เอกสารกำกับยา

RELPAX™

1. Name of the Medicinal Product

1.1 Product name

RELPAX™

1.2 Strength

40 mg

1.3 Pharmaceutical dosage form

Film-coated tablets

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Active Ingredient: eletriptan.

2.2 Quantitative declaration

RELPAX 40 mg Film-coated tablets

Each tablet contains 40 mg eletriptan as eletriptan hydrobromide.

For the full list of excipients, see section 6.1. **List of excipients**

3. Pharmaceutical Form

Film-coated tablets.

RELPAX 40 mg Film-coated tablets

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

4. Clinical Particulars

4.1 Therapeutic indications

Acute treatment of the headache phase of migraine attacks, with or without aura, in adults.

4.2 Posology and method of 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, if taken during the aura phase, has not been demonstrated to prevent migraine headache and therefore RELPAX should only be taken during the headache phase of migraine.

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 to the first dose of RELPAX within 2 hours, 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 have shown 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 80mg.

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. Use of RELPAX in the elderly is therefore not recommended.

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.

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 section **5.2. Pharmacokinetic Properties**).

Patients with 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.

Patients with renal Impairment

As the blood pressure effects of RELPAX are amplified in renal impairment (see section 4.4. **Special Warnings and Precautions for Use**), a 20 mg initial dose, is recommended in patients with mild or moderate renal impairment. The maximum daily dose should not exceed 40 mg. RELPAX is contra-indicated, in patients with severe renal impairment.

4.3 Contraindications

RELPAX is contraindicated in patients with

- hypersensitivity to eletriptan hydrobromide or to any of the excipients listed in 6.1 **List of excipients**.
- severe hepatic or severe renal impairment.
- moderately severe or severe hypertension, or untreated mild hypertension.
- confirmed coronary heart disease, including ischaemic heart disease (angina pectoris, previous myocardial infarction or confirmed silent ischaemia) Patients with coronary artery vasospasm (Prinzmetal's angina), objective or subjective symptoms of ischaemic heart disease.
- significant arrhythmias or heart failure.
- peripheral vascular disease.
- 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 section 4.5. **Interaction with other medicinal products and other forms of interaction**)
- concomitant administration of other 5-HT_1 receptor agonists with eletriptan.

4.4 Special warnings and precautions for use

RELPAX should not be used together with potent CYP3A4 inhibitors e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, josamycin and protease inhibitors (ritonavir, indinavir and nelfinavir).

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.

Eletriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat (see section 4.8. **Undesirable effects**). Where such symptoms are thought to indicate ischaemic heart disease, no further dose should be taken and

appropriate evaluation should be carried out.

Patients with cardiac failure

RELPAX should not be given without prior evaluation, to patients in whom unrecognised cardiac disease is likely, or to patients at risk of coronary artery disease (CAD) [e.g., patients with hypertension, diabetes, smokers or users of nicotine substitution therapy, men over 40 years of age, post-menopausal women and those with a strong family history of CAD]. Cardiac evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred, in patients without underlying cardiovascular disease when 5-HT_1 agonists have been administered. Patients in whom CAD is established, should not be given RELPAX (see section 4.3 **Contraindications**). 5-HT_1 receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischaemia or infarction, have been reported with 5-HT_1 receptor agonists.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St. John's wort (Hypericum perforatum).

Within the clinical dose range, slight and transient increases in blood pressure have been seen with eletriptan doses of 60 mg or greater. However, these increases have not been associated with clinical sequelae in the clinical trial programme. The effect was much more pronounced in renally impaired and elderly subjects. In renally impaired subjects, the range of mean maximum increases in systolic blood pressure was 14 -17 mmHg (normal 3 mmHg) and for diastolic blood pressure was 14 -21 mmHg (normal 4 mmHg). In elderly subjects, the mean maximum increase in systolic blood pressure was 23 mmHg compared with 13 mmHg in young adults (placebo 8 mmHg). Post-marketing reports of increases in blood pressure have also been received for patients taking 20 and 40 mg doses of eletriptan, and in non-renally impaired and non-elderly patients.

Medication overuse headache (MOH)

Prolonged use of any painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Serotonin syndrome

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with eletriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see section 4.5 **Interaction with other medicinal products and other forms of interaction**).

