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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZECUITY® safely and effectively. See full prescribing information for ZECUITY.

ZECUITY® (sumatriptan iontophoretic transdermal system)

Initial U.S. Approval: 1992

INDICATIONS AND USAGE

ZECUITY is a serotonin (5HT) 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 prevention of migraine attacks (1)

DOSAGE AND ADMINISTRATION

- For transdermal use only (2)
- Acute treatment of migraine: Single ZECUITY transdermal system (TDS) applied to dry, intact, non-irritated skin of upper arm or thigh (2)
- No more than two ZECUITY should be used in any 24 hour period; second TDS should be used no sooner than 2 hours after activation of first TDS (2)
- ZECUITY TDS should not be applied to a previous application site until that site remains erythema free for at least 3 days (2)

DOSAGE FORMS AND STRENGTHS

- Iontophoretic transdermal system: Delivers 6.5 mg of sumatriptan over 4 hours (3)

CONTRAINDICATIONS

- History of coronary artery disease (CAD) or coronary vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (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)
- Use of monoamine oxidase-A inhibitor in past 2 weeks (4)
- Hypersensitivity to sumatriptan or components of ZECUITY (4)
- Severe hepatic impairment (4)
- Allergic contact dermatitis to ZECUITY (4)

WARNINGS AND PRECAUTIONS

- *Magnetic Resonance Imaging procedure (MRI):* ZECUITY contains metal parts and must be removed before an MRI procedure (5.1)
- *Allergic contact dermatitis (ACD):* Discontinue ZECUITY if ACD is suspected (5.2)
- *Myocardial ischemia/infarction and Prinzmetal's angina:* Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.3)
- *Arrhythmias:* Discontinue ZECUITY if occurs (5.4)
- *Chest/throat/neck/jaw pain, tightness, pressure, or heaviness:* Generally not myocardial ischemia; evaluate high risk patients for CAD (5.5)
- *Cerebral hemorrhage, subarachnoid hemorrhage, and stroke:* Discontinue ZECUITY if occurs (5.6)
- *Gastrointestinal ischemia and infarction events, peripheral vasospastic reactions:* Discontinue ZECUITY if occurs (5.7)
- *Medication overuse headache:* Detoxification may be necessary (5.8)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) were application site pain, paresthesia, pruritus, warmth, and discomfort (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NuPathe Inc. at 1-855-ZECUITY 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: 0

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZECUITY 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 ZECUITY reconsider the diagnosis of migraine before ZECUITY is administered to treat any subsequent attacks.
- ZECUITY is not intended for the prevention of migraine attacks.

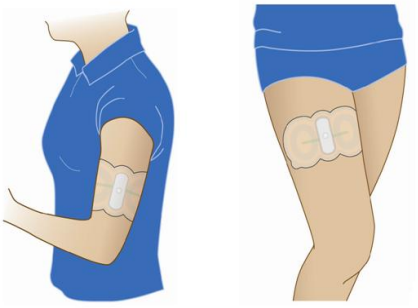
2 DOSAGE AND ADMINISTRATION

ZECUITY is for transdermal use only and is designed for patient self-administration to the upper arm or thigh (see Figure 1). ZECUITY should not be applied to other areas of the body. ZECUITY should not be cut.

The maximum recommended single dose is one ZECUITY iontophoretic transdermal system (TDS). No more than two ZECUITY TDS should be used in any 24 hour period, and the second ZECUITY TDS should be applied no sooner than 2 hours after activation of the first ZECUITY TDS. There is no evidence of benefit for the use of a second ZECUITY TDS to treat headache recurrence or incomplete headache relief during a migraine attack.

ZECUITY should be applied to dry intact, non-irritated skin on the upper arm or thigh on a site that is relatively hair free and is without scars, tattoos, abrasions, or other skin conditions (i.e., generalized skin irritation or disease including eczema, psoriasis, melanoma, contact dermatitis). ZECUITY should not be applied to a previous application site until the site remains erythema free for at least 3 days.

Figure 1: Applied Transdermal System



ZECUITY delivers 6.5 mg of sumatriptan over 4 hours. Once applied, the activation button must be pushed, and the red light emitting diode (LED) will turn on. ZECUITY TDS must be applied and

activated within 15 minutes of initiation of assembly. When dosing is completed, the system stops operating and the activation light turns off, signaling that the system can be removed. Once dosing is completed, the system cannot be reactivated. If the light turns off before 4 hours, dosing has stopped and ZECUITY can be removed. If headache relief is incomplete, a second ZECUITY TDS can be applied to a different site. *[see Patient Counseling Information (17)]*.

