

1. NAME OF THE MEDICINAL PRODUCT

RIZALT® 10 mg Tablets

RIZALT RPD® 10 mg Wafers

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIZALT 10 mg tablets

Each tablet contains 14.53 mg of rizatriptan benzoate (corresponding to 10 mg of the rizatriptan).

Excipient(s) with known effect

Lactose monohydrate 60.5 mg in the 10 mg tablet.

RIZALT RPD 10 mg Wafers

Each tablet contains 14.53 mg of rizatriptan benzoate (corresponding to 10 mg of the rizatriptan).

For the full list of excipients, see section 12.

3. PHARMACEUTICAL FORM

RIZALT 10 mg tablets

Tablet

10 mg tablets are pale pink, capsule-shaped, convex tablets, coded 267 on one side and plain on the other.

RIZALT RPD 10 mg Wafers

Wafer

10 mg wafers are white to off-white, round with a flat or slightly irregular surface and a modified square on one side and plain on the other side, with a peppermint flavour.

4. THERAPEUTIC INDICATIONS

RIZALT® Tablets and RIZALT RPD® 10 mg Wafers (orally disintegrating tablets) are indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use

- RIZALT should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with RIZALT, the diagnosis of migraine should be reconsidered before RIZALT is administered to treat any subsequent attacks.
- RIZALT is not indicated for use in the management of hemiplegic or basilar migraine [see *Contraindications* (6)].
- RIZALT is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of RIZALT have not been established for cluster headache.

5. DOSAGE AND ADMINISTRATION

5.1 Dosing Information in Adults

The recommended starting dose of RIZALT is 10 mg for the acute treatment of migraines in adults.

Redosing

Although the effectiveness of a second dose or subsequent doses has not been established in placebo-controlled trials, if the migraine headache returns, a second dose may be administered 2 hours after the first dose. The maximum daily dose should not exceed 30 mg in any 24-hour period. The safety of treating, on average, more than four headaches in a 30-day period has not been established.

5.2 Administration of RIZALT RPD 10 mg Wafers

For RIZALT RPD 10 mg Wafers, administration with liquid is not necessary. The wafers are packaged in a blister within an outer aluminum pouch and patients should not remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

5.3 Dosage Adjustment

Some patients should receive a lower dose of RIZALT, in particular the following patient groups:

- Patients taking propranolol
- *Moderate to severe hepatic impairment*
- Renal impairment: patients with creatinine clearance $<10 \text{ mL} / 1.73 \text{ m}^2$
- Elderly patients

If lower dose is not optional, the physician should consider alternative therapies for these patients, for example, other 5-HT_{1B/1D} agonists.

6 CONTRAINDICATIONS

RIZALT is contraindicated in patients with:

- Ischemic coronary artery disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), or other significant underlying cardiovascular disease [see *Warnings and Precautions* (7.1)].
- Coronary artery vasospasm including Prinzmetal's angina [see *Warnings and Precautions* (7.1)].
- History of stroke or transient ischemic attack (TIA) [see *Warnings and Precautions* (7.4)].
- Peripheral vascular disease (PVD) [see *Warnings and Precautions* (7.5)].
- Ischemic bowel disease [see *Warnings and Precautions* (7.5)].
- Uncontrolled hypertension [see *Warnings and Precautions* (7.8)].
- Recent use (i.e., within 24 hours) of another 5-HT₁ agonist, ergotamine-containing medication, or ergot-type medication (such as dihydroergotamine or methysergide) [see *Drug Interactions* (9.2 and 9.3)].
- Hemiplegic or basilar migraine [see *Therapeutic Indications* (4) (4)].
- Concurrent administration or recent discontinuation (i.e., within 2 weeks) of a MAO-A inhibitor [see *Drug Interactions* (9.5) and *Clinical Pharmacology* (13.2)].
- Hypersensitivity to the active substance or to any of the excipients listed in section 12 (angioedema and anaphylaxis seen) [see *Adverse Reactions* (8.2)]

7 WARNINGS AND PRECAUTIONS

7.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

RIZALT should not be given to patients with ischemic or vasospastic coronary artery disease. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of RIZALT. Some of these reactions occurred in patients without known coronary artery disease (CAD). 5-HT₁ agonists, including RIZALT may cause coronary artery vasospasm (Prinzmetal's Angina), even in patients without a history of CAD.

Triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) should have a cardiovascular evaluation prior to receiving RIZALT. If there is evidence of CAD or coronary artery vasospasm, RIZALT should not be administered [see *Contraindications* (6)]. For patients who have a negative cardiovascular evaluation, consideration should be given to administration of the first RIZALT dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following RIZALT administration. Periodic

cardiovascular evaluation should be considered in intermittent long-term users of RIZALT who have cardiovascular risk factors.

7.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT₁ agonists. Discontinue RIZALT if these disturbances occur.

7.3 Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure

As with other 5-HT₁ agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck and jaw commonly occur after treatment with RIZALT and are usually non-cardiac in origin. However, if a cardiac origin is suspected, patients should be evaluated. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT₁ agonists.

7.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT₁ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT₁ agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). Discontinue RIZALT if a cerebrovascular event occurs.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. RIZALT should not be administered to patients with a history of stroke or transient ischemic attack [see *Contraindications* (6)].

7.5 Other Vasospasm Reactions

5-HT₁ agonists, including RIZALT, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT₁ agonist, the suspected vasospasm reaction should be ruled out before receiving additional RIZALT doses.

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.

7.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

7.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including RIZALT particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [see *Drug Interactions* (9.5)]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms can occur within minutes to hours of receiving a new or a greater dose of a serotonergic medication. RIZALT treatment should be discontinued if serotonin syndrome is suspected [see *Drug Interactions* (9.4)].

7.8 Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients with and without a history of hypertension receiving 5-HT₁ agonists, including RIZALT. In healthy young adult male and female patients who received maximal doses of RIZALT (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. RIZALT is contraindicated in patients with uncontrolled hypertension [see *Contraindications* (6)].

8 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina [see *Warnings and Precautions* (7.1)].
- Arrhythmias [see *Warnings and Precautions* (7.2)].
- Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure [see *Warnings and Precautions* (7.3)].
- Cerebrovascular Events [see *Warnings and Precautions* (7.4)].
- Other Vasospasm Reactions [see *Warnings and Precautions* (7.5)].
- Medication Overuse Headache [see *Warnings and Precautions* (7.6)].
- Serotonin Syndrome [see *Warnings and Precautions* (7.7)].
- Increase in Blood Pressure [see *Warnings and Precautions* (7.8)].

8.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Incidence in Controlled Clinical Trials

Adverse reactions to RIZALT were assessed in controlled clinical trials that included over 3700 adult patients who received single or multiple doses of RIZALT Tablets. The most common adverse reactions during treatment with RIZALT ($\geq 5\%$ in either treatment group and greater than placebo) were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These adverse reactions appeared to be dose related.

Table 1 lists the adverse reactions (incidence $\geq 2\%$ and greater than placebo) after a single dose of RIZALT.

Table 1: Incidence ($\geq 2\%$ and Greater than Placebo) of Adverse Reactions After a Single Dose of RIZALT Tablets or Placebo

Adverse Reactions	% of Patients		
	RIZALT 5 mg (N=977)	RIZALT 10 mg (N=1167)	Placebo (N=627)
Atypical Sensations	4	5	4
Paresthesia	3	4	<2

<i>Pain and other Pressure Sensations</i>	6	9	3
Chest Pain:			
tightness/pressure and/or heaviness	<2	3	1
Neck/throat/jaw:			
pain/tightness/pressure	<2	2	1
Regional Pain:			
tightness/pressure and/or heaviness	<1	2	0
Pain, location unspecified	3	3	<2
<i>Digestive</i>	9	13	8
Dry Mouth	3	3	1
Nausea	4	6	4
<i>Neurological</i>	14	20	11
Dizziness	4	9	5
Headache	<2	2	<1
Somnolence	4	8	4
<i>Other</i>			
Asthenia/fatigue	4	7	2

