HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIZAFILM safely and effectively. See full prescribing information for RIZAFILM.

RizaFilm (rizatriptan) oral film
Initial U.S. Approval: 1998

----------INDICATIONS AND USAGE----------
RizaFilm is a serotonin (5-HT) 1B/1D receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults and in pediatric patients 12 to 17 years of age weighing 40 kg or more (1)
Limitations of Use:
- Use only after a clear diagnosis of migraine has been established (1)
- Not indicated for the preventive treatment of migraine (1)
- Not indicated for the treatment of cluster headache (1)

----------DOSAGE AND ADMINISTRATION----------
- RizaFilm is administered on the tongue (2.1)
- Adults: 10 mg single dose; separate repeat doses by at least two hours; maximum cumulative dosage in a 24-hour period is 30 mg (2.1)
- Pediatric patients 12 to 17 years of age weighing 40 kg or more: 10 mg single dose (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Oral film: 10 mg rizatriptan. (3)

----------CONTRAINDICATIONS----------
- History of ischemic heart disease or coronary artery vasospasm (4)
- History of stroke or transient ischemic attack (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT_1 agonist (e.g., another triptan), or of an ergotamine-containing medication (4)
- Hemiplegic or basilar migraine (4)
- MAO-A inhibitor used in the past 2 weeks (4)
- Co-administration with propranolol (4)
- Hypersensitivity to rizatriptan or any of the ingredients of RizaFilm (4)

----------WARNINGS AND PRECAUTIONS ----------
- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue dosing if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness; Generally not associated with myocardial ischemia; Evaluate patients at high risk (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue dosing if occurs (5.4)
- Gastrointestinal ischemic events, peripheral vasospastic reactions: Discontinue dosing if occurs (5.5)
- Hypersensitivity Reactions: angioedema and anaphylaxis have occurred (5.6)
- Medication overuse headache: Detoxification may be necessary (5.7)
- Serotonin syndrome: Discontinue dosing if occurs (5.8)

----------ADVERSE REACTIONS----------
The most common adverse reactions in adults were (incidence ≥5% and greater than placebo): asthenia/fatigue, somnolence, pain/pressure sensation, dizziness, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gensco Pharma at 1-866-608-6284 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
• Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RizaFilm™ is indicated for the acute treatment of migraine with or without aura in adults and in pediatric patients 12 to 17 years of age weighing 40 kg or more.

Limitations of Use

- RizaFilm 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 RizaFilm, the diagnosis of migraine should be reconsidered before RizaFilm is administered to treat any subsequent attacks.
- RizaFilm is not indicated for the preventive treatment of migraine.
- Safety and effectiveness of RizaFilm have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information in Adults

The recommended dose of RizaFilm in adults is 10 mg administered on the tongue. The maximum cumulative dose that may be given in 24 hours is 30 mg, with doses separated by at least 2 hours. The safety of treating, on average, more than four headaches in a 30-day period has not been established.

2.2 Dosing Information in Pediatric Patients (12 to 17 Years of Age)

The recommended dose of RizaFilm in patients weighing 40 kg or more is 10 mg administered on the tongue.

The efficacy and safety of treatment with more than one dose of RizaFilm within 24 hours in pediatric patients 12 to 17 years of age have not been established.

2.3 Administration of RizaFilm Oral Films

For RizaFilm oral films, administration with liquid is not necessary. Oral films are packaged individually in child-resistant aluminum pouches with a tear notch. To open the pouch, fold on the dotted line and tear open at the notch. Place the oral film on the tongue, where it will disintegrate within approximately two minutes and can be swallowed with saliva.

3 DOSAGE FORMS AND STRENGTHS

RizaFilm 10 mg oral films are white to off-white, rectangular strips of 2.2 cm x 2.75 cm with a blue identifier “RIZA10” on one side.

4 CONTRAINDICATIONS

RizaFilm 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 (5.1)]*
- Coronary artery vasospasm including Prinzmetal's angina *[see Warnings and Precautions (5.1)]*
- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.2)]*
- History of stroke or transient ischemic attack (TIA) *[see Warnings and Precautions (5.4)]*
- Peripheral vascular disease (PVD) *[see Warnings and Precautions (5.5)]*
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*

- Uncontrolled hypertension *[see Warnings and Precautions (5.9)]*
- Recent use (i.e., within 24 hours) of another 5-HT_1 agonist, ergotamine-containing medication, or ergot-type medication (such as dihydroergotamine or methysergide) *[see Drug Interactions (7.2 and 7.3)]*
- Hemiplegic or basilar migraine
- Concurrent administration or recent discontinuation (i.e., within 2 weeks) of a MAO-A inhibitor *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*
- Concurrent administration of propranolol *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*
- Hypersensitivity to rizatriptan or any ingredients in RizaFilm (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.6)]*

5 WARNINGS AND PRECAUTIONS

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

RizaFilm 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 rizatriptan benzoate. Some of these reactions occurred in patients without known coronary artery disease (CAD). 5-HT_1 agonists, including RizaFilm may cause coronary artery vasospasm (Prinzmetal's Angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) before receiving RizaFilm. If there is evidence of CAD or coronary artery vasospasm, RizaFilm is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first RizaFilm dose in a medically supervised setting and performing an electrocardiogram (ECG) immediately following RizaFilm administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of RizaFilm.

