SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RELERT 20 mg
RELERT 40 mg
RELERT 80 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
RELERT 20mg:
Each film-coated tablet contains approximately 23mg lactose. Also contains Sunset yellow FCF aluminium lake (E110).
RELERT 40mg:
Each film-coated tablet contains approximately 5mg lactose. Also contains Sunset yellow FCF aluminium lake (E110).
RELERT 80mg:
Each film-coated tablet contains approximately 90mg lactose. Also contains Sunset yellow FCF aluminium lake (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Round, convex orange tablets debossed with "REP 20", "REP 40" or "REP 80" on one side and "VLE" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Acute treatment of the headache phase of migraine attacks, with or without aura.

4.2 Posology and method of administration
Posology
RELERT 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 5.1 Pharmacodynamic Properties – Further information on Clinical Trials).
The maximum daily dose should not exceed 160mg (see section 4.8 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 4.4 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 4.4 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 contraindicated in patients with severe renal impairment.

4.3 Contraindications
RELERT is contraindicated in patients with:
- hypersensitivity to eletriptan hydrobromide or to any of the excipients listed in 6.1.
- 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 24hr before or after treatment with eletriptan (see section 4.5).
- concomitant administration of other 5-HT_1 receptor agonists with eletriptan.

4.4 Special warnings and precautions for use

RELERT should not be used together with potent CYP3A4 inhibitors e.g., 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, which 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.

Eletriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat (see section 4.8). 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 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 section 4.3). 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 14-17mmHg (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.

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).

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 FCF aluminium lake (E110) which may cause allergic reactions.

RELERT tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say 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 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.

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). Therefore, RELERT 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).

4.6 Fertility, pregnancy and lactation
Pregnancy: For RELERT 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. RELERT 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 RELERT 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
RELERT has moderate influence on the 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.

4.8 Undesirable effects
Summary of the safety profile
RELERT has been administered in clinical trials to over 5000 subjects, taking one or two doses of RELERT 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 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:			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-HT1 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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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 haemodialysis or peritoneal dialysis has on the serum concentrations of eletriptan.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective Serotonin ($5HT_1$) 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 RELERT in the acute treatment of migraine has been evaluated in 10 placebo-controlled trials involving more than 6000 patients (in 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 59-77% for the 80 mg dose, 54-65% for the 40 mg dose, 47-54% for the 20 mg 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 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.

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 80 mg dose of RELERT than with normal volunteers (see section 4.4). 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 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 (20-80 mg).

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 (40 mg three times daily and 80 mg two times daily), the accumulation of eletriptan over 7 days was greater than predicted (approximately 40%).

Distribution

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

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 inhibitor**s**. *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 (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, hypromellose, magnesium stearate, titanium dioxide (E171), glycerol triacetate, sunset yellow FCF aluminium lake (E110).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and content of the container

Blister.
Approved pack sizes: 2, 3, 4, 5, 6, 10 tablets. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Dexcel Pharma Technologies Ltd.

10 Hakidma St., Yokneam Illit 2069200, Israel

8. MARKETING AUTHORISATION NUMBERS

Relert 20mg: 124-28-30370
Relert 40mg: 124-29-30371
Relert 80mg: 124-30-30372

Revised in April 2025 according to MOH guidelines.