The ZECUITY TDS should remain in place for 4 hours or until the red LED light goes off. The iontophoretic device can be secured with medical tape if needed.

The safety of using more than 4 ZECUITY in one month has not been established.

ZECUITY is for single use only. After use, the TDS should be folded so the adhesive side sticks to itself and safely discarded away from children and pets. ZECUITY contains lithium-manganese dioxide batteries; it should be disposed in accordance with state and local regulations.

3 DOSAGE FORMS AND STRENGTHS

Iontophoretic transdermal system: 6.5 mg over 4 hours.

4 CONTRAINDICATIONS

ZECUITY 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 (5.3)]*.
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.4)]*.
- History of stroke, transient ischemic attack (TIA), or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.6)]*.
- Peripheral vascular disease *[see Warnings and Precautions (5.7)]*.
- Ischemic bowel disease *[see Warnings and Precautions (5.7)]*.
- Uncontrolled hypertension *[see Warnings and Precautions (5.10)]*.
- Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist *[see Drug Interactions (7.1, 7.3)]*.
- Concurrent administration of an MAO-A inhibitor or recent (within 2 weeks) use of a MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.
- Known hypersensitivity to sumatriptan or components of ZECUITY *[see Warnings and Precautions (5.2, 5.11)]*.
- Severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.
- Allergic contact dermatitis to ZECUITY *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Injury During Magnetic Resonance Imaging (MRI) Procedure

Zecuity contains metal parts and must be removed before an MRI procedure.

5.2 Allergic Contact Dermatitis

Use of ZECUITY may lead to allergic contact dermatitis (ACD). In two long-term open-label studies where patients were allowed to treat multiple migraine attacks for up to 1 year, the overall adverse event rate of ACD was 4%. ZECUITY should be discontinued if ACD is suspected. Erythema is commonly seen with use of ZECUITY and is not by itself an indication of sensitization. Following sensitization with ZECUITY, erythematous plaque and/or erythemato-vesicular or erythemato-bullous eruptions may develop. Clinical course is characterized by crescendo phenomenon of worsening pruritus and appearance over time with slower resolution to normal of affected skin areas.

Patients sensitized from use of ZECUITY, as evidenced by development of ACD, may develop systemic sensitization or other systemic reactions if sumatriptan-containing products are taken via other routes, e.g., orally or subcutaneously. It is possible that some patients who developed ACD with sumatriptan by exposure to ZECUITY, and who have developed systemic sensitization, may not be able to take sumatriptan in any form.

Patients who develop ACD with ZECUITY and require treatment with sumatriptan via other routes should receive their first subsequent dose under close medical supervision.

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

The use of ZECUITY 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 sumatriptan. Some of these reactions occurred in patients without known CAD. 5-HT_1 agonists, including ZECUITY, may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to using ZECUITY. Do not use ZECUITY 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 using the first ZECUITY TDS in a medically supervised setting and performing an electrocardiogram (ECG) upon activation of ZECUITY. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ZECUITY.

5.4 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 ZECUITY if these disturbances occur. ZECUITY is contraindicated in patients with

Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [*see Contraindications (4)*].

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

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

5.6 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.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. ZECUITY is contraindicated in patients with a history of stroke or TIA [*see Contraindications (4)*].

5.7 Other Vasospasm Reactions

5-HT_1 agonists, including ZECUITY, 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 a vasospastic reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before using ZECUITY [*see Contraindications (4)*].

Reports of 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 have not been clearly established.

5.8 Medication Overuse Headache

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

5.9 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including ZECUITY, particularly during coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [*see Drug Interactions (7.4)*]. 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 ZECUITY if serotonin syndrome is suspected.

5.10 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 ZECUITY. ZECUITY is contraindicated in patients with uncontrolled hypertension [*see Contraindications (4)*].

5.11 Anaphylactic/Anaphylactoid Reactions

Anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan. 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. ZECUITY is contraindicated in patients with prior serious anaphylactic reaction.

5.12 Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. ZECUITY should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

5.13 Electrically-active Implantable or Body-worn Medical Devices

ZECUITY should not be applied in areas near or over electrically-active implantable or body-worn medical devices (e.g., implantable cardiac pacemaker, body-worn insulin pump, implantable deep brain stimulator).