5.2 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-HT_1 agonists. Discontinue RizaFilm if these disturbances occur. RizaFilm is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorder.

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

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with rizatriptan, the active moiety in RizaFilm, and are usually noncardiac in origin. However, perform a cardiac evaluation if these patients are at a high cardiac risk. The use of RizaFilm is contraindicated in patients with CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 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 RizaFilm if a cerebrovascular event occurs.

Before treating headaches in patients not previously diagnosed with migraine or in patients who present with atypical symptoms, exclude other potentially serious neurological conditions. RizaFilm is contraindicated in patients with a history of stroke or transient ischemic attack.

5.5 Other Vasospasm Reactions

5-HT_1 agonists, including RizaFilm, 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-HT_1 agonist, rule out the suspected vasospasm reaction before receiving additional RizaFilm doses.

Transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists has not been clearly established.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, have occurred in patients receiving rizatriptan, the active moiety in RizaFilm. Such reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. RizaFilm is contraindicated in patients with a history of hypersensitivity reaction to rizatriptan.

5.7 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 the 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.

5.8 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including RizaFilm, particularly during coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors *[see Drug Interactions (7.5)]*. 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. RizaFilm treatment should be discontinued if serotonin syndrome is suspected *[see Drug Interactions (7.4) and Patient Counseling Information (17)]*.

5.9 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-HT_1 agonists, including rizatriptan benzoate. In healthy young adult male and female patients who received maximal doses of rizatriptan benzoate (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. RizaFilm is contraindicated in patients with uncontrolled hypertension *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following serious 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 (5.1)]*
- Arrhythmias *[see Warnings and Precautions (5.2)]*
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure *[see Warnings and Precautions (5.3)]*

- Cerebrovascular Events *[see Warnings and Precautions (5.4)]*
- Other Vasospasm Reactions *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Medication Overuse Headache *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.9)]*

6.1 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.

The studies described below were conducted with rizatriptan benzoate tablets; adverse reactions with RizaFilm are expected to be similar to rizatriptan benzoate tablets.

Adults

Incidence in Controlled Clinical Trials

Adverse reactions to rizatriptan benzoate were assessed in controlled clinical trials that included over 3700 adult patients who received single or multiple doses of rizatriptan benzoate tablets. The most common adverse reactions during treatment with rizatriptan benzoate (≥5% in either treatment group and greater than placebo) were asthenia/fatigue, somnolence, pain/pressure sensation, dizziness, and nausea.

Table 1 lists the adverse reactions (incidence ≥2% and greater than placebo) after a single dose of rizatriptan benzoate in adults.

Table 1: Incidence (≥2% and Greater than Placebo) of Adverse Reactions After a Single Dose of Rizatriptan Benzoate Tablets or Placebo in Adults

Adverse Reactions	Rizatriptan Benzoate 10 mg (N=1167) %	Placebo (N=627) %
Atypical Sensations	5	4
Paresthesia	4	<2
Pain and other Pressure Sensations	9	3
Chest Pain: tightness/pressure and/or heaviness	3	1
Pain, location unspecified	3	<2
Neck/throat/jaw: pain/tightness/pressure	2	1
Regional Pain: tightness/pressure and/or heaviness	2	0
Digestive	13	8
Nausea	6	4
Dry mouth	3	1
Neurological	20	11
Dizziness	9	5
Somnolence	8	4
Headache	2	<1
Other		
Asthenia/fatigue	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, 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 Rizatriptan Benzoate in Adults

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 rizatriptan benzoate 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 rizatriptan benzoate and reported an event divided by the total number of patients exposed to rizatriptan benzoate (N=3716). All reported events occurred at an incidence ≥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, and abdominal distention.

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

Neurological/Psychiatric: Frequent were hypoesthesia, euphoria, and tremor. Infrequent were vertigo, insomnia, confusion/disorientation, 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 and hot flashes.

Pediatric Patients 12 to 17 Years of Age

Incidence in Controlled Clinical Trials in Pediatric Patients

Adverse reactions to rizatriptan benzoate orally disintegrating tablets were assessed in a controlled clinical trial for the acute treatment of migraine (Study 7) that included a total of 1382 pediatric patients (including those 12-17 years of age), of which 977 (72%) were administered at least one dose of study treatment (rizatriptan benzoate orally disintegrating tablets and/or placebo) *[see Clinical Studies (14.2)]*. The incidence of adverse reactions reported for pediatric patients in the acute clinical trial was similar in patients who received rizatriptan benzoate tablets to those who received placebo. The adverse reaction pattern in pediatric patients is expected to be similar to that in adults.

