RELPAX®
Eletriptan Hydrobromide

1. TRADE NAME OF THE MEDICINAL PRODUCT

RELPAX®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 20 mg, 40 mg or 80 mg eletriptan as eletriptan hydrobromide

3. PHARMACEUTICAL FORM

Film-coated tablets

The 20 mg tablet is a 6.25 mm orange film-coated standard round convex tablets with a clear overcoat, engraved with ‘REP 20’ on one side and ‘Pfizer’ on the reverse.

The 40 mg tablet is an 8.0 mm orange film-coated standard round convex tablets with a clear overcoat, engraved with ‘REP 40’ on one side and ‘Pfizer’ on the reverse.

The 80 mg tablet is a 10.0 mm orange film-coated standard round convex tablets with a clear overcoat, engraved with ‘REP 80’ on one side and ‘Pfizer’ on the reverse.

Not all presentations may be available locally.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Acute treatment of migraine with or without aura.

4.2 Posology and method of administration

Eletriptan 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.

Eletriptan 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 eletriptan 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 eletriptan 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 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 section **4.4 Special warnings and special precautions for use)**.

Adolescents (12-17 years of age)

In a clinical trial in adolescents, a high placebo response rate was observed. The efficacy of eletriptan 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 eletriptan in children have not been evaluated. Therefore, the use of eletriptan is not recommended in this age group (see section **5.2 Pharmacokinetic properties**).

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. As eletriptan has not been studied in patients with severe hepatic impairment, it is contraindicated in these patients.

Renal Impairment

As the blood pressure effects of eletriptan are amplified in renal impairment (see section **4.4 Special warnings and special precautions for use**), a 20 mg initial dose is recommended in patients with mild or moderate renal impairment. The maximum

single dose is 40 mg in these patients. The maximum daily dose should not exceed 80 mg.

4.3 Contraindications

Patients with hypersensitivity to eletriptan hydrobromide or to any of the excipients.

Patients with severe hepatic impairment.

Patients with severe renal impairment.

As with other 5-hydroxytryptamine type 1 (5-HT_1) receptor agonists, the following contra-indications are based on the pharmacodynamic properties of eletriptan:

Patients with uncontrolled hypertension.

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

Patients with coronary artery vasospasm, objective or subjective symptoms of ischemic heart disease or Prinzmetal's angina.

Patients with significant arrhythmias or heart failure.

Patients with peripheral vascular disease.

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

Administration of ergotamine, or derivatives of ergotamine (including methysergide) within 24 hours before or after treatment with eletriptan (see section **4.5 Interactions with other medicinal products and other forms of interaction**).

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 special precautions for use

Serotonin Syndrome

Co-administration of eletriptan with other drugs having serotonergic activity, such as Serotonin–norepinephrine reuptake inhibitor (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 drugs (see section **4.5 Interactions with other medicinal products and other forms of interaction –** Interaction with serotonergic active drugs).

Eletriptan use with potent CYP3A4 inhibitors, e.g. ketoconazole, itraconazole, erythromycin, clarithromycin and protease inhibitors (ritonavir, indinavir and nelfinavir) is not recommended (see section **4.5 Interactions with other medicinal products and other forms of interaction**).

As with other 5-HT_1 receptor agonists, eletriptan should only be used where a clear diagnosis of migraine has been established. Eletriptan is not indicated for the management of hemiplegic, ophthalmoplegic, or basilar migraine.

As with other 5-HT_1 receptor agonists, eletriptan should not be given for the treatment of 'atypical' headaches, i.e. headaches that 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 for patients at risk of cardiovascular disease (see section **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.

Eletriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat. Where such symptoms are thought to indicate ischemic heart disease, no further dose should be taken and appropriate evaluation should be carried out.

Eletriptan should not be given without prior evaluation, to patients 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 eletriptan.

5-HT1 receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischemia or infarction, have been reported with 5-HT1 receptor agonists.