6 ADVERSE REACTIONS

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

- Allergic Contact Dermatitis *[see Warnings and Precautions (5.2)]*
- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina *[see Warnings and Precautions (5.3)]*
- Arrhythmias *[see Warnings and Precautions (5.4)]*
- Chest, throat, neck, and/or jaw pain/tightness/pressure *[see Warnings and Precautions (5.5)]*
- Cerebrovascular events *[see Warnings and Precautions (5.6)]*
- Other vasospasm reactions *[see Warnings and Precautions (5.7)]*

- Medication overuse headache *[see Warnings and Precautions (5.8)]*
- Serotonin syndrome *[see Warnings and Precautions (5.9)]*
- Increase in blood pressure *[see Warnings and Precautions (5.10)]*
- Anaphylactic/anaphylactoid reactions *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

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

In two long-term, open-label studies in which patients were allowed to treat multiple migraine attacks for up to 1 year, 15% (99 out of 662) withdrew from the study because of adverse reaction. The most common adverse reactions leading to withdrawal from the study were contact dermatitis (4%) and application site pain (4%).

The most common adverse reactions (≥ 5%) in a controlled single dose study were application site pain, paresthesia, pruritus, warmth, and discomfort.

Controlled single dose acute migraine study

Table 1 lists adverse reactions that occurred at a frequency of 2% or greater in a controlled clinical study of ZECUITY in patients with acute migraine (Study 1) [*see Clinical Studies (14.1)*]. In that study, patients randomized to the control group used the same activated iontophoretic transdermal delivery system (TDS) as patients randomized to ZECUITY, with the only difference being the absence of sumatriptan in the drug reservoir. Therefore, patients in the control group were exposed to same TDS-related risks as patients in the ZECUITY group, minus the risks related to sumatriptan. Only reactions that occurred at a frequency of 2% or more in patients treated with ZECUITY or control are included in Table 1.

Table 1: Adverse Reactions Reported by at least 2% of Patients in Study 1

	Percent of Subjects Reporting	
Adverse Reaction	**ZECUITY (n = 234)**	**Control (n = 235)**
Application site pain	26%	17%
Application site paresthesia	9%	16%
Application site pruritus	8%	7%
Application site warmth	6%	3%
Application site discomfort	6%	6%
Application site irritation	4%	2%
Application site discoloration	3%	1%

The incidence of “atypical sensations” adverse events (paresthesia, sensation warm/cold) and “pain and other pressure sensations” (chest pain/tightness/pressure/heaviness or neck/throat/jaw pain, tightness, pressure or heaviness) was 2% each in ZECUITY-treated patients, vs. 0% in the control group. Application site bruising was reported in 2 ZECUITY-treated patients (0.9%) vs. no patient in the control group.

Subgroup analyses of age (≤41 years, >41 years), race (Caucasian, non-Caucasian) and body mass index (BMI) (≤25.7 mg/kg^2, >25.7 mg/kg^2) showed no difference between subgroups for adverse events.

Skin Irritation Examination

In Study 1, patients performed their own examination of the TDS application site at 4, 12, and 24 hours post TDS activation, and daily thereafter until resolution. Skin irritation examination scores are summarized in Table 2. The median time to "no redness" was 2.6 days for Zecuity compared with 0.3 day in the control group.

Table 2: Subject Self-examination Skin Irritation Scoring

Time-point		ZECUITY (n = 234)	Control (n = 235)
4 hours	No or minimal redness	39%	73%
	Moderate redness	55%	24%
	Intense redness	4%	1%
	Intense redness with blisters/broken skin	2%	2%
12 hours	No or minimal redness	69%	90%
	Moderate redness	27%	9%
	Intense redness	2%	0%
	Intense redness with blisters/broken skin	2%	1%
24 hours	No or minimal redness	79%	93%
	Moderate redness	19%	6%
	Intense redness	1%	0%
	Intense redness with blisters/broken skin	1%	1%

Application site reactions across clinical studies (Controlled single dose acute migraine study and long term safety studies)

In the controlled and uncontrolled clinical studies combined (n = 796 unique ZECUITY-treated subjects), the frequency of application site reactions of clinical interest is presented in Table 3.

Table 3: Application Site Reactions

Event	Percent of Subjects Reporting (N = 796)
Discoloration	5%
Contact Dermatitis	4%
Irritation	4%
Vesicles	3%
Bruising	2%
Erosion	0.4%

7 DRUG INTERACTIONS

7.1 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 ZECUITY within 24 hours of each other is contraindicated *[see Contraindications (4)]*.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of ZECUITY in patients receiving MAO-A inhibitors is contraindicated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, coadministration of ZECUITY and other 5-HT_1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.

