SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

RELPAX® 20 mg Tablets

RELPAX® 40 mg Tablets

RELPAX® 80 mg Tablets

COMPOSITION:

RELPAX 20 mg tablets: Each tablet contains 20 mg eletriptan as eletriptan hydrobromide.

RELPAX 40 mg tablets: Each tablet contains 40 mg eletriptan as eletriptan hydrobromide.

RELPAX 80 mg tablets: Each tablet contains 80 mg eletriptan as eletriptan hydrobromide.

RELPAX film-coated tablets contain the following inactive ingredients: Croscarmellose sodium, glycerol triacetate, hypromellose, lactose, magnesium stearate, microcrystalline cellulose and sunset yellow aluminium lake and titanium dioxide as colourants.

Contains sugar.

RELPAX 20 mg tablets contain 23 mg lactose per tablet.

RELPAX 40 mg tablets contain 46 mg lactose per tablet.

RELPAX 80 mg tablets contain 92 mg lactose per tablet.

CATEGORY AND CLASS:

A 7.3 Migraine preparations

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Eletriptan is a selective agonist at the vascular 5-HT_{1B} and neuronal 5-HT_{1D} receptors. Eletriptan also exhibits affinity for the 5-HT_{1F} receptor, which may contribute to its anti-migraine mechanism of action. Eletriptan has modest affinity for the human recombinant 5-HT_{1A}, 5-HT_{2B}, 5-HT_{1E} and 5-HT_{7} receptors.

Eletriptan inhibits neurogenic inflammation in the dura mater of animals.

Pharmacokinetic properties:

Absorption:

Eletriptan is 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 at approximately 1,5 hours after oral dosing. Linear pharmacokinetics were demonstrated over the clinical dose range (20 mg to 80 mg).

The AUC and C_{max} of eletriptan were increased by approximately 20 % to 30 % following oral administration with a high fat meal. Following oral administration during a migraine attack, there was a reduction of approximately 30 % in AUC and T_{max} was increased to 2,8 hours.

On multiple dosing (40 mg three times daily and 80 mg twice daily), the medicine accumulation over 7 days was greater than predicted (approximately 40 %).

Distribution:

The volume of distribution of eletriptan following intravenous administration is 138 L indicating distribution into the tissues.

Eletriptan is only moderately protein bound (approximately 85 %).

Metabolism:

In vitro studies indicate that eletriptan is primarily metabolised by hepatic cytochrome P-450 enzyme CYP3A4. This finding is substantiated by increased plasma concentration 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 that there is no clinically relevant effect of CYP2D6 polymorphism on the pharmacokinetics of eletriptan.

There are two major circulating metabolites identified that significantly contribute to plasma radioactivity following administration of C^{14}-labelled eletriptan. The metabolite formed by N-oxidation has demonstrated no activity in animal *in vitro* models. The metabolite formed by N-demethylation has been demonstrated to have similar activity to eletriptan in animal *in vitro* models. 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 % to 20 % of those of the parent drug, and so would not be expected to significantly contribute to the therapeutic action of eletriptan.

Elimination:

Mean total plasma clearance of eletriptan following intravenous administration is 36 litres per hour with a resultant plasma half-life of approximately 4 hours.

The mean renal clearance following oral administration is approximately 3,9 litres per hour. Non-renal clearance accounts for approximately 90 % of the total clearance indicating that eletriptan is eliminated primarily by metabolism.

Pharmacokinetics in special patient groups:

Elderly (over 65 years of age):

Though not statistically significant, there is a small reduction (16 %) in clearance associated with a statistically significant increased half-life (from approximately 4,4 hours to 5,7 hours) between elderly (65 to 93 years) and younger adult subjects.

Hepatic impairment:

Subjects with hepatic impairment (Child-Pugh A [score 5 – 6] and B [score 7 – 9]) 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 impairment***:**

Subjects with mild (creatinine clearance 61 to 89 ml/min), moderate (creatinine clearance 31 to 60 ml/min) or severe (creatinine clearance < 30 ml/min) renal impairment did not have any statistically significant alterations in their eletriptan pharmacokinetics or plasma protein binding. However, blood pressure increased significantly in patients with renal impairment.

INDICATIONS:

Acute treatment of migraine with or without aura in adults and adolescents 18 years and older.

CONTRAINDICATIONS:

- Patients with hypersensitivity to eletriptan hydrobromide or to any of the excipients.
- Patients with severe hepatic impairment (Child-Pugh class C [score > 9]).