The frequencies of adverse reactions in clinical trials did not increase when up to three doses were taken within 24 hours. Adverse reaction frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse reactions were not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Other Events Observed in Association with the Administration of RIZALT

In the following section, the frequencies of less commonly reported adverse events are presented that were not reported in other sections of the labeling. Because the reports include events observed in open studies, the role of RIZALT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used RIZALT and reported an event divided by the total number of patients exposed to RIZALT (N=3716). All reported events occurred at an incidence $\geq 1\%$, or are believed to be reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least ($>$)1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

General: Infrequent was facial edema. Rare were syncope and edema/swelling.

Atypical Sensations: Frequent were warm sensations.

Cardiovascular: Frequent was palpitation. Infrequent were tachycardia, cold extremities, and bradycardia.

Digestive: Frequent were diarrhea and vomiting. Infrequent were dyspepsia, tongue edema, abdominal distention, and thirst.

Musculoskeletal: Infrequent were muscle weakness, stiffness, myalgia and muscle cramp/spasm.

Neurological/Psychiatric: Frequent were hypoesthesia, mental acuity decreased, euphoria and tremor. Infrequent were vertigo, insomnia, confusion/disorientation, ataxia, gait abnormality, memory impairment, and agitation.

Respiratory: Frequent was dyspnea. Infrequent was pharyngeal edema.

Special Senses: Infrequent were blurred vision and tinnitus. Rare was eye swelling.

Skin and Skin Appendage: Frequent was flushing. Infrequent were sweating, pruritus, rash, and urticaria. Rare was erythema, hot flashes.

The adverse reaction profile seen with RIZALT RPD Wafers was similar to that seen with RIZALT Tablets.

8.2 Postmarketing Experience

The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated include all except those already listed in other sections of the labeling or those too general to

be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of RIZALT in their causation cannot be reliably determined.

Neurological/Psychiatric: Seizure, serotonin syndrome

General: Allergic conditions including anaphylaxis/anaphylactoid reaction, angioedema, wheezing, and toxic epidermal necrolysis [see *Contraindications* (6)].

Special Senses: Dysgeusia.

Musculoskeletal: facial pain, myalgia;

Cardiovascular disorders: arrhythmia; bradycardia;

Gastrointestinal disorders: ischemic colitis;

Investigations: ECG abnormalities.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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>

9 DRUG INTERACTIONS

9.1 Propranolol

Concomitant treatment with RIZALT and propranolol is not recommended as propranolol has been shown to increase the plasma AUC of rizatriptan by 70% [see *Dosage and Administration* (5.3) and *Clinical Pharmacology* (13.2)].

9.2 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and RIZALT within 24 hours is contraindicated [see *Contraindications* (6)].

9.3 Other 5-HT₁ Agonists

Because their vasospastic effects may be additive, co-administration of RIZALT and other 5-HT₁ agonists within 24 hours of each other is contraindicated [see *Contraindications* (6)].

9.4 SSRIs/SNRIs and Serotonin Syndrome

Cases of serotonin syndrome have been reported during co-administration of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) [see *Warnings and Precautions* (7.7)].

9.5 Monoamine Oxidase Inhibitors

RIZALT is contraindicated in patients taking MAO-A inhibitors and non-selective MAO inhibitors. A specific MAO-A inhibitor increased the systemic exposure of rizatriptan and its metabolite [see *Contraindications* (6) and *Clinical Pharmacology* (13.2)].

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Available human data on the use of RIZALT in pregnant women are not sufficient to draw conclusions about drug-associated risk for major birth defects and miscarriage.

In animal studies, developmental toxicity was observed following oral administration of rizatriptan during pregnancy (decreased fetal body weight in rats) or throughout pregnancy and lactation (increased mortality, decreased body weight, and neurobehavioral impairment in rat offspring) at maternal plasma exposures greater than that expected at therapeutic doses in humans [see *Animal Data*].

