HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELETRIPTAN safely and effectively. See full prescribing information for ELETRIPTAN.
Eletriptan hydrobromide tablets, for oral use
Initial U.S. Approval: 2002

INDICATIONS AND USAGE

Eletriptan is a serotonin (5-HT$_{1B/1D}$) receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults (1)
Limitations of Use:
- Use only after a clear diagnosis of migraine has been established (1)
- Not indicated for the prophylactic therapy of migraine (1)
- Not indicated for the treatment of cluster headache (1)

DOSAGE AND ADMINISTRATION

- Single dose: 20 mg or 40 mg (2)
- Maximum single dose: 40 mg (2)
- May repeat dose after 2 hours if needed; not to exceed 80 mg in any 24-hour period (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg and 40 mg (3)

CONTRAINDICATIONS

- History of coronary artery disease (CAD) or coronary artery vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or history or current evidence of hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing medication (4)
- Hypersensitivity to eletriptan (angioedema and anaphylaxis seen) (4)
- Within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, or nelfinavir (4)

WARNINGS AND PRECAUTIONS

- Myocardial ischemia/infarction or Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue eletriptan if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not myocardial ischemia; evaluate high risk patients for CAD (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, or stroke: Discontinue eletriptan if occurs (5.4)
- Gastrointestinal ischemia or infarction events, or peripheral vasospastic reactions: Discontinue eletriptan if occurs (5.5)
- Medication overuse headache: Detoxification may be necessary (5.6)
- Serotonin syndrome: Discontinue eletriptan if occurs (5.7, 7.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% and > placebo) were asthenia, nausea, dizziness, and somnolence. These reactions appear to be dose-related. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact 1-800-438-1985 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: 4/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Eletriptan is indicated for the acute treatment of migraine with or without aura in adults.
Limitations of Use:
- Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with eletriptan, reconsider the diagnosis of migraine before eletriptan is administered to treat any subsequent attacks.
- Eletriptan is not intended for the prevention of migraine attacks.
- Safety and effectiveness of eletriptan have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

The maximum recommended single dose is 40 mg.
In controlled clinical trials, single doses of 20 mg and 40 mg were effective for the acute treatment of migraine in adults. A greater proportion of patients had a response following a 40 mg dose than following a 20 mg dose *[see Clinical Studies (14)]*.
If the migraine has not resolved by 2 hours after taking eletriptan, or returns after transient improvement, a second dose may be administered at least 2 hours after the first dose. The maximum daily dose should not exceed 80 mg. The safety of treating an average of more than 3 migraine attacks in a 30-day period has not been established.

3 DOSAGE FORMS AND STRENGTHS

20 mg Tablets: Orange, round, convex shaped, film-coated, with "PFIZER" and "REP20" debossed.
40 mg Tablets: Orange, round, convex shaped, film-coated, with "PFIZER" and "REP40" debossed.

4 CONTRAINDICATIONS

Eletriptan is contraindicated in patients with:
- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or 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, transient ischemic attack (TIA), or history or current evidence of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*.
- Peripheral vascular disease *[see Warnings and Precautions (5.5)]*.
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*.
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*.
- Recent use (i.e., within 24 hours) of another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist, ergotamine-containing medication, or ergot-type medication such as dihydroergotamine (DHE) or methysergide *[see Drug Interactions (7.1)]*.
- Hypersensitivity to eletriptan (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.9)]*.
- Recent use (i.e., within at least 72 hours) of the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, or nelfinavir *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

Eletriptan should only be used where a clear diagnosis of migraine has been established.

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

Eletriptan is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of eletriptan. Some of these reactions occurred in patients without known CAD. Eletriptan 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) prior to receiving eletriptan. Do not use eletriptan if there is evidence of CAD or coronary artery vasospasm *[see Contraindications (4)]*. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first eletriptan dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following administration of eletriptan. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of eletriptan.

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 eletriptan if these disturbances occur. Eletriptan is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Contraindications (4)]*.