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

Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs or SNRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. ZECUITY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When sumatriptan was administered intravenously to pregnant rabbits daily throughout the period of organogenesis, embryolethality was observed at doses at or close to those producing maternal toxicity. Oral administration of sumatriptan to rabbits during organogenesis was associated with increased incidences of fetal vascular and skeletal abnormalities; the highest no-effect dose for these effects was 15 mg/kg/day. The intravenous administration of sumatriptan to pregnant rats throughout organogenesis did not produce evidence of embryolethality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryolethality or teratogenicity.

8.3 Nursing Mothers

It is not known whether sumatriptan is excreted in human milk following transdermal administration. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZECUITY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Two controlled clinical trials evaluated sumatriptan nasal spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a single attack. The trials did not establish the efficacy of sumatriptan nasal spray compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single-attack studies, 3 multiple-attack studies) evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age dependent, with younger patients reporting events more commonly than older adolescents.

Post-marketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available, the use of ZECUITY in patients under 18 years of age is not recommended.

8.5 Geriatric Use

Clinical trials of ZECUITY 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 subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to using ZECUITY *[see Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed after intravenous administration of sumatriptan injection *[see Contraindications (4)]*. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, injection site reactions (desquamation, hair loss, and scab formation), and paralysis.

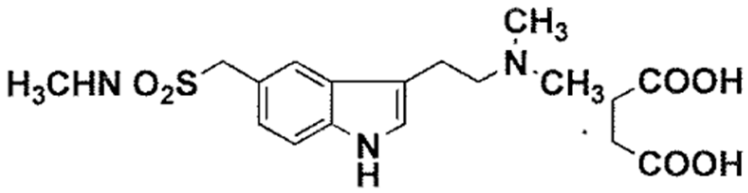
The apparent elimination half-life of sumatriptan after ZECUITY administration is about 3 hours *[see Clinical Pharmacology 12.3)]*, and therefore monitoring of patients after overdose with ZECUITY should continue for at least 15 hours or while symptoms or signs persist.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

ZECUITY (sumatriptan iontophoretic transdermal system) is a disposable, single use system designed to deliver sumatriptan through the skin using iontophoresis. Iontophoresis is a non-invasive method of delivering a drug through the skin using a low electrical current. The ZECUITY electronics, powered by two coin cell lithium batteries, control the amount of current applied and the rate and amount of sumatriptan delivered.

Sumatriptan succinate, the active component of ZECUITY, is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT_1) agonist (triptan). Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and has the following structure:



The empirical formula is $C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$ representing a molecular weight of 413.5.

Sumatriptan succinate is a white to off-white powder that is freely soluble in water. Each ZECUITY iontophoretic transdermal system contains 86 mg sumatriptan (base) as the succinate salt in an aqueous formulation. ZECUITY, upon activation, delivers 6.5 mg of sumatriptan through the skin over 4 hours *[see Dosage and Administration (2)]*.

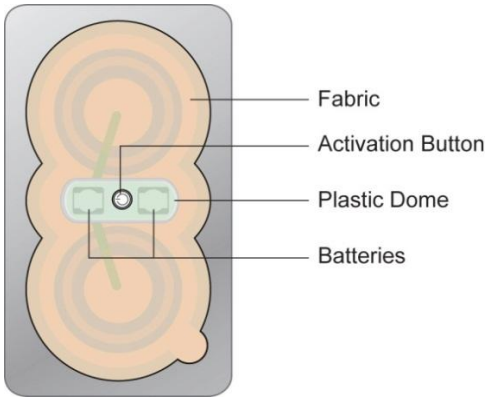
ZECUITY iontophoretic transdermal system is composed of an iontophoretic device and a drug reservoir card. The reservoir card contains 2 non-woven pads and 2 different gel formulations; one a sumatriptan succinate formulation and the other a sodium salt formulation. The sumatriptan succinate formulation and pad contains the following inactive ingredients: purified water, basic butylated methacrylate copolymer (polyamine), lauric acid, adipic acid, methylparaben and a non-woven viscose pad. The salt formulation

and pad contains: purified water, hydroxypropylcellulose, sodium chloride, methylparaben and a non-woven viscose pad. ZECUITY is a non-sterile product.