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The reported rate of major birth defects among deliveries to women with migraine range from 2.2% to 2.9% and the reported rate of miscarriage was 17%, which are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with migraine, there is an increased risk of adverse perinatal outcomes in the mother, including pre-eclampsia and gestational hypertension.

Data

Human Data

The Pregnancy Registry for RIZALT did not identify any pattern of congenital anomalies or other adverse birth outcomes over the period of 1998 to 2018. However, the lack of identification of any pattern should be viewed with caution, as the number of prospective reports with outcome information was low and did not provide sufficient power to detect an increased risk of individual birth defects associated with the use of RIZALT. Additionally, there was significant loss to follow-up in the prospective pregnancy reports, further complicating this assessment of an association between RIZALT and any pattern of congenital anomalies or other adverse birth outcomes.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 157 births with first-trimester exposure to rizatriptan, 7 infants were born with malformations (relative risk 1.01 [95% CI: 0.40 to 2.08]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for triptans before pregnancy only compared with a population control group. Of the 310 women who redeemed prescriptions for rizatriptan during the first trimester, 10 had infants with major congenital malformations (OR 1.03 [95% CI: 0.55 to 1.93]), while for the 271 women who redeemed prescriptions for rizatriptan before, but not during, pregnancy, 12 had infants with major congenital malformations (OR 1.48 [95% CI: 0.83 to 2.64]), each compared with the population comparison group.

Animal Data

When rizatriptan (0, 2, 10, or 100 mg/kg/day) was administered orally to pregnant rats throughout organogenesis, a decrease in fetal body weight was observed at the highest doses tested. At the mid dose (10 mg/kg/day), which was a no-effect dose for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 15 times that in humans at the maximum recommended human dose (MRHD) of 30 mg/day. When rizatriptan (0, 5, 10, or 50 mg/kg/day) was administered orally to pregnant rabbits throughout organogenesis, no adverse fetal effects were observed. Plasma exposure (AUC) at the highest dose tested was 115 times that in humans at the MRHD. Placental transfer of drug to the fetus was demonstrated in both species.

Oral administration of rizatriptan (0, 2, 10, or 100 mg/kg/day) to female rats prior to and during mating and continuing throughout gestation and lactation resulted in reduced body weight in offspring from birth and throughout lactation at all but the lowest dose tested (2 mg/kg/day). Plasma exposure (AUC) at the no-effect dose (2 mg/kg/day) for adverse effects on postnatal development was similar to that in humans at the MRHD.

Oral administration of rizatriptan (0, 5, 100, or 250 mg/kg/day) throughout organogenesis and lactation resulted in neonatal mortality, reduced body weight (which persisted into adulthood), and impaired neurobehavioral function in offspring at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose for adverse effects on postnatal development (5 mg/kg/day) was approximately 8 times that in humans at the MRHD.

10.2 Lactation

Risk Summary

There are no data on the presence of rizatriptan or any active metabolites in human milk, or on the effects of rizatriptan on the breastfed infant, or on milk production.

Rizatriptan was excreted in rat milk, with levels in milk approximately 6 times those in maternal plasma.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RIZALT or RIZALT RPD and any potential adverse effects on the breastfed infant from RIZALT or RIZALT RPD or from the underlying maternal condition.

Data

Following oral administration of rizatriptan to lactating rats at a dose of 100 mg/kg/day, drug concentrations of rizatriptan in milk samples exceeded maternal plasma drug concentrations by approximately 6-fold.

10.3 Pediatric Use

RIZALT is not recommended for use in patients under 18 years of age.

10.4 Geriatric Use

Clinical studies of RIZALT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Although the pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults ($n=17$), in general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of coronary artery disease) should have a cardiovascular evaluation prior to receiving RIZALT [see *Warnings and Precautions* (7.1)].

10.5 Patients with Phenylketonuria

RIZALT 10mg RPD Wafers contains aspartame, a source of phenylalanine. Each RIZALT 10-mg RPD Wafers contains 3.75mg aspartame, corresponding to 2.1 mg phenylalanine. It may be harmful for patients with phenylketonuria.