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

Sensations of tightness, pain, and pressure in the chest, throat, neck, and jaw commonly occur after treatment with eletriptan and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. Eletriptan is contraindicated in patients with CAD or Prinzmetal's variant angina *[see Contraindications (4)]*.

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.
Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with symptoms atypical of migraine, other potentially serious neurological conditions need to be excluded. Eletriptan is contraindicated in patients with a history of stroke or TIA *[see Contraindications (4)]*.

5.5 Other Vasospasm Reactions

Eletriptan may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of a vasospastic reaction following the use of any 5-HT$_1$ agonist, rule out a vasospastic reaction before receiving additional eletriptan doses *[see Contraindications (4)]*.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g. ergotamine, triptans, opioids, or combination of these 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 acute migraine drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with eletriptan, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase (MAO) inhibitors *[see Drug Interactions (7.3)]*. 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 usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue eletriptan if serotonin syndrome is suspected.

5.8 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 treated with 5-HT$_1$ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with eletriptan. Eletriptan is contraindicated in patients with uncontrolled hypertension *[see Contraindications (4)]*.

5.9 Anaphylactic/Anaphylactoid Reactions

There have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving eletriptan. 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. Eletriptan is contraindicated in patients with a history of hypersensitivity reaction to eletriptan *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in other sections of the prescribing information:
- Myocardial ischemia and myocardial infarction, and Prinzmetal's angina *[see Warnings and Precautions (5.2)]*
- Arrhythmias *[see Warnings and Precautions (5.3)]*
- Chest, throat, neck, and/or jaw pain/tightness/pressure *[see Warnings and Precautions (5.4)]*
- Cerebrovascular events *[see Warnings and Precautions (5.4)]*
- Other vasospasm reactions *[see Warnings and Precautions (5.5)]*
- Medication overuse headache *[see Warnings and Precautions (5.6)]*
- Serotonin syndrome *[see Warnings and Precautions (5.7)]*
- Increase in blood pressure *[see Warnings and Precautions (5.8)]*
- Hypersensitivity reactions *[see Contraindications (4) and 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.
Among 4,597 patients who treated the first migraine headache with eletriptan in short-term placebo-controlled trials, the most common adverse reactions reported with treatment with eletriptan were asthenia, nausea, dizziness, and somnolence. These reactions appear to be dose-related.
In long-term open-label studies where patients were allowed to treat multiple migraine attacks for up to 1 year, 128 (8.3%) out of 1,544 patients discontinued treatment due to adverse reactions.
Table 1 lists adverse reactions that occurred in the subset of 5,125 migraineurs who received eletriptan doses of 20 mg, 40 mg and 80 mg or placebo in worldwide placebo-controlled clinical trials.
Only adverse reactions that were more frequent in an eletriptan treatment group compared to the placebo group with an incidence greater than or equal to 2% are included in Table 1.

Table 1: Adverse Reactions Incidence in Placebo-Controlled Migraine Clinical Trials: Reactions Reported by ≥ 2% Patients Treated with Eletriptan and More Than Placebo

Adverse Reaction Type	Placebo (n=988)	Eletriptan 20 mg (n=431)	Eletriptan 40 mg (n=1774)	Eletriptan 80 mg (n=1932)
ATYPICAL SENSATIONS				
Paresthesia	2%	3%	3%	4%
Flushing/feeling of warmth	2%	2%	2%	2%
PAIN AND PRESSURE SENSATIONS				
Chest – tightness/pain/pressure	1%	1%	2%	4%
Abdominal – pain/discomfort/stomach pain/cramps/pressure	1%	1%	2%	2%
DIGESTIVE				
Dry mouth	2%	2%	3%	4%
Dyspepsia	1%	1%	2%	2%
Dysphagia – throat tightness/difficulty swallowing	0.2%	1%	2%	2%
Nausea	5%	4%	5%	8%
NEUROLOGICAL				
Dizziness	3%	3%	6%	7%
Somnolence	4%	3%	6%	7%
Headache	3%	4%	3%	4%
OTHER				
Asthenia	3%	4%	5%	10%

The frequency of adverse reactions in clinical trials did not increase when up to 2 doses of eletriptan were taken within 24 hours. The incidence of adverse reactions in controlled clinical trials was not affected by gender, age, or race of the patients. Adverse reaction frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (e.g., SSRIs, beta blockers, calcium channel blockers, tricyclic antidepressants), estrogen replacement therapy or oral contraceptives.