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product also contains sunset yellow which may cause allergic reactions.

RELPAX 40 mg tablets contain less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets can be informed that these medicinal products are essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on eletriptan

In the pivotal clinical trials of eletriptan no evidence of interaction with beta-blockers, tricyclic antidepressants, selective serotonin reuptake 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 reuptake inhibitors, estrogen-based hormone replacement therapy, estrogen-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. Therefore there is no expectation of an 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 increases 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 for erythromycin and from 4.8 to 8.3 hours for ketoconazole (see section 5.2. **Pharmacokinetic properties**). 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).

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 (e.g., 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.

Effect of eletriptan on other medicinal products

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

Selective Serotonin Reuptake Inhibitors (SSRIs) / Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Serotonin Syndrome:

There have been reports describing patients with symptoms compatible with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) and triptans (see section 4.4 **Special warnings and precautions for use**).

4.6 Fertility, pregnancy and lactation

Pregnancy

For RELPAX no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. RELPAX should be used during pregnancy only if clearly needed.

Breast-feeding

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

RELPAX has moderate influence on the ability to drive and use machines. Migraine or treatment with RELPAX may cause drowsiness or dizziness in some patients. Patients should be advised to evaluate their ability to perform complex tasks such as driving during migraine attacks and following administration of RELPAX.

4.8 Undesirable effects

Summary of the safety profile

RELPAX has been administered in clinical trials to over 5,000 subjects, taking one or two doses of RELPAX 20 or 40 or 80 mg. The most common adverse reactions noted were asthenia, somnolence, nausea and dizziness. In randomised clinical studies using doses of 20, 40 and 80 mg, a trend for a dose-dependency of the incidence of adverse events has been shown.

Tabulated list of adverse reactions

The following adverse reactions (with an incidence ≥1% and higher than placebo) were reported in patients treated with therapeutic doses in clinical trials. Events are categorized by frequency as common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), or rare (≥1/10,000 to <1/1,000).

System Organ	Common	Uncommon	Rare

Class			
Infections and infestations:	pharyngitis, and rhinitis		respiratory tract infection
Blood and the lymphatic system disorders:			lymphadenopathy
Metabolism and nutrition disorders:		anorexia	
Psychiatric disorders:		thinking abnormal, agitation, confusion, depersonalisation, euphoria, depression, and insomnia	emotional lability
Nervous system disorders:	somnolence, headache, dizziness, tingling or abnormal sensation, hypertonia, hypoaesthesia, and myasthenia	tremor, hyperaesthesia, ataxia, hypokinesia, speech disorder, stupor, and taste perversion	
Eye disorders:		abnormal vision, eye pain, photophobia, and lacrimation disorder	conjunctivitis

Ear and labyrinth disorders:	vertigo	ear pain, tinnitus	
Cardiac disorders:	palpitation, and tachycardia		bradycardia
Vascular disorders:	flushing	peripheral vascular disorder	shock
Respiratory, thoracic and mediastinal disorders:	throat tightness	dyspnea, respiratory disorder and yawning	asthma and voice alteration
Gastrointestinal disorders:	abdominal pain, nausea, dry mouth, and dyspepsia	diarrhoea, and glossitis	constipation, oesophagitis, tongue oedema and eructation
Hepato-biliary disorders:			hyperbilirubinaemia, and increased AST
Skin and subcutaneous tissue disorders:	sweating	rash and pruritis	skin disorder and urticaria
Musculoskeletal, connective tissue and bone disorders:	back pain, myalgia	arthralgia, arthrosis and bone pain	arthritis, myopathy and twitching
Renal and urinary disorders:		increased urinary frequency, urinary tract disorder and polyuria	
Reproductive system and breast disorders:			breast pain and menorrhagia

General disorders and administration site conditions:	feeling hot, asthenia, chest symptoms (pain, tightness, pressure), chills and pain	malaise, face oedema, thirst, oedema and peripheral oedema	

The common adverse events seen with eletriptan are typical of adverse events reported with 5-HT_1 agonists as a class

In post-marketing experience, the following undesirable effects have been reported:
Immune System Disorders:Allergic reactions, some of which may be serious, including angioedema

Nervous System Disorders:
Serotonin syndrome, rare cases of syncope, cerebrovascular accident

Vascular Disorders:
Hypertension

Cardiac Disorders:
Myocardial ischaemia or infarction, arteriospasm coronary

Gastrointestinal Disorders:
As with some other 5HT 1B/1D agonists, rare reports of ischaemic colitis have been received, vomiting.