11 OVERDOSAGE

No overdoses of RIZALT were reported during clinical trials in adults.

Some adult patients who received 40 mg of RIZALT either a single dose or as two doses with a 2-hour interdose interval had dizziness and somnolence.

In a clinical pharmacology study in which 12 adult subjects received RIZALT, at total cumulative doses of 80 mg (given within four hours), two of the subjects experienced syncope, dizziness, bradycardia including third degree AV block, vomiting, and/or incontinence.

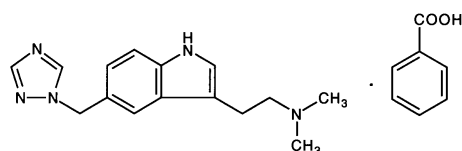
In addition, based on the pharmacology of RIZALT, hypertension or myocardial ischemia could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with RIZALT. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

12 DESCRIPTION

RIZALT contains rizatriptan benzoate, a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

RIZALT Tablets are available for oral administration in a strength of 10 mg (corresponding to 14.53 mg of the benzoate salt). RIZALT RPD Wafers are available in the strength of 10 mg (corresponding to 14.53 mg of the benzoate salt). Each compressed tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, magnesium stearate, and ferric oxide (red).

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint Naefco P.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT_{1B/1D} receptors. RIZALT presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-HT_{1B/1D} receptors located on intracranial blood vessels and sensory nerves of the trigeminal system.

13.2 Pharmacokinetics

Absorption

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the RIZALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, RIZALT was administered without regard to food.

The bioavailability and C_{max} of rizatriptan were similar following administration of RIZALT Tablets and RIZALT RPD Wafers, but the rate of absorption is somewhat slower with RIZALT RPD Wafers, with T_{max} delayed by up to 0.7 hour. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

Distribution

The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

Metabolism

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-HT_{1B/1D} receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-HT_{1B/1D} receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-HT_{1B/1D} receptor.

Elimination

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10-mg oral administration of ¹⁴C-rizatriptan. Following oral administration of ¹⁴C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

The plasma half-life of rizatriptan in males and females averages 2-3 hours.

Cytochrome P450 Isoforms

Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (K_i =1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Special Populations

Geriatric: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic impairment: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of subjects with normal hepatic function; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency.

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m²), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in subjects with normal renal function. In hemodialysis patients, (creatinine clearance <2 mL/min/1.73 m²), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function.

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

Drug Interactions

[See also Drug Interactions (9).]

Monoamine oxidase inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (e.g., moclobemide) or nonselective MAO inhibitors [type A and B] (e.g., isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when RIZALT 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors [see Contraindications (6) and Drug Interactions (9.5)].

Propranolol: In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy adult subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a four-fold increase was observed in one subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol [see Dosage and Administration (5.3) and Drug Interactions (9.1)].

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Paroxetine: In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for two weeks and a single dose of RIZALT 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine [see Warnings and Precautions (7.7), Drug Interactions (9.4)].

Oral contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of RIZALT (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral carcinogenicity studies of rizatriptan were conducted in mice (100 weeks) and rats (106 weeks) at doses of up to 125 mg/kg/day. There was no evidence of an increase in tumor incidence related to rizatriptan in either species. Plasma exposures (AUC) at the highest dose tested were approximately 150 (mice) and 240 times (rats) that in humans at the maximum recommended human dose (MRHD) of 30 mg/day.

Mutagenesis

Rizatriptan was neither mutagenic nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, *in vitro* mammalian cell mutagenesis and chromosomal aberration assays, and the *in vivo* chromosomal aberration assay in mouse.

Impairment of Fertility

Oral administration of rizatriptan (0, 2, 10, or 100 mg/kg/day) to female rats prior to and during mating and continuing throughout gestation and lactation resulted in no effect on fertility however, altered estrous cyclicity and delays in time to mating were observed at the highest dose tested. Plasma exposure at the no-effect dose (10 mg/kg/day) for reproductive toxicity was approximately 15 times that in humans at the MRHD.