Other Events Observed in Association with the Administration of Rizatriptan Benzoate Orally Disintegrating Tablets in Pediatric Patients

In the following section, the frequencies of less commonly reported adverse events are presented. Because the reports include events observed in open studies, the role of rizatriptan benzoate orally disintegrating tablets 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 pediatric patients (including those 12 to 17 years of age) who used rizatriptan benzoate orally disintegrating tablets and reported an event divided by the total

number of patients exposed to rizatriptan benzoate orally disintegrating tablets (N=1068). All reported events occurred at an incidence ≥1%, or are believed to be reasonably associated with the use of the drug. Events are further classified within system organ class and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in (>)1/100 pediatric patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 pediatric patients, and rare adverse experiences are those occurring in fewer than 1/1000 patients.

General: Frequent was fatigue.

Ear and labyrinth disorders: Infrequent was hypoacusis.

Gastrointestinal disorders: Frequent was abdominal discomfort.

Nervous system disorders: Infrequent were coordination abnormal, disturbance in attention, and presyncope.

Psychiatric disorders: Infrequent was hallucination.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of rizatriptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neurological/Psychiatric: Seizure.

General: Allergic conditions including anaphylaxis/anaphylactoid reaction, angioedema, wheezing, and toxic epidermal necrolysis *[see Contraindications (4)]*.

Special Senses: Dysgeusia.

7 DRUG INTERACTIONS

7.1 Propranolol

Because propranolol increases the exposure of rizatriptan and dosage adjustment is not possible with RizaFilm, concomitant use of RizaFilm with propranolol is contraindicated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

7.2 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 RizaFilm within 24 hours is contraindicated *[see Contraindications (4)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, co-administration of RizaFilm and other 5-HT_1 agonists within 24 hours of each other is contraindicated *[see Contraindications (4)]*.

7.4 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 (5.7)]*.

7.5 Monoamine Oxidase Inhibitors

Because of an increase in the systemic exposure of rizatriptan and its metabolite, RizaFilm is contraindicated in patients taking MAO-A inhibitors and non-selective MAO inhibitors *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data on the use of rizatriptan 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 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 rizatriptan 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 rizatriptan. Additionally, there was significant loss to follow-up in the prospective pregnancy reports, further complicating this assessment of an association between rizatriptan 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 the drug to the fetus was demonstrated in both species.

Oral administration of rizatriptan (0, 2, 10, or 100 mg/kg/day) to female rats before 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.

8.2 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 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 RizaFilm and any potential adverse effects on the breastfed infant from RizaFilm or the underlying maternal condition.

Data

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

8.4 Pediatric Use

The safety and effectiveness of RizaFilm for the acute treatment of migraine have been established in pediatric patients 12 years of age and older weighing 40 kg or more based on an adequate and well-controlled study with rizatriptan benzoate tablets *[see Clinical Studies (14.2)]*.

The incidence of adverse reactions reported for pediatric patients in the acute clinical trial was similar in patients who received rizatriptan benzoate tablets to those who received placebo. The adverse reaction pattern in pediatric patients is expected to be similar to that in adults.

Safety and effectiveness of RizaFilm in pediatric patients under 12 years of age and weighing less than 40 kg have not been established.

8.5 Geriatric Use

Clinical studies of rizatriptan benzoate 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.

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥65 years) and younger adults (n=17) *[see Clinical Pharmacology (12.3)].*

Geriatric patients who have cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of coronary artery disease) should have a cardiovascular evaluation before receiving RizaFilm *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

No overdoses of rizatriptan benzoate were reported during clinical trials in adults.

Some adult patients who received 40 mg of rizatriptan benzoate either in 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 rizatriptan benzoate, 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 the long-term, open label study, involving 606 treated pediatric migraineurs 12 to 17 years of age (of which 432 were treated for at least 12 months), 151 patients (25%) took two 10-mg doses of Rizatriptan Benzoate Orally Disintegrating Tablets within a 24-hour period. Adverse reactions for 3 of these patients included abdominal discomfort, fatigue, and dyspnea.

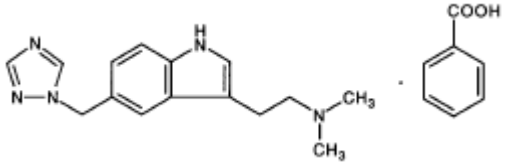
In addition, based on the pharmacology of rizatriptan benzoate, hypertension or myocardial ischemia could occur after overdosage. Gastrointestinal decontamination, (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with RizaFilm. Clinical and 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.

11 DESCRIPTION

RizaFilm contains rizatriptan benzoate, a selective 5-hydroxytryptamine1B/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.