6.2 Postmarketing Experience

The following adverse reaction(s) have been identified during post approval use of eletriptan. 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: seizure
Digestive: vomiting

7 DRUG INTERACTIONS

7.1 Ergot-Containing Drugs Including Other 5-HT$_{1B/1D}$ Agonists

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 [DHE] or methysergide) and eletriptan within 24 hours of each other is contraindicated. Concomitant use of other 5-HT$_1$ agonists within 24 hours of eletriptan treatment is contraindicated *[see Contraindications (4)]*.

7.2 CYP3A4 Inhibitors

Potent CYP3A4 inhibitors significantly increase the exposure of eletriptan. Eletriptan should not be used within at least 72 hours of treatment with potent CYP3A4 inhibitors *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

7.3 Selective Serotonin Reuptake Inhibitors/Serotonin and Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during co-administration of triptans and SSRIs, SNRIs, TCAs and MAO inhibitors *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. In reproductive toxicity studies in pregnant animals, oral administration of eletriptan was associated with developmental toxicity (decreased fetal and pup weights and an increased incidence of fetal structural abnormalities) at clinically relevant plasma exposures. Eletriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
When pregnant rats were administered eletriptan during the period of organogenesis at doses of 10, 30 or 100 mg/kg/day, fetal weights were decreased and the incidences of vertebral and sternebral variations were increased at 100 mg/kg/day (approximately 12 times the maximum recommended human dose [MRHD] of 80 mg/day on a mg/m^2 basis). The 30 and 100 mg/kg/day doses were also maternally toxic, as evidenced by decreased maternal body weight gain during gestation. The no-effect dose for developmental toxicity in rats was 30 mg/kg/day, which is approximately 4 times the MRHD on a mg/m^2 basis.
When doses of 5, 10, or 50 mg/kg/day were given to pregnant rabbits throughout organogenesis, fetal weights were decreased at 50 mg/kg/day, which is approximately 12 times the MRHD on a mg/m^2 basis. The incidences of fused sternebrae and vena cava deviations were increased at all doses. Maternal toxicity was not evident at any dose. A no-effect dose for developmental toxicity in rabbits was not established; the lowest dose tested (5 mg/kg/day) is similar to the MRHD on a mg/m^2 basis.

8.3 Nursing Mothers

Eletriptan is excreted in human milk. Caution should be exercised when eletriptan is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.
The efficacy of eletriptan tablets (40 mg) in patients 11-17 was not established in a randomized, placebo-controlled trial of 274 adolescent migraineurs *[see Clinical Studies (14)]*. Adverse reactions observed were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse reactions that are similar in nature to those reported rarely in adults. Long-term safety of eletriptan was studied in 76 adolescent patients who received treatment for up to one year. A similar profile of adverse reactions to that of adults was observed. The long-term safety of eletriptan in pediatric patients has not been established.

8.5 Geriatric Use

Blood pressure was increased to a greater extent in elderly subjects than in young subjects. The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults *[see Clinical Pharmacology (12.3)]*. In clinical trials, there were no apparent differences in efficacy or the incidence of adverse reactions between patients under 65 years of age and those 65 and above.

8.6 Hepatic Impairment

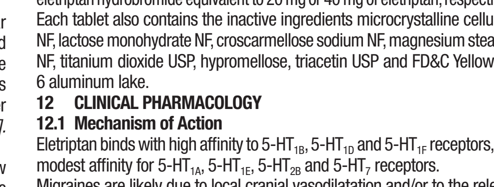
The effect of severe hepatic impairment on eletriptan metabolism has not been evaluated. Eletriptan is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The elimination half-life of eletriptan is about 4 hours *[see Clinical Pharmacology (12.3)]*, therefore monitoring of patients after overdose with eletriptan should continue for at least 20 hours or longer while symptoms or signs persist.
There is no specific antidote to eletriptan.
It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentration of eletriptan.