Oral administration of rizatriptan (0, 5, 35, or 250 mg/kg/day) to male rats prior to and during mating resulted in no impairment of fertility or reproductive performance. Plasma exposure (AUC) at the highest dose tested was approximately 550 times that in humans at the MRHD.

15 CLINICAL STUDIES

The efficacy of RIZALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours post-dose were evaluated. A second dose of RIZALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either RIZALT 5 or 10 mg compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the four controlled studies are summarized in Table 2.

Table 2: Response Rates 2 Hours Following Treatment of Initial Headache in Studies 1, 2, 3, and 4

Study	Placebo	RIZALT Tablets 5 mg	RIZALT Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,† (n=456)
2 [‡]	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

* p-value <0.05 in comparison with placebo.

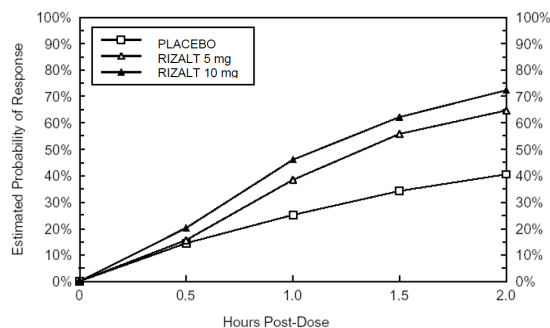
† p-value <0.05 in comparison with 5 mg.

‡ Results for initial headache only.

Comparisons of drug performance based upon results obtained in different clinical trials may not be reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving an initial headache response within 2 hours following treatment in pooled Studies 1, 2, 3, and 4 is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving an Initial Headache Response by 2 Hours in Pooled Studies 1, 2, 3, and 4*

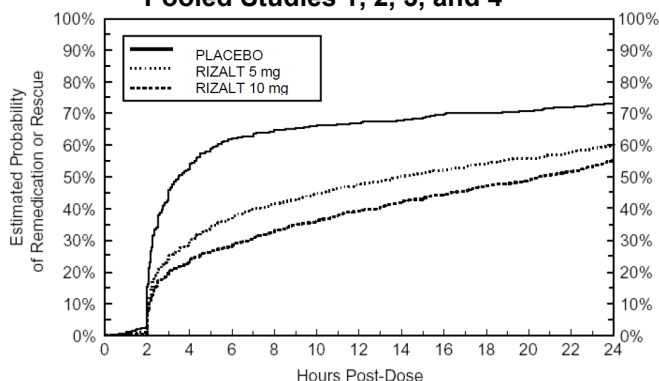


* Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with RIZALT or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 1, 2, 3, and 4). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of RIZALT compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Patients Taking a Second Dose of RIZALT Tablets or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment in Pooled Studies 1, 2, 3, and 4*



* This Kaplan-Meier plot is based on data obtained in 4 placebo-controlled outpatient clinical trials (Studies 1, 2, 3, and 4). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. In two additional similar studies, efficacy was unaffected by relationship to menses. There were insufficient data to assess the impact of race on efficacy.

RIZALT RPD Wafers

The efficacy of RIZALT RPD was established in two multicenter, randomized, placebo-controlled trials that were similar in design to the trials of RIZALT Tablets (Studies 5 and 6). Patients were instructed to treat a moderate to severe headache. Patients treated in these studies were primarily female (88%) and Caucasian (95%), with a mean age of 42 years (range 18-72).

In both studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either RIZALT RPD 5 or 10 mg compared to those who received placebo. The results from Studies 5 and 6 are summarized in Table 3.