RizaFilm oral film is available for oral administration in a 10 mg strength (equivalent to 14.53 mg rizatriptan benzoate). Each oral film contains the following inactive ingredients: ammonium glycyrrhizate, butylated hydroxytoluene, copovidone, cupric chloride, ethylcellulose, FD&C Blue No. 1, hydroxypropyl cellulose, isopropyl alcohol, levomenthol, methyl ethyl ketone, sodium acetate, sucralose, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-$HT_{1B/1D}$ receptors. RizaFilm 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.

12.2 Pharmacodynamics

Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported in patients treated with rizatriptan, with and without a history of hypertension *[see Warnings and Precautions (5.9)]*.

12.3 Pharmacokinetics

Absorption

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the rizatriptan benzoate 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, rizatriptan benzoate tablets were administered without regard to food.

The bioavailability and C_{max} of rizatriptan were similar following administration of rizatriptan benzoate tablets and rizatriptan benzoate orally disintegrating tablets, but the rate of absorption is somewhat slower with the orally disintegrating tablets, 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.

Following a single dose of 10mg RizaFilm, the mean C_{max} and AUC_{inf} of rizatriptan were 23.79 (± 8.36) ng/mL and 84.54 (± 18.65) ng·hr/mL, respectively; the maximum peak plasma concentrations were achieved in 1.4 hours.

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 ^{14}C-rizatriptan. Following oral administration of ^{14}C-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.

Following administration of RizaFilm, the mean plasma half-life of rizatriptan is 2 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 (Ki =1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

Specific 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).

Pediatric: The pharmacokinetics of rizatriptan was determined in pediatric migraineurs 12 to 17 years of age. Exposures following single-dose administration of 10 mg rizatriptan benzoate orally disintegrating tablets to pediatric patients weighing ≥40 kg (88 lbs.) were similar to those observed following single-dose administration of 10 mg rizatriptan benzoate orally disintegrating tablets to adults.

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.

Patients with 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.

Patients with Renal Impairment: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m^2), 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 m^2), 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

Monoamine Oxidase Inhibitors: In a drug interaction study, when rizatriptan benzoate 10 mg tablets were administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg three times a day, 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 *[see Contraindications (4) and Drug Interactions (7.5)]*. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors.

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%, and a four-fold increase was observed in one subject *[see Contraindications (4) and Drug Interactions (7.1)]*. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol.

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 rizatriptan benzoate tablet 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 (5.7), Drug Interactions (7.4), and Patient Counseling Information (17)]*.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

14 CLINICAL STUDIES

The studies described below establishing effectiveness for the acute treatment of migraine with or without aura were conducted with rizatriptan benzoate tablets. The efficacy of RizaFilm is based on a relative bioavailability study comparing RizaFilm 10 mg oral film to rizatriptan benzoate 10 mg tablets *[see Clinical Pharmacology (12.3)]*.

14.1 Adults

The efficacy of rizatriptan benzoate 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 rizatriptan benzoate 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 rizatriptan 10 mg compared to those who received 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

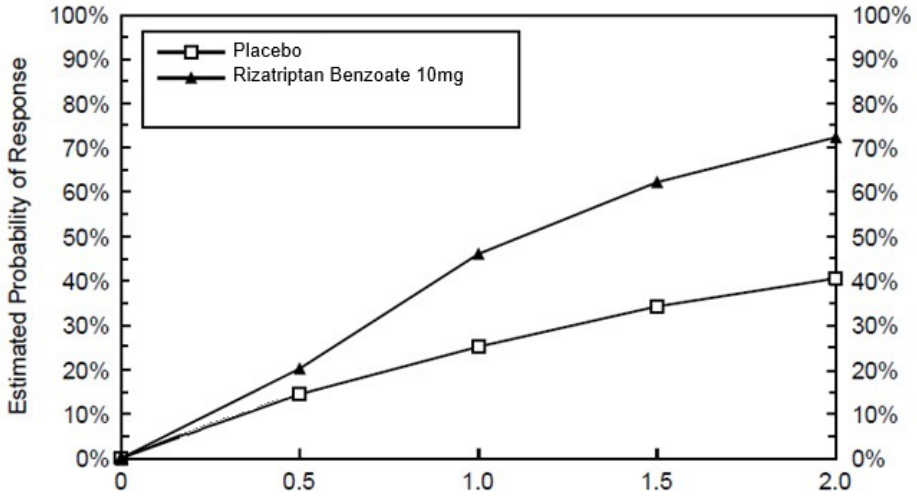
Study	Placebo	Rizatriptan tablets 10 mg
1	35% (n=304)	71%* (n=456)
2**	37% (n=82)	77%* (n=320)
3	23% (n=80)	–
4	40% (n=159)	67%* (n=385)

* p-value <0.05 in comparison with placebo
** 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*