11 DESCRIPTION

Eletriptan tablets contain eletriptan hydrobromide, which is a selective 5-hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist. Eletriptan hydrobromide is chemically designated as (R)-3-[(1-Methyl-2-pyrrolidinyl) methyl]-5-[2-(phenylsulfonyl)ethyl]-1H-indole monohydrobromide, and it has the following chemical structure:



The empirical formula is $C_{22}H_{26}N_2O_2S$. HBr, representing a molecular weight of 463.43. Eletriptan hydrobromide is a white to light pale colored powder that is readily soluble in water.
Each eletriptan tablet for oral administration contains 24.2 or 48.5 mg of eletriptan hydrobromide equivalent to 20 mg or 40 mg of eletriptan, respectively. Each tablet also contains the inactive ingredients microcrystalline cellulose NF, lactose monohydrate NF, croscarmellose sodium NF, magnesium stearate NF, titanium dioxide USP, hypromellose, triacetin USP and FD&C Yellow No. 6 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eletriptan binds with high affinity to 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors, has modest affinity for 5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{2B}$ and 5-HT$_7$ receptors.
Migraines are likely due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of eletriptan for the treatment of migraine headache is thought to be due to the agonist effects at the 5-HT$_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.3 Pharmacokinetics

Absorption: Eletriptan is well absorbed after oral administration with peak plasma levels occurring approximately 1.5 hours after dosing to healthy subjects. In patients with moderate to severe migraine the median T_{max} is 2.0 hours. The mean absolute bioavailability of eletriptan is approximately 50%. The oral pharmacokinetics are slightly more than dose-proportional over the clinical dose range. The AUC and C_{max} of eletriptan are increased by approximately 20 to 30% following oral administration with a high fat meal. Eletriptan can be taken with or without food.
Distribution: The volume of distribution of eletriptan following IV administration is 138L. Plasma protein binding is moderate and approximately 85%.
Metabolism: The N-demethylated metabolite of eletriptan is the only known active metabolite. This metabolite causes vasoconstriction similar to eletriptan in animal models. Though the half-life of the metabolite is estimated to be about 13 hours, the plasma concentration of the N-demethylated metabolite is 10-20% of parent drug and is unlikely to contribute significantly to the overall effect of the parent compound.
In vitro studies indicate that eletriptan is primarily metabolized by cytochrome P-450 enzyme CYP3A4 *[see Contraindications (4) and Drug Interactions (7.2)]*.
Elimination: The terminal elimination half-life of eletriptan is approximately 4 hours. Mean renal clearance (CL_R) following oral administration is approximately 3.9 L/h. Non-renal clearance accounts for about 90% of the total clearance.
Special Populations
Age: The pharmacokinetics of eletriptan are generally unaffected by age. Blood pressure was increased to a greater extent in elderly subjects than in young subjects *[see Use in Specific Populations (8.5)]*. The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults. There is a statistically significant increased half-life (from about 4.4 hours to 5.7 hours) between elderly (65 to 93 years of age) and younger adult subjects (18 to 45 years of age) *[see Use in Specific Populations (8.5)]*.
Gender: The pharmacokinetics of eletriptan are unaffected by gender.
Race: A comparison of pharmacokinetic studies run in western countries with those run in Japan has indicated an approximate 35% reduction in the exposure of eletriptan in Japanese male volunteers compared to western males. Population pharmacokinetic analysis of two clinical studies indicates no evidence of pharmacokinetic differences between Caucasians and non-Caucasian patients.
Menstrual Cycle: In a study of 16 healthy females, the pharmacokinetics of eletriptan remained consistent throughout the phases of the menstrual cycle.
Renal Impairment: There was no significant change in clearance observed in subjects with mild, moderate or severe renal impairment, though blood pressure elevations were observed in this population *[see Warnings and Precautions (5.8)]*.