- 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.
- Peripheral arterial insufficiency.
- Patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Administration of ergotamine, or derivatives of ergot within 24 hours before or after treatment with RELPAX (see INTERACTIONS).
- Concomitant administration of other 5-HT_1 receptor agonists.
- RELPAX use with potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, josamycin and protease inhibitors (ritonavir, indinavir and nelfinavir), is not recommended as plasma levels may double or triple (see INTERACTIONS).
- RELPAX has not been systematically evaluated for use in patients with heart failure. Use in these patients is not recommended.
- Children and adolescents (less than 18 years), as safety and efficacy have not been demonstrated.

WARNINGS AND SPECIAL PRECAUTIONS:

Serotonin syndrome:

Co-administration of RELPAX with other medicines having serotonergic activity, such as serotonin-norepinephrine re-uptake inhibitors (SNRIs) and selective serotonin re-uptake inhibitors (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 medicines (see INTERACTIONS **–** Interaction with serotonergic active medicine).

RELPAX use with potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, josamycin and protease inhibitors (ritonavir, indinavir and nelfinavir), is not recommended as plasma levels may double or triple.

RELPAX should only be used where a clear diagnosis of migraine has been established. RELPAX is not indicated for the management of hemiplegic, ophthalmoplegic or basilar migraine.

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 RELPAX is recommended for patients in whom cardiovascular disease is likely, or for patients at risk of cardiovascular disease (see CONTRAINDICATIONS).

Within the clinical dose range, slight and transient increases in blood pressure have been seen with RELPAX doses of 60 mg or greater. The effect was more pronounced in renally impaired and elderly subjects.

In a clinical pharmacology study, a single oral dose of 80 mg 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 mmHg to 17 mmHg for systolic blood pressure or 14 mmHg to 21 mmHg for diastolic blood pressure and was greater than that observed in the normal subjects (3 – 4 mmHg).

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

Use in children:

Use in children less than 18 years is not recommended as safety and efficacy have not been demonstrated (see CONTRAINDICATIONS).

Effects on ability to drive and use machines:

Migraine or treatment with some 5-HT_1 receptor agonists, including RELPAX, may cause dizziness or drowsiness 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.

Lactose:

RELPAX contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g.

galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take RELPAX.

INTERACTIONS:

Effect of other medicines on RELPAX:

Population pharmacokinetic analysis of clinical studies has suggested that the following medicines: beta-blockers, tricyclic antidepressants, SSRIs, oestrogen-based hormone replacement therapy, oestrogen-containing oral contraceptives and calcium channel blockers are unlikely to have an effect on the pharmacokinetic properties of RELPAX (see Interaction with serotonergic active medicines).

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 was 1,3-fold, 2,7-fold and 2,0-fold, respectively. These effects are not considered clinically significant, as there were no associated increases in blood pressure or adverse events compared to administering RELPAX alone (see WARNINGS AND SPECIAL PRECAUTIONS).

In clinical studies with erythromycin (1 000 mg) and ketoconazole (400 mg) specific and potent inhibitors of CYP3A4, significant increases in the eletriptan C_{max} (2 fold and 2,7-fold) and AUC (3,6 fold and 5,9-fold), respectively, were observed. This increased exposure was associated with an increase in RELPAX $t_{1/2}$ from 4,6 to 7,1 hours with erythromycin and from 4,8 to 8,3 hours with ketoconazole (see PHARMACOLOGICAL ACTION – Pharmacokinetic properties and WARNINGS AND SPECIAL PRECAUTIONS). Therefore, RELPAX should not be used together with potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, josamycin and protease inhibitors (ritonavir, indinavir and nelfinavir) (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

In clinical studies with oral caffeine/ergotamine administered 1 and 2 hours after RELPAX, minor though additive increases in blood pressure were observed. Therefore, it is recommended that either ergot-containing medications (e.g. dihydroergotamine) should not be taken within 24 hours of RELPAX dosing. Conversely, at least 24 hours should elapse after the administration of an ergot-containing preparation before RELPAX is given.

Effect of RELPAX on other medicines:

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

Interaction with serotonergic active medicines:

Co-administration of 5-HT agonists, including RELPAX, with medicines having serotonergic activity such as SSRIs, SNRIs, pethidine, tramadol and St. John's Wort (*Hypericum perforatum*) may increase the risk of serotonin syndrome. If concomitant treatment with RELPAX and a serotonergic active medicine is clinically warranted, caution is advised. Careful observation of the patient is warranted, particularly during treatment initiation or dose increase of either medicine (see WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION:

Pregnancy:

The safety of RELPAX in pregnant women has not been established.