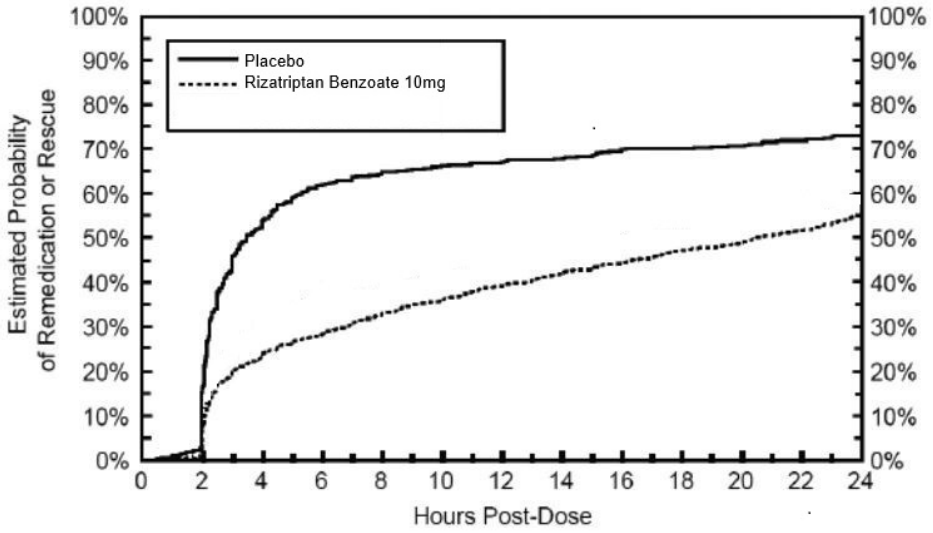


***** Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan benzoate tablets or placebo. The averages displayed are based on pooled data from 4 placebo-controlled, outpatient trials providing evidence of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

Rizatriptan Benzoate Orally Disintegrating Tablets

The efficacy of rizatriptan benzoate orally disintegrating tablets was established in two multicenter, randomized, placebo-controlled trials that were similar in design to the trials of rizatriptan benzoate 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 rizatriptan benzoate orally disintegrating tablets 10 mg compared to those who received placebo. The results from Studies 5 and 6 are summarized in Table 3.

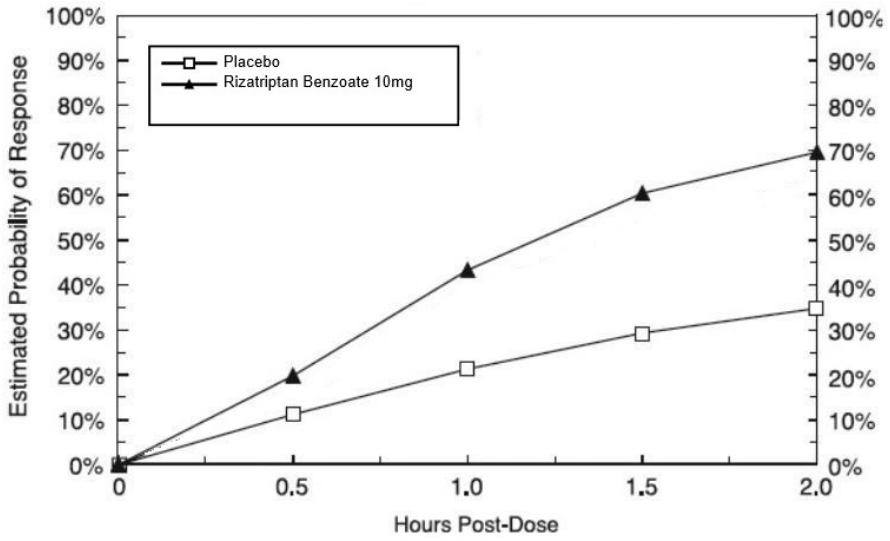
Table 3: Response Rates 2 Hours Following Treatment of Initial Headache in Studies 5 and 6

Study	Placebo		Rizatriptan orally disintegrating tablets 10 mg	
5	47%	(n=98)	66%*	(n=113)
6	28%	(n=180)	74%*	(n=186)

* p-value <0.01 in comparison with placebo

The estimated probability of achieving an initial headache response by 2 hours following treatment with rizatriptan benzoate orally disintegrating tablets in pooled Studies 5 and 6 is depicted in Figure 3.

Figure 3: Estimated Probability of Achieving an Initial Headache Response with Rizatriptan Benzoate Orally Disintegrating Tablets by 2 Hours in Pooled Studies 5 and 6*