Table 3: Response Rates 2 Hours Following Treatment of Initial Headache in Studies 5 and 6

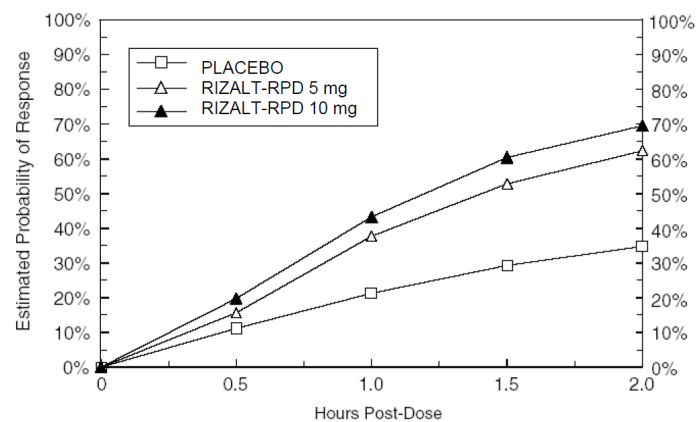
Study	Placebo	RIZALT RPD 5 mg	RIZALT RPD 10 mg
5	47% (n=98)	66%* (n=100)	66%* (n=113)
6	28% (n=180)	59%* (n=181)	74%*,† (n=186)

* p-value <0.01 in comparison with placebo.

† p-value <0.01 in comparison with 5 mg.

The estimated probability of achieving an initial headache response by 2 hours following treatment with RIZALT RPD in pooled Studies 5 and 6 is depicted in Figure 3.

Figure 3: Estimated Probability of Achieving an Initial Headache Response with RIZALT RPD by 2 Hours in Pooled Studies 5 and 6*

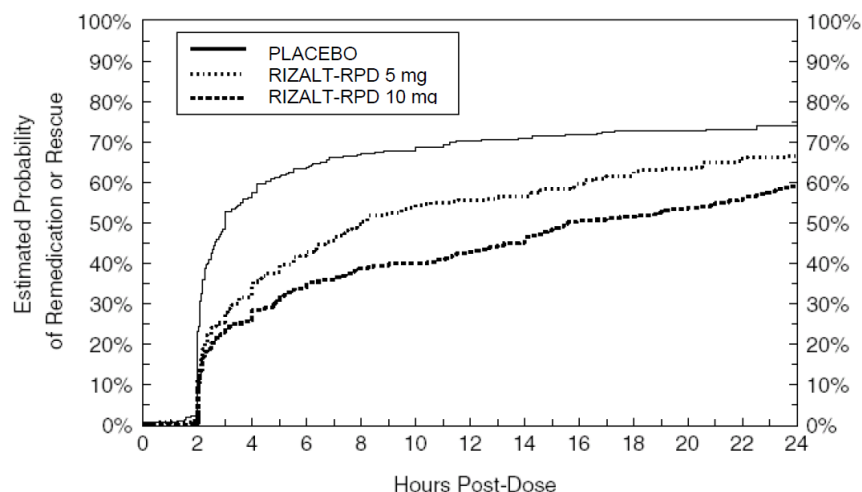


* Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with RIZALT RPD or placebo. The averages displayed are based on pooled data from 2 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 5 and 6). Patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of RIZALT RPD as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain response in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 4.

Figure 4: Estimated Probability of Patients Taking a Second Dose of RIZALT RPD or Other Medication for Migraines Over the 24 Hours Following the Initial Dose of Study Treatment in Pooled Studies 5 and 6*



*This Kaplan-Meier plot is based on data obtained in 2 placebo-controlled outpatient clinical trials (Studies 5 and 6). Patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Remedication was not allowed within 2 hours post-dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

RIZALT 10 mg Tablets are supplied in Carton of 2, 3, 6 and 12 tablets (not all package sizes may be marketed).

RIZALT RPD 10 mg Wafers have a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet). They are supplied as follows: carton of 2, 3, 6 and 12 wafers (not all package sizes may be marketed).

Storage

Store RIZALT 10 mg Tablets and RIZALT RPD 10 mg Wafers below 30°C.

Shelf life

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

Manufacturer:

Merck Sharp & Dohme Corp., New Jersey, USA.

License holder:

Merck Sharp & Dohme (Israel – 1996) Company Ltd., POB. 7121, Petah-Tiqva 49170.

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