Hepatic Impairment: Subjects with mild or moderate hepatic impairment demonstrated an increase in both AUC (34%) and half-life. The C_{max} was increased by 18%. No dose adjustment is necessary in subjects with mild or moderate hepatic impairment. The effects of severe hepatic impairment on eletriptan metabolism have not been evaluated *[see Use in Specific Populations (8.6)]*.
Drug Interaction Studies
CYP3A4 inhibitors: *In vitro* studies have shown that eletriptan is metabolized by the CYP3A4 enzyme. A clinical study demonstrated about a 3-fold increase in C_{max} and about a 6-fold increase in the AUC of eletriptan when combined with ketoconazole. The half-life increased from 5 hours to 8 hours and the T_{max} increased from 2.8 hours to 5.4 hours. Another clinical study demonstrated about a 2-fold increase in C_{max} and about a 4-fold increase in AUC when erythromycin was co-administered with eletriptan. It has also been shown that co-administration of verapamil and eletriptan yields about a 2-fold increase in C_{max} and about a 3-fold increase in AUC of eletriptan, and that co-administration of fluconazole and eletriptan yields about a 1.4-fold increase in C_{max} and about a 2-fold increase in AUC of eletriptan.
Eletriptan is contraindicated within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition *[see Contraindications (4)]*.
Propranolol: The C_{max} and AUC of eletriptan were increased by 10 and 33%, respectively, in the presence of propranolol. No interactive increases in blood pressure were observed. No dosage adjustment appears to be needed for patients taking propranolol.
The effect of eletriptan on other drugs: The effect of eletriptan on enzymes other than cytochrome P450 has not been investigated. *In vitro* human liver microsome studies suggest that eletriptan has little potential to inhibit CYP1A2, 2C9, 2E1 and 3A4 at concentrations up to 100 μM. While eletriptan has an effect on CYP2D6 at high concentration, this effect should not interfere with metabolism of other drugs when eletriptan is used at recommended doses. There is no *in vitro* or *in vivo* evidence that clinical doses of eletriptan will induce drug metabolizing enzymes. Therefore, eletriptan is unlikely to cause clinically important drug interactions mediated by these enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Eletriptan was administered to rats and mice in the diet for 104 weeks. In rats, the incidence of testicular interstitial cell adenomas was increased at the high dose of 75 mg/kg/day, but not at 15 mg/kg/day, a dose associated with plasma exposures (AUC) approximately 2 times that in humans at the MRHD of 80 mg/day. In mice, the incidence of hepatocellular adenomas was increased at the high dose of 400 mg/kg/day, but not a dose of 90 mg/kg/day, associated with plasma AUC approximately 7 times that in humans at the MRHD.
Mutagenesis
Eletriptan was negative in in vitro (bacteria reverse mutation (Ames), mammalian cell gene mutation (CHO/ HGPRT), chromosomal aberration assay in human lymphocytes) and in vivo (mouse micronucleus) assays.
Impairment of Fertility
In a fertility and early embryonic development study, eletriptan (50, 100, or 200 mg/kg/day) was orally administered to male and female rats prior to and throughout mating and continuing in females to implantation. Plasma exposures (AUC) were 4, 8 and 16 times in males and 7, 14 and 28 times in females, respectively, that in humans at the MRHD. Dose-related decreases in the number of corpora lutea, implants, and viable fetuses per dam were observed at all doses. Prolongation of the estrus cycle was observed at the highest dose tested. Male fertility parameters were not affected.

