RELERT TABLETS

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20mg, 40mg and 80mg eletriptan (as hydrobromide).

Excipients with known effect:
Each film-coated tablet of Relert 20 mg contains 23 mg lactose monohydrate and Sunset yellow.
Each film-coated tablet of Relert 40 mg contains 46 mg lactose monohydrate and Sunset yellow.
Each film-coated tablet of Relert 80 mg contains 92 mg lactose monohydrate and Sunset yellow.

For the full list of excipients, see section 6.1.

2. PHARMACEUTICAL FORM

Film-coated tablet.
Round, convex orange tablets debossed with ‘REP 20’, ‘REP 40’ and ‘REP 80’on one side and ‘Pfizer’ on the other.

3. CLINICAL PARTICULARS

3.1 Therapeutic Indications
Acute treatment of the headache phase of migraine attacks, with or without aura.

3.2 Posology and Method of Administration

PosologyRELERT 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 during a migraine attack.

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

RELERT 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 the migraine headache recurs within 24 hours of an initial response, a second dose of the same strength of RELERT 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 RELERT 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 show that the majority of patients who do not respond to the treatment of an attack are still likely to respond to the treatment of a subsequent attack.

Patients who do not obtain satisfactory efficacy after an appropriate trial of 40mg, (e.g. good tolerability and failure to respond in 2 out of 3 attacks), may be effectively treated with 80mg in subsequent migraine attacks (see section 4.1 Pharmacodynamic Properties – Further information on Clinical Trials).
The maximum daily dose should not exceed 160mg (see section 3.8 Undesirable effects).

Elderly (over 65 years of age)
Safety and efficacy in patients over 65 years of age have not been systematically evaluated due to the small number of such patients in clinical trials. Use of RELERT in the elderly is therefore not recommended.

Blood pressure effects may be more marked in this population than in younger adults (see section 3.4 Special warnings and 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 RELERT 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 RELERT has not been established in this population and its use is therefore not recommended in this age group.

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

Renal impairment
As the blood pressure effects of RELERT are amplified in renal impairment (see 3.4 Special warnings and precautions for use), a 20mg initial dose, is recommended in patients with mild or moderate renal impairment. The maximum daily dose should not exceed 40mg. RELERT is contra-indicated, in patients with severe renal impairment**.**

3.3 Contraindications

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

Patients with severe hepatic or severe renal impairment.

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

Patients with moderately severe or severe hypertension or untreated mild 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 (Prinzmetal's angina), objective or subjective symptoms of ischaemic heart disease.

Patients with significant arrhythmias or heart failure.

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 24hr before or after treatment with RELERT (see 3.5 Interactions with other medicinal products and other forms of interaction).

Concomitant administration of other 5-HT_1 receptor agonists with eletriptan**.**

3.4 Special warnings and precautions for use

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

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

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 3.5 - Interaction with other medicinal products and other forms of interaction – Interaction with serotonergic active drugs).

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

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

RELERT 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.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5 HT1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5 HT1 agonists have not been clearly established.

RELERT can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat (see 3.8 '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

RELERT should not be given without prior cardiovascular 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 RELERT **(**see 3.3 Contra-indications). 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 60mg or greater. 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 -17mmHg (normal 3mmHg) and for diastolic blood pressure was 14 -21mmHg (normal 4mmHg). In elderly subjects, the mean maximum increase in systolic blood pressure was 23mmHg compared with 13mmHg in young adults (placebo 8mmHg). 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.

3.5 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; see Interaction with serotonergic active drugs).

Population pharmacokinetic analysis of clinical studies has suggested that the following medicinal products (beta-blockers, tricyclic antidepressants, selective serotonin re-uptake inhibitors, oestrogen based hormone replacement

therapy, oestrogen containing oral contraceptives and calcium channel blockers) are unlikely to have an effect on the pharmacokinetic properties of eletriptan (see Interaction with serotonergic active drugs).

Eletriptan is not a substrate for monoamine oxidase (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 (160mg), verapamil (480mg) and fluconazole (100mg) 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 (1000mg) and ketoconazole (400mg), 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 4.2 Pharmacokinetic Properties). Therefore, RELERT should not be used together with potent CYP3A4 inhibitors eg 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.