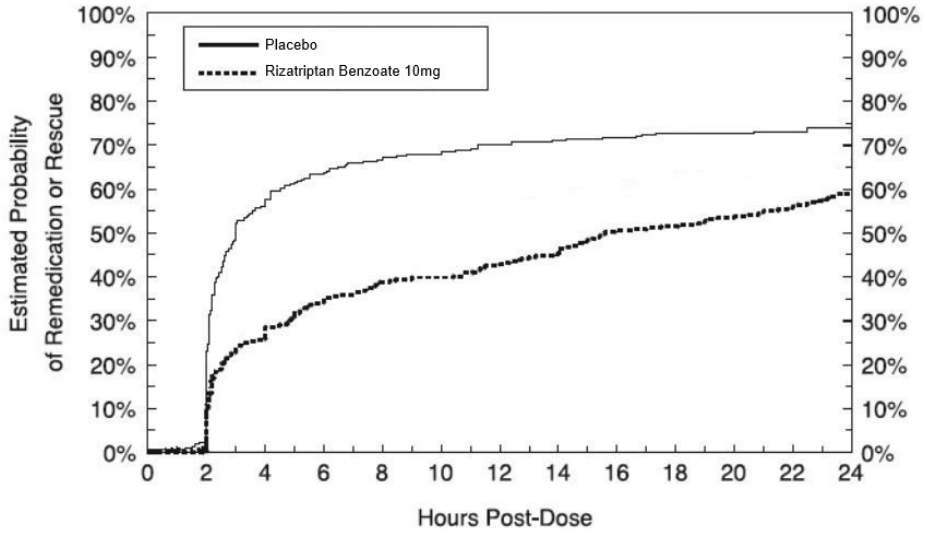


* Figure 3 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with rizatriptan benzoate orally disintegrating tablets or placebo. The averages displayed are based on pooled data from 2 placebo-controlled, outpatient trials providing evidence of efficacy (Studies 5 and 6). Patients taking additional treatment or not achieving headache response before 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 rizatriptan benzoate orally disintegrating tablets 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 Rizatriptan Benzoate Orally Disintegrating Tablets 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.

14.2 Pediatric Patients 12 to 17 Years of Age

The efficacy of rizatriptan benzoate orally disintegrating tablets in pediatric patients 12 to 17 years of age was evaluated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial (Study 7). Patients had to have at least a 6-month history of migraine attacks (with or without aura) usually lasting 3 hours or more (when untreated). The patient population was historically non-responsive to NSAIDs and acetaminophen therapy.

Patients were instructed to treat a single migraine attack with headache pain of moderate to severe intensity. The treatment phase of the study had two stages. Stage 1 was used to identify placebo non-responders, who then entered into Stage 2, in which patients were randomized to rizatriptan benzoate orally disintegrating tablets or placebo. Using a weight-based dosing strategy, patients 12 to 17 years of age and weighing greater than or equal to 40 kg received rizatriptan benzoate orally disintegrating tablets 10 mg or placebo.

Of the total pediatric population in Study 7, including those weighing 40 kg or more, sixty-one percent of the patients were Caucasian, and fifty-six percent of the patients were female. The percentage of patients achieving the primary efficacy endpoint of no headache pain at 2 hours after treatment was significantly greater in patients who received rizatriptan benzoate orally disintegrating tablets, compared with those who received placebo (33% vs. 24%). Study 7 results are summarized in Table 4.

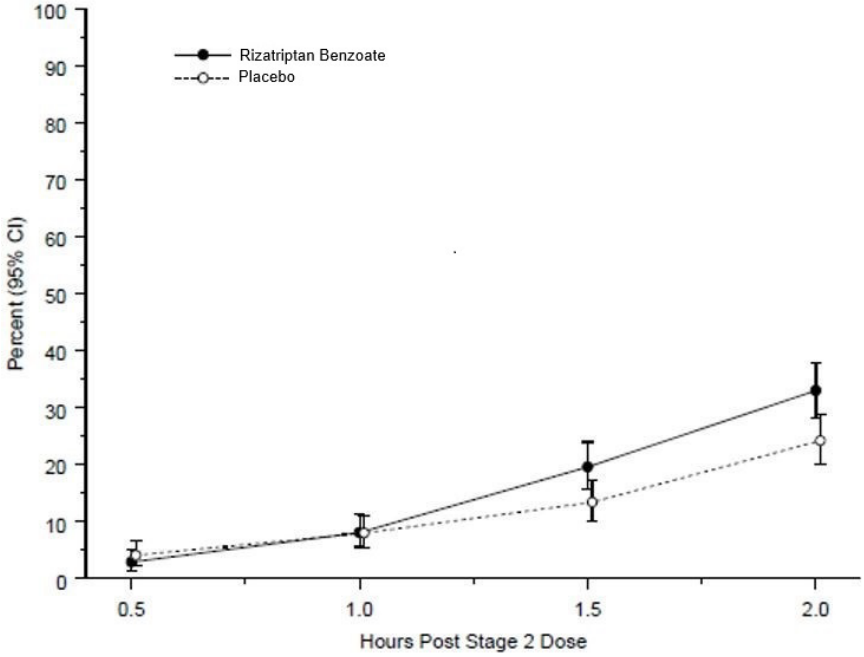
Table 4: Response Rates 2 Hours Following Treatment of Initial Headache in Pediatric Patients (including 12 to 17 Years of Age) in Study 7

Endpoint	Placebo	Rizatriptan orally disintegrating tablets	p-Value
No headache pain at 2 hours post-dose	24% (n/m = 94/388)	33% (n/m = 126/382)	0.01

n = Number of evaluable patients with no headache pain at 2 hours post-dose.
m = Number of evaluable patients in population.