14 CLINICAL STUDIES

The efficacy of eletriptan in the acute treatment of migraines was evaluated in eight randomized, double-blind placebo-controlled studies. All eight studies used 40 mg. Seven studies evaluated an 80 mg dose and two studies included a 20 mg dose.
In all eight studies, randomized patients treated their headaches as outpatients. Seven studies enrolled adults and one study enrolled adolescents (age 11 to 17). Patients treated in the seven adult studies were predominantly female (85%) and Caucasian (94%) with a mean age of 40 years (range 18 to 78). In all studies, patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, vomiting, photophobia and phonophobia were also assessed.
Maintenance of response was assessed for up to 24 hours post dose. In the adult studies, a second dose of eletriptan or other medication was allowed 2 to 24 hours after the initial treatment for both persistent and recurrent headaches. The incidence and time to use of these additional treatments were also recorded.
In the seven adult studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving eletriptan at all doses compared to those who received placebo. The two-hour response rates from these controlled clinical studies are summarized in Table 2.

Table 2: Percentage of Patients with Headache Response (Mild or No Headache) 2 Hours Following Treatment

	Placebo	Eletriptan 20 mg	Eletriptan 40 mg	Eletriptan 80 mg
Study 1	23.8% (n=126)	54.3%* (n=129)	65.0%* (n=117)	77.1%* (n=118)
Study 2	19.0% (n=232)	NA	61.6%* (n=430)	64.6%* (n=446)
Study 3	21.7% (n=276)	47.3%* (n=273)	61.9%* (n=281)	58.6%* (n=290)
Study 4	39.5% (n=86)	NA	62.3%* (n=175)	70.0%* (n=170)
Study 5	20.6% (n=102)	NA	53.9%* (n=206)	67.9%* (n=209)
Study 6	31.3% (n=80)	NA	63.9%* (n=169)	66.9%* (n=160)
Study 7	29.5% (n=122)	NA	57.5%* (n=492)	NA

* p value < 0.05 vs placebo
NA - Not Applicable
Comparisons of the performance of different drugs based upon results obtained in different clinical trials are never reliable. Because studies are generally 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 is depicted in Figure 1.

Figure 1: Estimated Probability of Initial Headache Response Within 2 Hours*

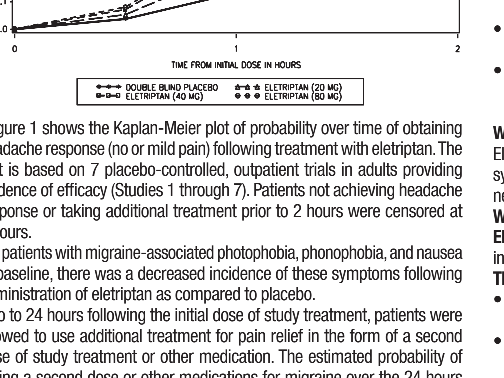
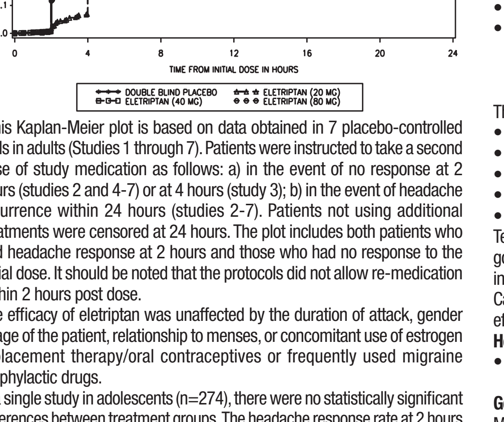


*Figure 1 shows the Kaplan-Meier plot of probability over time of obtaining headache response (no or mild pain) following treatment with eletriptan. The plot is based on 7 placebo-controlled, outpatient trials in adults providing evidence of efficacy (Studies 1 through 7). Patients not achieving headache response or taking additional treatment 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 eletriptan as compared to placebo.
Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of taking a second dose or other medications for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: Estimated Probability of Taking a Second Dose/Other Medication Over the 24 Hours Following the First Dose*