4.9 Overdose

Subjects have received single doses of 120 mg without significant adverse effects. However based on the pharmacology of this class, hypertension or other more serious cardiovascular symptoms could occur on 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 hemodialysis or peritoneal dialysis has on the serum concentrations of eletriptan.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Serotonin (5-HT_1) receptor agonists, ATC code NO2CC06.

Mechanism of Action:
Eletriptan is a 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 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.

Clinical efficacy and safety
The efficacy and safety of RELPAX in the acute treatment of migraine has been evaluated in 10 placebo-controlled trials involving more than 6,000 patients (all treatment groups) at doses of 20 to 80 mg. Headache relief occurred as early as 30 minutes following oral dosing. Response rates (i.e., reduction of moderate or severe headache pain to no or mild pain) 2 hours after dosing were 59% to 77% for the 80 mg dose, 54% to 65% for the 40 mg dose, 47% to 54% for the 20 mg dose, and 19% to 40% following placebo. RELPAX was also effective in the treatment of associated symptoms of migraine such as vomiting, nausea, photophobia and phonophobia.
The recommendation for dose titration to 80 mg, is derived from open label long term studies and from a short term double blind study, where only a trend towards statistical significance was observed.
RELPAX remains effective in menstrually associated migraine. RELPAX, if taken during the aura phase, has not been demonstrated to prevent migraine headache and therefore RELPAX should only be taken during the headache phase of migraine.

In a non-placebo controlled pharmacokinetic study of patients with renal impairment, larger elevations in blood pressure were recorded after an 80 mg dose of RELPAX than with normal volunteers (see section 4.4 **Special warnings and precautions for use**). This cannot be explained by any pharmacokinetic changes and so may represent a specific pharmacodynamic response to eletriptan in patients with renal impairment.

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} is 1.5 hours after oral dosing. Linear pharmacokinetics were demonstrated over the clinical dose range (20 mg-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.

Following repeated doses (20 mg three times daily) for 5 to 7 days, the pharmacokinetics of eletriptan remained linear and accumulation was predictable. On multiple dosing of larger doses (40 mg three times daily and 80 mg twice daily), the accumulation of eletriptan 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%).

Biotransformation

In vitro studies indicate that eletriptan is primarily metabolized by hepatic cytochrome P450 enzyme CYP3A4. This finding is substantiated by increased plasma concentrations of eletriptan following co-administration with erythromycin and ketoconazole, known selective and potent CYP3A4 inhibitors. *In vitro* studies also indicate a small involvement of CYP2D6, although clinical studies do not indicate any evidence of polymorphism with this enzyme.

There are two major circulating metabolites identified that significantly contribute to plasma

radioactivity following administration of C^{14}-labeled 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 feces.

The plasma concentrations of the N-demethylated active metabolite are only 10% to 20% of those of 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 L/h with a resultant plasma half-life of approximately 4 hours. The mean renal clearance 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

Gender

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

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 (65-93 years) and younger adult subjects.

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 (6-11 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.

Patients with hepatic impairment

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.

Patients with renal impairment

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 their eletriptan pharmacokinetics or plasma protein binding. Blood pressure elevations were observed in this group.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction.

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, titanium dioxide (E171), hypromellose, glycerol triacetate and Sunset Yellow Aluminium Lake (E110).

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC.

Keep the container tightly closed.

6.5 Nature and contents of container

PVC/Aclar blister with aluminum foil backing containing 2, 3, 4, 6 or 10 tablets in a carton 1 blister

Not all pack size may be marketed.

7. Marketing Authorization Holder

Viatris (Thailand) Limited

8. Marketing Authorization Numbers

1C 15045/64 (N)

9. Date of Authorization

28 May 2021

10. Date of Revision of the Text

18 January 2024