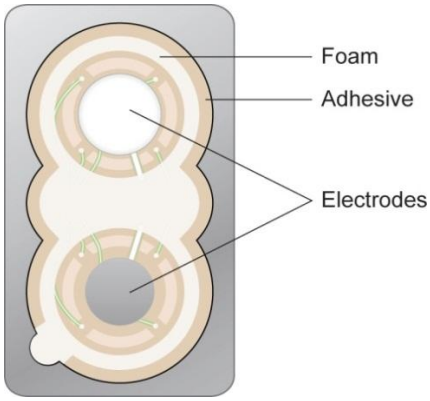
The iontophoretic device consists of medical grade adhesive fabric and foam and a plastic dome that contains an activation button, batteries, and electronics (see Figure 2).

Figure 2: Iontophoretic Device

Top View

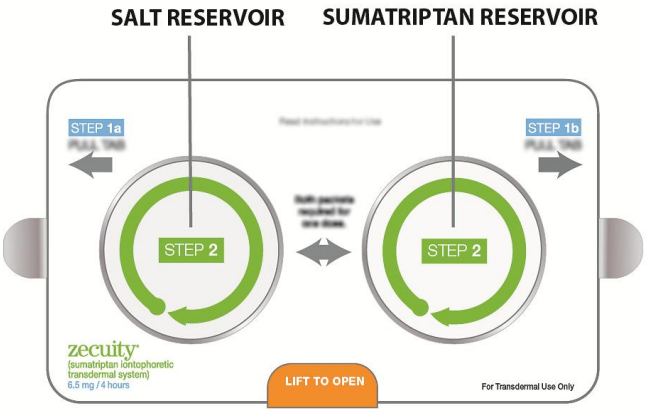


Bottom View



The sumatriptan and salt pads are housed in individual reservoirs. Each reservoir is sealed by a foil strip that is removed prior to transfer of the pads to the iontophoretic device (see Figure 3). The iontophoretic device and foil reservoirs are co-packaged in a single unit pouch *[see Patient Counseling Information (17)]*.

Figure 3: Reservoir Card



For ZECUITY to function, the pads must completely cover the electrodes *[see Patient Counseling Information (17)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sumatriptan is the active component of ZECUITY. Sumatriptan binds with high affinity to human cloned 5-$HT_{1B/1D}$ receptors. Sumatriptan 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.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of sumatriptan for the treatment of migraine headaches 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.

12.2 Pharmacodynamics

Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported in patients treated with sumatriptan, with and without a history of hypertension *[see Warnings and Precautions (5.10)]*.

Peripheral (Small) Arteries: In healthy volunteers (N = 18), a trial evaluating the effects of sumatriptan on peripheral (small vessel) arterial reactivity failed to detect a clinically significant increase in peripheral resistance.

Heart Rate: Transient increases in blood pressure observed in some subjects in clinical trials carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics

Absorption and Bioavailability: Following ZECUITY administration to the upper arm the maximum mean sumatriptan serum concentration (C_{max}) was 22 ng/mL, the mean total area under the curve (AUC_{0-inf}) was 110 hr*ng/mL, and the median t_{max} was 1.1 hours. The mean C_{max} and mean AUC_{0-inf} measured after ZECUITY administration were approximately 37% and 45% of the values measured after administration of 100 mg Imitrex® tablets, respectively.

The effect of ZECUITY application to the upper arm versus thigh was assessed in 19 healthy subjects. The application sites are considered interchangeable as the relative bioavailability of sumatriptan following application of the ZECUITY TDS to these two sites was comparable.

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1000 ng/mL, is between 14% and 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. The apparent volume of distribution of sumatriptan is 2.4 L/kg.

Metabolism: *In vitro* studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the A isoenzyme. No new metabolites were identified in comparison with the oral sumatriptan tablets. Most of a radiolabeled sumatriptan dose that is excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.

Elimination: After a single ZECUITY dose in 9 subjects, 11% of the sumatriptan dose was excreted in the urine as unchanged sumatriptan and 69% as the indole acetic acid metabolite. After a single ZECUITY dose, the mean sumatriptan half-life was 3.1 hours.

Migraine Effect: Similar pharmacokinetic values were observed during a migraine attack compared to a migraine-free period following ZECUITY administration on the upper arm in 18 patients with a diagnosis of migraine.

External Heat Source: A heat effect study in 12 healthy adult subjects demonstrated similar pharmacokinetic values without and with the application of an external heat source (40°C heat wrap placed over top of the ZECUITY TDS for the 4 hour dosing period).

Special Populations:

Age: The pharmacokinetics of sumatriptan after ZECUITY administration to the upper arm were compared for 8 healthy elderly subjects versus 8 paired gender and race matched healthy young adult subjects. No significant pharmacokinetic differences were observed. *[see Use In Specific Populations (8.5)]*.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined.