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 **3.4 – Special warning and precautions for use)**

3.6 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 foetus.

Lactation:
Eletriptan is excreted in human breast milk. In one study of 8 women given a single dose of 80mg, 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 RELERT to women who are breast-feeding. Infant exposure can be minimised by avoiding breast-feeding for 24 hours after treatment.

3.7 Effects on ability to drive and use machines

Migraine or treatment with RELERT 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 RELERT.

3.8 Undesirable effects

RELERT has been administered in clinical trials to over 5000 subjects, taking one or two doses of RELERT 20, 40 or 80mg. RELERT 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 most common adverse reactions noted were asthenia, somnolence, nausea and dizziness. In randomised clinical studies using doses of 20, 40 and 80mg, a trend for a dose-dependency of the incidence of adverse events has been shown.

Tabular 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 Class	Common	Uncommon	Rare
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:			hyperbilirubinemia, 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 RELERT 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: Serotonin syndrome, rare cases of syncope, cerebrovascular accident.

Vascular Disorders: Hypertension.

Gastrointestinal Disorders: as with some other 5HT 1B/1D agonists, rare reports of ischaemic colitis have been received, vomiting.
Cardiac Disorders: Myocardial ischemia or infarction, arteriospasm coronary.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

3.9 Overdose

Subjects have received single doses of 120mg 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 haemodialysis or peritoneal dialysis has on the serum concentrations of eletriptan.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Selective serotonin ($5HT_1$) agonist ATC code: NO2C C06 .

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 RELERT in the acute treatment of migraine has been evaluated in 10 placebo-controlled trials involving more than 6000 patients (all treatment groups)who received RELERT at doses of 20 to 80mg. Headache relief occurred as early as 30 minutes following oral dosing compared to those on placebo. Increasing efficacy is observed at 1 and 2 hours. Response rates (i.e. reduction of moderate or severe headache pain to no or mild pain) 2 hours after dosing were 59-77% for the 80mg dose, 54-65% for the 40mg dose,
47-54% for the 20mg dose, and 19-40% following placebo. RELERT was also effective in the treatment of associated symptoms of migraine such as vomiting, nausea, photophobia and phonophobia.

The recommendation for dose titration to 80mg, 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.

Patients who responded to RELERT 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.

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

RELERT remains effective in menstrually associated migraine. RELERT, if taken during the aura phase, has not been demonstrated to prevent migraine headache and therefore RELERT 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 80mg dose of RELERT than with normal volunteers (see Section 3.4). This cannot be explained by any pharmacokinetic changes and so may represent a specific pharmacodynamic response to eletriptan in patients with renal impairment.

4.2 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 median T_{max} is 1.5 hours after oral dosing. Linear pharmacokinetics were demonstrated over the clinical dose range (20-80mg).

The AUC and C_{max} of eletriptan were increased by approximately 20-30% 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 5-7 days, the pharmacokinetics of eletriptan remained linear and accumulation was predictable. On multiple dosing of larger doses (40mg three times daily and 80mg twice daily), the accumulation of eletriptan over 7 days was greater than predicted (approximately 40%).

Distribution

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

Biotransformation
In vitro studies indicate that eletriptan is primarily metabolised by hepatic cytochrome P-450 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}-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 10-20% of those of parent and so would not be expected to significantly contribute to the therapeutic action of eletriptan.

Elimination

Mean total plasma clearance of eletriptan following IV 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 (40mg and 80mg) 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.

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 61-89ml/min), moderate (creatinine clearance 31-60ml/min) or severe (creatinine clearance <30ml/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.

4.3 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Special precautions for storage

Do not store above 30°C.

5.2 Instructions for Use and Handling

No special requirements.

5.3 List of Excipients

Core Tablet: Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate.

Film coat: titanium dioxide (E171), hypromellose, lactose monohydrate, glycerol triacetate and Sunset Yellow Aluminium lake (E110).

Manufacturer: Pfizer Manufacturing Deutschland GmbH, Illertissen, Germany
License Holder: Pfizer PFE Pharmaceuticals Israel Ltd.,
9 Shenkar St., Herzliya Pituach 46725

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