The observed percentage of pediatric patients achieving no headache pain within 2 hours following initial treatment with rizatriptan benzoate orally disintegrating tablets is shown in Figure 5.

Figure 5: Observed Percentage of Patients Reporting No Headache Pain by 2 Hours Post-Dose in Study 7



The prevalence of the exploratory endpoints of absence of migraine-associated symptoms (nausea, photophobia, and phonophobia) at 2 hours after taking the dose was not statistically significantly different between patients who received rizatriptan benzoate orally disintegrating tablets and those who received placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RizaFilm oral film, 10 mg is a white flexible rectangular strip of 2.2 cm × 2.75 cm with an imprint "RIZA10" in edible blue ink on one side. Each oral film is individually packaged in an aluminum laminate pouch. It is supplied as follows:

NDC 35781-0600-8. 1 carton of 18 individually packaged films.

16.2 Storage and Handling

Store RizaFilm at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep product in pouch until ready to use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Administration Instructions

Advise patients to fold the pouch on the dotted line and tear open at the notch. Inform patients that administration with liquids is not necessary. Direct patients to place RizaFilm oral film on the tongue, where it will disintegrate and be swallowed with saliva *[see Dosage and Administration (2.3)]*.

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, and Cerebrovascular Events

Inform patients that RizaFilm may cause serious cardiovascular side effects such as myocardial infarction or stroke. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5)]*.

Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the use of RizaFilm or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.7), Drug Interactions (7.4), and Clinical Pharmacology (12.3)]*

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Pregnancy

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.2)]*.

Ability to Perform Complex Tasks

Since migraines or treatment with RizaFilm may cause somnolence and dizziness, instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of RizaFilm.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including angioedema and anaphylaxis, have occurred in patients receiving rizatriptan. Inform patients that such reactions can be life threatening or fatal and to seek immediate medical attention if they have anaphylactic symptoms *[see Warnings and Precautions (5.6)]*.

Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) *[see Warnings and Precautions (5.7)]*.

RizaFilm® is manufactured by:
IntelGenx Corp.
Saint-Laurent, Quebec H4S 1Y2 Canada

RizaFilm® is manufactured for:
Gensco Pharma
Doral, FL 33122

Patient Information
RizaFilm™ (ri' zah film)
rizatriptan
oral film

What is RizaFilm?

- RizaFilm is a prescription medicine that belongs to a class of medicines called Triptans. RizaFilm is available as oral films.
- RizaFilm is used to treat migraine attacks with or without aura in adults and in children 12 to 17 years of age who weigh 40 kg or more.
- RizaFilm is not to be used to prevent migraine attacks.
- It is not known if RizaFilm is safe and effective for the treatment of cluster headaches.
- It is not known if RizaFilm is safe and effective in children under 12 years of age and who weigh less than 40 kg.

Do not take RizaFilm if you:

- have or have had heart problems.
- have or have had a stroke or a transient ischemic attack (TIA).
  have or have had blood vessel problems including ischemic bowel disease, or narrowing of blood vessels in your legs, arms, and stomach, or kidney (peripheral vascular disease)
- have uncontrolled high blood pressure.
- have taken other Triptan medicines in the last 24 hours.
- have taken ergot-containing medicines in the last 24 hours.
- have hemiplegic or basilar migraines.
- take a monoamine oxidase (MAO) inhibitor or have taken a MAO inhibitor within the last 2 weeks.
- take propranolol.
- are allergic to rizatriptan or any of the ingredients in RizaFilm. See the end of this leaflet for a complete list of ingredients in RizaFilm.

Talk to your doctor before taking this medicine if you have any of the conditions listed above or if you are not sure if you take any of these medicines.

Before you take RizaFilm, tell your doctor about all of your medical conditions, including if you:

- have or have had heart problems, high blood pressure, chest pain, or shortness of breath.
- have any risk factors for heart problems or blood vessel problems such as:
  - high blood pressure.
  - high cholesterol.
  - smoking.
  - obesity.
  - diabetes.
  - family history of heart problems.
  - you are post-menopausal.
- have kidney or liver problems.
- are pregnant or plan to become pregnant. It is not known if RizaFilm will harm your unborn baby. If you become pregnant while taking RizaFilm, talk to your healthcare provider.
- are breastfeeding or plan to breastfeed. It is not known if RizaFilm passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take RizaFilm.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

RizaFilm and other medicines may affect each other causing side effects. RizaFilm may affect the way other medicines work, and other medicines may affect how RizaFilm works.

Especially tell your doctor if you take:

- propranolol containing medicines such as Inderal, Inderal LA, or Innopran XL
- medicines used to treat mood disorders, including selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take RizaFilm?