Lactation:

RELPAX is excreted in human breast milk. Women using RELPAX should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

RELPAX tablets should be taken as early as possible after the onset of migraine headache.

RELPAX tablets should not be used prophylactically.

RELPAX should only be taken during the headache phase of migraine.

The tablets should be swallowed whole with water.

Adults (18 to 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 may be used 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 to the first dose of RELPAX within 2 hours, a second dose should not be taken for the same attack. Clinical trials have shown that the majority of patients who do not respond to the treatment of an initial attack respond to the treatment of a subsequent attack.

Patients who do not obtain satisfactory efficacy with 40 mg may have the dose increased to 80 mg in a subsequent migraine attack.

The maximum total daily dose should not exceed 160 mg.

A 20 mg dose of RELPAX is recommended in patients receiving erythromycin and other specific potent CYP3A4 inhibitors e.g. ketoconazole, itraconazole and clarithromycin. The total daily intake should not exceed 40 mg for these patients.

Elderly (over 65 years of age):

Safety and efficacy in patients over 65 have not been systematically evaluated due to the 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 SPECIAL PRECAUTIONS).

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.

Renal impairment:

As the blood pressure effects of RELPAX are amplified in renal impairment, doses higher than 40 mg should not be used (see WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS:

RELPAX has been administered in clinical trials to more than 5 000 patients.

The incidence and severity of side effects seen in patients who took two doses of the same strength to treat a single attack were similar to these observed in patients who had taken only one dose.

The following side effects (with an incidence ≥ 1 % and higher than placebo) were reported in patients treated with therapeutic doses in clinical trials.

The following side effects have been reported in patients treated with therapeutic doses. Side effects are categorised by frequency as common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), or rare (≥ 1/10 000 and < 1/1 000).

MedDRA system organ class	**Frequency**	**Side effect**
Nervous system disorders	Common	Dizziness, headache, hypertonia, hypoesthesia, myasthenia, paraesthesia, somnolence
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitation, tachycardia
Vascular disorders	Common	Sensation of warmth or flushing
Respiratory, thoracic and mediastinal disorders	Common	Pharyngitis, throat tightness
Gastrointestinal disorders	Common	Abdominal pain, dry mouth, dyspepsia, nausea
Skin and subcutaneous tissue disorders	Common	Sweating
Musculoskeletal, connective tissue and bone disorders	Common	Back pain, myalgia
General disorders and administration site conditions	Common	Asthenia, chest symptoms (pain, tightness, pressure), chills, pain

Post-marketing side effects:

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

MedDRA system organ class	**Side effect**
Immune system disorders	Allergic reaction, some of which may be serious, including angioedema
Nervous system disorders	Syncope
Vascular	Hypertension
Gastrointestinal disorders	Vomiting, ischaemic colitis

Cardiac disorders	Myocardial ischaemia or infarction, coronary arteriospasm
Skin and subcutaneous tissue disorders	Pruritus, rash, urticaria

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In cases of overdose, standard supportive measures should be adopted as required. The elimination half-life of RELPAX is about 4 hours, and therefore monitoring of patients and provision of general supportive therapy after overdose with RELPAX 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 RELPAX.

IDENTIFICATION:

RELPAX 20 mg tablets: Orange, standard round convex film-coated tablets, debossed with “REP 20” on one side and ”VLE” on the other.

RELPAX 40 mg tablets: Orange, standard round convex film-coated tablets, debossed with “REP 40” on one side and ”VLE” on the other.

RELPAX 80 mg tablets: Orange, standard round convex film-coated tablets, debossed with “REP 80” on one side and ”VLE” on the other.

PRESENTATION:

Aclar blister packs containing 2 or 4 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep container tightly closed.

Keep out of the reach of children.

REGISTRATION NUMBERS:

RELPAX 20 mg tablets: 34/7.3/0077

RELPAX 40 mg tablets: 34/7.3/0078

RELPAX 80 mg tablets: 34/7.3/0079

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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Manufacturer: Pfizer Italia S.r.l., Ascoli Piceno, Italy

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 18 December 2001

Date of last SAHPRA approval: 06 June 2019

BOTSWANA: S2

RELPAX 20 mg – Reg. No.: BOT1001622

RELPAX 40 mg – Reg. No.: BOT1001620

RELPAX 80 mg – Reg. No.: BOT1001621

NAMIBIA: NS2

RELPAX 20 mg – Reg. No.: 04/7.3/1241

RELPAX 40 mg – Reg. No.: 04/7.3/1242

RELPAX 80 mg – Reg. No.: 04/7.3/1243