*This Kaplan-Meier plot is based on data obtained in 7 placebo-controlled trials in adults (Studies 1 through 7). Patients were instructed to take a second dose of study medication as follows: a) in the event of no response at 2 hours (studies 2 and 4-7) or at 4 hours (study 3); b) in the event of headache recurrence within 24 hours (studies 2-7). 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. It should be noted that the protocols did not allow re-medication within 2 hours post dose.
The efficacy of eletriptan was unaffected by the duration of attack, gender or age of the patient, relationship to menses, or concomitant use of estrogen replacement therapy/oral contraceptives or frequently used migraine prophylactic drugs.
In a single study in adolescents (n=274), there were no statistically significant differences between treatment groups. The headache response rate at 2 hours was 57% for both eletriptan 40 mg Tablets and placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Eletriptan hydrobromide tablets containing 20 mg or 40 mg eletriptan (base) as the hydrobromide salt. Eletriptan hydrobromide tablets are orange, round, convex shaped, film-coated tablets with appropriate debossing.
They are supplied in the following strengths and package configurations:
Eletriptan Tablets

Package Configuration	Tablet Strength (mg)	NDC Code	Debossing
Blister of 6 tablets	20 mg	59762-2321-1	REP20 and Pfizer
Blister of 6 tablets	40 mg	59762-2322-1	REP40 and Pfizer

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA Approved Patient Labeling (Patient Information)
Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospastic Reactions, and Cerebrovascular Events
Inform patients that eletriptan may cause serious cardiovascular adverse reactions such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular reactions can occur without warning symptoms, instruct patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and instruct them to ask for medical advice when observing any indicative sign or symptoms. Instruct patients to seek medical advice if they have symptoms of other vasospastic reactions *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5, and 5.8)]*.
Anaphylactic/Anaphylactoid Reactions
Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving eletriptan. 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 *[see Contraindications (4)]*.
Medication Overuse Headache
Inform patients that use of drugs to treat acute migraines 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 (5.6)]*.
Serotonin Syndrome
Inform patients about the risk of serotonin syndrome with the use of eletriptan or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.7) and Drug Interactions (7.3)]*.
Pregnancy
Inform patients that eletriptan should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.
Nursing Mothers
Inform patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.3)]*.

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Peapack, NJ 07977

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Patient Information
Eletriptan hydrobromide
Tablets

Please read this information before you start taking eletriptan and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.
What is the most important information I should know about eletriptan?
Eletriptan can cause serious side effects, including:
Heart attack and other heart problems. Heart problems may lead to death. Stop taking eletriptan and get emergency medical help right away if you have any of the following symptoms of a heart attack:
- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- chest pain or chest discomfort that feels like an uncomfortable heavy 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

Eletriptan is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:
- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease
- are a female who has gone through menopause
- are a male over age 40

Serotonin syndrome. Serotonin syndrome is a serious and life-threatening problem that can happen in people taking eletriptan, especially if eletriptan is taken with anti-depressant medicines called selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs). Ask your doctor or pharmacist for a list of these medicines if you are not sure.
Call your doctor right away if you have any of the following symptoms of serotonin syndrome:
- mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles
- trouble walking
- nausea, vomiting, or diarrhea

What is eletriptan?
Eletriptan is a prescription medicine used to treat acute migraine headaches with or without aura in adults.
Eletriptan is for people who have been diagnosed with migraine headaches.
Eletriptan is not used to prevent or decrease the number of migraine headaches you have.
It is not known if eletriptan is safe and effective to treat cluster headaches.
It is not known if eletriptan is safe and effective in children.
Who should not take eletriptan?
Do <u>not</u> take eletriptan if you:
- have heart problems or a history of heart problems
- have or have had a stroke or problems with your blood circulation
- have hemiplegic or basilar migraines. If you are not sure if you have these types of migraines, ask your doctor
- have narrowing of the blood vessels in your legs, arms, stomach, or kidney (peripheral vascular disease)
- have ischemic bowel disease
- have uncontrolled high blood pressure
- have taken any of the following medicines in the last 24 hours:
- other "triptans" or triptan combination products such as:
- almotriptan (Axert®)
- frovatriptan (Frova®)
- naratriptan (Amerge®)
- rizatriptan (Maxalt®)
- sumatriptan (Imitrex®)
- sumatriptan and naproxen sodium, (Treximet®)
- zolmitriptan (Zomig®)
- ergotamines such as:
- Bellergal-S®
- Cafergot®
- Ergomar®
- Wigraine®
- dihydroergotamines such as:
- D.H.E. 45® or Migranal® or methysergide (Sansert®)
- have taken the following medicines within the last 72 hours:
- ketoconazole (Nizoral®)
- itraconazole (Sporanox®)
- nefazodone (Serzone®)
- troleandomycin (TAO®)
- clarithromycin (Biaxin®)
- ritonavir (Norvir®)
- nelfinavir (Viracept®)
- are allergic to eletriptan or any of the ingredients in eletriptan. See the end of this leaflet for a complete list of ingredients in eletriptan.