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 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 medicinal product can lead to daily chronic headaches. Overuse of all triptans has been reported primarily in patients with chronic daily headache.

4.5 Interactions 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, SSRI and flunarizine was reported, but data from formal clinical interaction studies with these medicinal products are not available (other than propranolol, see below; Interactions with serotonergic active drugs).

Population pharmacokinetic analysis of clinical studies has suggested that the following medicinal products (beta-blockers, tricyclic antidepressants, SSRIs, 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 (see Interactions with serotonergic active drugs).

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 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 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-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 eletriptan $t_{1/2}$ from 4.6 to 7.1 hours with erythromycin and from 4.8 to 8.3 hours with ketoconazole (see section **5.2 Pharmacokinetic properties**). Therefore, eletriptan 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 medicaments

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.

Interaction with serotonergic active drugs

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 (see section **4.4 Special warnings and special precautions for use**).

4.6 Pregnancy and lactation

Pregnancy

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

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 eletriptan to women who are breast-feeding. Infant exposure can be minimized by avoiding breast-feeding for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

Migraine or treatment with some 5-HT_1 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 eletriptan.

4.8 Undesirable 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 ≥1% and higher than placebo) were reported in patients treated with therapeutic doses in clinical trials:

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.

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 additional 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.

Vascular Disorders: Hypertension.

Gastrointestinal Disorders: Vomiting, rare cases of colitis ischaemic.

Cardiac Disorders: Myocardial ischemia or infarction, arteriospasm coronary.

Skin and Subcutaneous Tissue Disorders: Pruritus, rash, urticaria.

4.9 Overdose

Subjects have received single doses of 120 mg without significant adverse effects. However, 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) Agonist, ACT code N02CC.

Mechanism of Action

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 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.

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 humans.

Further information on clinical trials

The efficacy and safety of eletriptan in the acute treatment of migraine have been evaluated in more than 5000 patients.

In controlled clinical trials, patients treated with eletriptan had significantly higher response rates as early as 30 minutes following oral dosing compared to those on placebo. Increasing efficacy is observed at 1 and 2 hours.

Headache response 2 hours after dosing was significantly higher than placebo for all doses, ranging in individual studies from 59% to 77% (80 mg), 54% to 65% (40 mg), 47% to 54% (20 mg) and 19% to 40% (placebo).

Eletriptan was also effective in the treatment of associated symptoms of migraine such as vomiting, nausea, photophobia and phonophobia.

Patients who responded to eletriptan had low rates of recurrence. The rate of recurrence decreased in a dose- related manner. Patients who experienced recurrence from phase II/III adult studies were 35.5%, 28.2%, 23.2% and 20.6% for placebo, 20 mg, 40 mg and 80 mg doses, respectively.

Eletriptan has been shown to be effective in the treatment of recurrence of migraine headache.

Eletriptan is consistently effective in migraine with or without aura and in menstrually associated migraine. Eletriptan, if taken during the aura phase, has not been demonstrated to prevent migraine headache and, therefore, eletriptan should only be

taken during the headache phase of migraine.

5.2 Pharmacokinetic properties

Absorption

Eletriptan is rapidly and well absorbed across the gastro-intestinal 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 (20mg-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 drug 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 metabolized by hepatic 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 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}-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 (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 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.

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.

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, croscarmellose sodium, magnesium stearate, titanium dioxide (E171), hypromellose, glycerol triacetate and Sunset Yellow Aluminum Lake (E110).

6.2 Incompatibilities

None.

6.3 Shelf life

Refer to Outer Carton for shelf life.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and content of container

Aluminium blister packs containing 6 and 30 tablets (20, 40, 80 mg) with or without wallets.

Not all presentations may be available locally.

6.6 Instructions for use and handling

None.

7. PRODUCT OWNER

Viatris Inc
1000 Mylan Blvd
Canonsburg PA 15317
United States

REL-SIN-0421/0
Date of last revision: April 2021