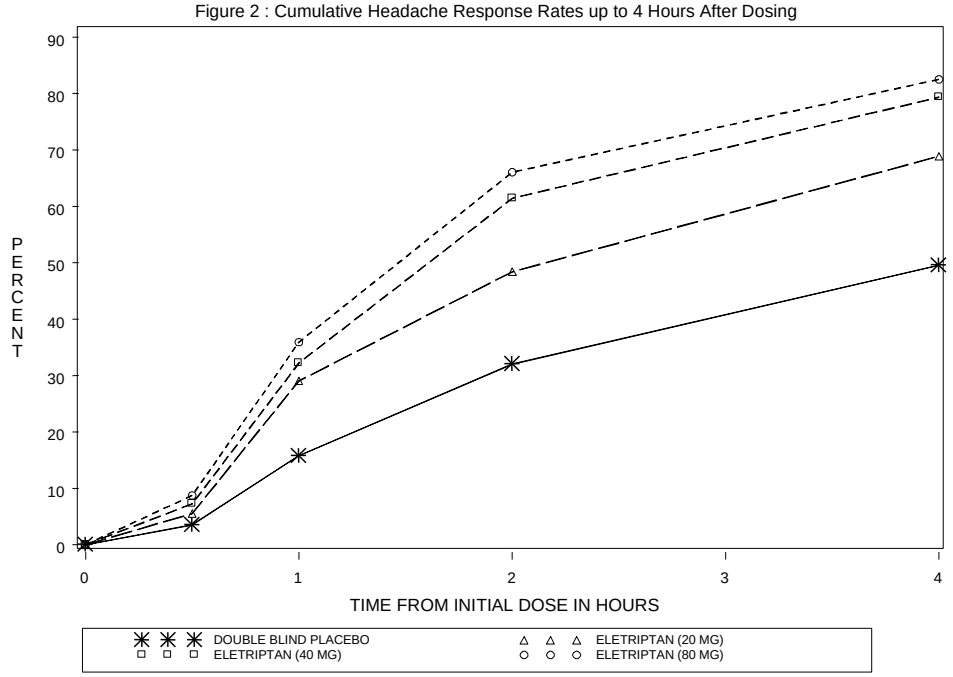
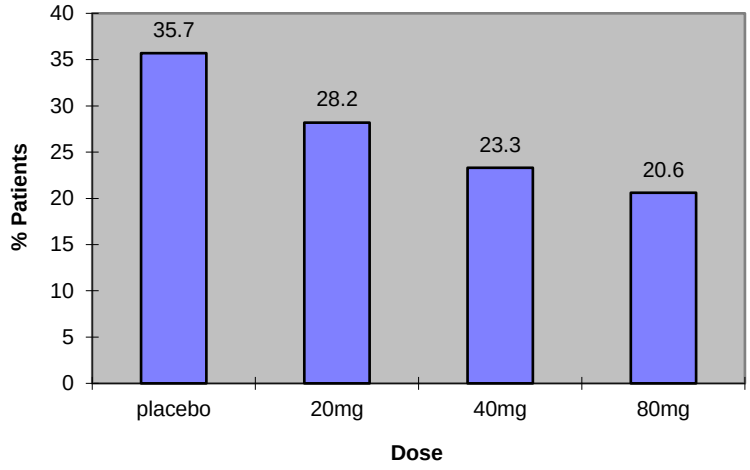


Figure 2 shows the cumulative headache response rate following treatment with RELPAX.

RELPAX 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 RELPAX 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 estrogen 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.

5.2 PHARMACOKINETIC PROPERTIES

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 tid) for 5 - 7 days, the pharmacokinetics of eletriptan remained linear and accumulation was predictable. On multiple dosing of larger doses (40 mg tid and 80 mg bid), the drug accumulation over 7 days was greater than predicted (approximately 40%).

Distribution

The volume of distribution of eletriptan following IV 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 known selective and potent CYP3A4 inhibitors ketoconazole and erythromycin (see 4.3 CONTRAINDICATIONS). *In-vitro* studies also indicate a small involvement of CYP2D6 although clinical studies do not indicate any evidence of polymorphism with regard to this enzyme.

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.

Excretion

Mean total plasma clearance (CL) of eletriptan following IV administration is 36 L/h with a resultant plasma half-life of approximately 4 hours. The mean renal clearance (CLR) 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).

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 (see 4.4 Special warnings and precautions for use - Use in Children below 17 years of age).

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 (see 4.4 Special warnings and precautions for use - Use in Children below 17 years of age).

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, T1/2 or plasma protein binding of eletriptan. In renally impaired subjects, eletriptan increased blood pressure to a larger degree than in matched healthy subjects. A single 80 mg dose showed a significant increase in T_{max} (5.6 hours) in patients with severe renal impairment when compared to normal subjects (2.58 hours), although other parameters were not affected.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Gene mutation tests in bacterial and mammalian cells and clastogenicity assays *in vitro* and *in vivo* were negative.

Carcinogenicity

There was no indication of a carcinogenic potential for humans in life time 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. Systemic exposure at that dose, based on free plasma AUC values, was about fourteen times that in humans at the maximum recommended dose. In rats, the high dose of 75 mg/kg resulted in systemic exposure about six times that in humans at the maximum recommended dose. There was no evidence of an increase in tumours related to eletriptan administration.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each RELPAX tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, Opadry Orange (OY-LS-23016) USA (ARTG PI No: 3482) or Opadry Orange (OY-LS-23016) UK (ARTG PI No: 3481) and Opadry YS-2-19114-A Clear UK (ARTG PI No: 3088) or Opadry Clear YS-2-19114-A USA (ARTG PI No: 3089).

6.2 INCOMPATIBILITIES

See 4.5 INTERACTIONS WITH OTHER MEDICINE AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

RELPAX tablets are packaged in Al/Al, or PVC/Aclar/Al blister packs of 1 (40 mg only) 2, 4 and 6 tablets.

Not all dosage strengths, pack sizes or presentation are marketed in Australia.

Australian Register of Therapeutic Goods (ARTG)

AUST R 68356 - RELPAX eletriptan hydrobromide 40mg tablet blister pack

AUST R 68358 - RELPAX eletriptan hydrobromide 80mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

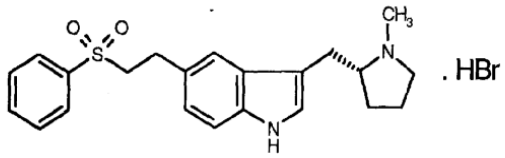
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Eletriptan is a white to pale coloured powder that is readily soluble in water.

Chemical structure



It is chemically designated as (R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1H-indole hydrobromide. The empirical formula is C22H26N2O2S . HBr, representing a molecular weight of 463.43.

CAS Number

143322-58-1 for eletriptan

177834-92-3 for eletriptan hydrobromide.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

13/10/2000

10 DATE OF REVISION

08/09/2023

Summary Table of changes

Section changed	Summary of new information
All	Editorial updates
3	Update of pharmaceutical form to change the embossing on the tablets from “Pfizer” to “VLE”
6.5	Include the ARTG numbers

RELPAX_pi\Sep23/01