What should I tell my doctor before taking eletriptan?
Before you take eletriptan, tell your doctor if you:
- have heart problems or family history of heart problems or stroke
- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- are a female who has gone through menopause
- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. It is not known if eletriptan will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Eletriptan passes into your breast milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you take eletriptan.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your doctor will decide if you can take eletriptan with your other medicines. Eletriptan and other medicines may affect each other causing side effects.
Especially tell your doctor if you take anti-depressant medicines called:
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin and 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 or pharmacist when you get a new medicine.
How should I take eletriptan?
- Take eletriptan exactly as your doctor tells you to take it.
- Your doctor will tell you how much eletriptan to take and when to take it.
- Your doctor may change your dose if needed. Do not change your dose without first talking to your doctor.
- Take 1 eletriptan tablet as soon as you feel a migraine coming on.
- If you do not get any relief after your first eletriptan tablet, do not take a second tablet without first talking with your doctor.
- If your headache comes back or you only get some relief from your headache, you can take a second tablet 2 hours after the first tablet.
- Do not take more than a total of 80 mg of eletriptan tablets in a 24-hour period.
- If you take too much eletriptan, call your doctor or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take eletriptan so you can talk to your doctor about how well eletriptan is working for you.

What should I avoid while taking eletriptan?
Eletriptan can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.
What are the possible side effects of eletriptan?
Eletriptan may cause serious side effects. See "What is the most important information I should know about eletriptan?"
These serious side effects include:
- **changes in color or sensation in your fingers and toes (Raynaud's syndrome)**
- **stomach and intestinal problems (gastrointestinal and colonic ischemic events).** Symptoms of gastrointestinal and colonic ischemic events include:
- sudden or severe stomach pain
- stomach pain after meals
- weight loss
- nausea or vomiting
- constipation or diarrhea
- bloody diarrhea
- fever
- **problems with blood circulation to your legs and feet (peripheral vascular ischemia).** Symptoms of peripheral vascular ischemia include:
- cramping and pain in your legs or hips
- feeling of heaviness or tightness in your leg muscles
- burning or aching pain in your feet or toes while resting
- numbness, tingling, or weakness in your legs
- cold feeling or color changes in 1 or both legs or feet
- **medication overuse headaches.** Some people who take too many eletriptan may have worse headaches (medication overuse headache). If your headaches get worse, your doctor may decide to stop your treatment with eletriptan.

The most common side effects of eletriptan include:
- dizziness
- nausea
- weakness
- tiredness
- drowsiness

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of eletriptan. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.
How should I store eletriptan?
- Store eletriptan at room temperature between 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of eletriptan
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use eletriptan for a condition for which it was not prescribed. Do not give eletriptan to other people, even if they have the same symptoms you have. It may harm them.
This Patient Information summarizes the most important information about eletriptan. If you would like more information about eletriptan, talk with your doctor. You can ask your doctor or pharmacist for information on eletriptan that is written for health professionals.
For more information go to http://www.greenstonellc.com or call 1-800-438-1985.
What are the ingredients in eletriptan?
Active ingredient: eletriptan hydrobromide
Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, titanium dioxide, hypromellose, triacetin, and FD&C Yellow No. 6 aluminum lake.

This product's label may have been updated. For current full prescribing information, please visit www.greenstonellc.com.

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