- Take RizaFilm exactly as your doctor tells you to take it.
- Your doctor will tell you how much RizaFilm to take and when to take it.
- **To take RizaFilm**:
  - Leave RizaFilm oral film in the aluminum pouch it comes in until you are ready to take it.
  - When you are ready to take it:

- Remove the oral film from the aluminum pouch by folding the pouch on the dotted line and tearing it open at the tear notch.
- Place the oral film on the tongue.
- The oral film will disintegrate in about 2 minutes and can be swallowed with saliva. No liquid is required to take the oral film.

- If your headache comes back after your first RizaFilm dose:
  - For adults: a second dose may be taken at least 2 hours after the first dose. Do not take more than 30 mg of RizaFilm in a 24-hour period (for example, do not take more than 3 10-mg oral films in a 24-hour period).
  - For children 12 to 17 years of age: It is not known if taking more than 1 dose of RizaFilm in 24 hours is safe and effective. Talk to your doctor about what to do if your headache does not go away or comes back.
- If you take too much RizaFilm, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking RizaFilm?

RizaFilm may cause dizziness, weakness, or fainting. If you have these symptoms, do not drive a car, use machinery, or do anything that needs you to be alert.

What are the possible side effects of RizaFilm?

RizaFilm may cause serious side effects. Call your doctor or go to the nearest hospital emergency room right away if you think you are having any of the serious side effects of RizaFilm including:

- **heart attack and other heart problems.** Symptoms of a heart attack may include:
  - chest discomfort in the center of your chest that lasts for more than a few minutes or that goes away and comes back
  - chest discomfort that feels like uncomfortable pressure, squeezing, fullness or pain
  - pain or discomfort in your arms, back, neck, jaw or stomach
  - shortness of breath with or without chest discomfort
  - breaking out in a cold sweat
  - nausea or vomiting
  - feeling lightheaded
- **stroke.** Symptoms of a stroke may include the following sudden symptoms:
  - numbness or weakness in your face, arm or leg, especially on one side of your body
  - confusion, problems speaking or understanding
  - problems seeing in 1 or both of your eyes
  - problems walking, dizziness, loss of balance or coordination
  - severe headache with no known cause
- **blood vessel problems.** Symptoms of blood vessel problems may include:
  - stomach pain
  - bloody diarrhea
  - vision problems
  - coldness and numbness of hands and feet
- **allergic reactions**. Allergic reactions that can lead to death have happened in people who take rizatriptan, an ingredient in RizaFilm. Symptoms of an allergic reaction may include:
  - swelling of your face, eyes, lips, mouth, or tongue
  - trouble breathing
  - hives (itchy bumps)
- **medication overuse headache.** Some people who use too much migraine medicine, such as RizaFilm, for 10 or more days each month may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with RizaFilm.
- **serotonin syndrome.** A condition called serotonin syndrome can happen when Triptan medicines such as RizaFilm are taken with certain other medicines. Symptoms of serotonin syndrome may include:
  - agitation
  - hallucinations
  - coma
  - fast heartbeat
  - fast changes in your blood pressure
  - increased body temperature
  - muscle spasm
  - loss of coordination
  - nausea, vomiting or diarrhea
- **increased blood pressure**.

The most common side effects of RizaFilm in adults include:

- having a lack of energy
- feeling sleepy or tired

- pain or pressure in your chest or throat
- dizziness
- nausea

Adverse reactions in children are expected to be similar to those in adults.

Tell your doctor if you have any side effect that bothers you or that does not go away.

If you take RizaFilm too often, this may result in you getting chronic (lasting a long time) headaches. In such cases, you should contact your doctor, as you may have to stop taking RizaFilm.

These are not all the possible side effects of RizaFilm. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to Gensco Pharma at 1-866-608-6284 or FDA at 1-800-FDA-1088.

How should I store RizaFilm?

- Store RizaFilm at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep RizaFilm in its aluminum pouch until you are ready to take it.

Keep RizaFilm and all medicines out of the reach of children.

General information about the safe and effective use of RizaFilm.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use RizaFilm for a condition for which it was not prescribed. Do not give RizaFilm to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or doctor for information about RizaFilm that is written for health professionals.

What are the ingredients in RizaFilm?

Active ingredient in RizaFilm: rizatriptan.

Inactive ingredients in RizaFilm: ammonium glycyrrhizate, butylated hydroxytoluene, copovidone, cupric chloride, ethylcellulose, FD&C Blue No. 1, hydroxypropyl cellulose, isopropyl alcohol, levomenthol, methyl ethyl ketone, sodium acetate, sucralose, titanium dioxide, and triacetin.

RizaFilm Oral Films are manufactured by:
IntelGenx Corp.
Saint-Laurent, Quebec, H4S 1Y2 Canada

RizaFilm Oral Films are manufactured for:
Gensco Pharma
Doral, FL, 33122

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 12/2023