Hepatic Impairment: The effect of mild to moderate hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls. The pharmacokinetics of subcutaneously administered sumatriptan in patients with severe hepatic impairment has not been studied. The use of ZECUITY in this population is contraindicated *[see Contraindications (4)]*.

Race: The effect of race on sumatriptan pharmacokinetics after ZECUITY administration was assessed in an analysis of 8 pooled Phase 1 studies with 168 healthy subjects (50 non-Caucasian and 118 Caucasian). C_{max} is about 8% lower and AUC_{0-4} hours is about 10% lower in non-Caucasian compared to Caucasian subjects, respectively. These differences are not expected to be clinically significant.

Gender: No effect of gender on sumatriptan pharmacokinetics was identified in a study in 17 healthy subjects (8 male and 9 female).

Drug Interaction Studies: *Monoamine Oxidase-A Inhibitors:* In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of sumatriptan, resulting in a 2-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life. *[see Contraindications (4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage. Mice were dosed for 78 weeks and rats were dosed for 104 weeks. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in two gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). It was not clastogenic in two cytogenetics assays (in vitro human lymphocyte assay and in vivo rat micronucleus assay).

Impairment of Fertility: A fertility study by the subcutaneous route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, demonstrated no evidence of impaired fertility. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. It is not clear whether the problem is associated with the treatment of males or females or both.

13.2 Animal Toxicology and/or Pharmacology

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established.

Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg/day) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

14 CLINICAL STUDIES

14.1 Acute Migraine Attack – Placebo Controlled Efficacy Study

The efficacy of ZECUITY in the acute treatment of migraine headaches with or without aura was demonstrated in a randomized, double-blind, controlled study (Study 1).

Patients in Study 1 were predominantly female (85%) and Caucasian (82%), with a mean age of 41 years. Patients were instructed to treat a migraine headache of moderate to severe pain with a single ZECUITY TDS or matching TDS with no sumatriptan in the drug reservoir. Additional medications were allowed as rescue therapy beginning 2 hours after the initial treatment.

The primary efficacy endpoint in Study 1 was the proportion of patients who had no headache pain at 2 hours post TDS activation. Absence of nausea, photophobia, and phonophobia at 2 hours post TDS activation were assessed as secondary endpoints. Headache pain relief, defined as a reduction in migraine-related headache pain severity from moderate or severe pain to mild or no pain, was also assessed. As shown in Table 4, a significantly greater proportion of patients had no headache pain, had headache pain relief, no nausea, no phonophobia, or no photophobia at two hours after TDS activation in the ZECUITY treatment group than in the control group.

Table 4: Percentage of Patients with No Headache Pain, With Headache Pain Relief, No Nausea, No Photophobia, and No Phonophobia Two Hours After TDS Activation

Two Hours After ZECUITY TDS Activation	ZECUITY (n = 226)	Placebo (n = 228)	*p* value
No Headache Pain	18%	9%	0.0092
With Headache Pain Relief	53%	29%	<0.0001
No Nausea	84%	63%	<0.0001
No Photophobia	51%	36%	0.0028
No Phonophobia	55%	39%	0.0002

Analyses of the relationship between age, race, gender, or BMI and response showed no significant differences in response rates.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZECUITY contains 86 mg sumatriptan that delivers 6.5 mg of sumatriptan over 4 hours.

After use, fold used system so the adhesive side sticks to itself and safely discard away from children and pets. ZECUITY contains lithium-manganese dioxide batteries; dispose in accordance with state and local regulations.

Store at room temperature, between 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F). Do not store in the refrigerator or freezer.

ZECUITY is packaged individually in a sealed pouch. ZECUITY is supplied in cartons of 4 systems, NDC 51759-101-04.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

How to Use ZECUITY

Advise patients to carefully read the Patient Instructions for Use. Only patients who are able to understand and follow the instructions should use ZECUITY.

Advise patients that the ZECUITY iontophoretic transdermal system (TDS) must be properly applied and activated within 15 minutes of initiating Step 1 (Pull Tabs) of the Patient Instructions for Use, or the TDS will not operate.

Advise patients not to bathe, shower or swim while wearing ZECUITY.

Advise patients that upon removal of the ZECUITY TDS, most patients experience some skin redness under the transdermal system, which usually disappears within 24 hours.

Advise patients that Zecuity is single-use and should not be cut. Advise patients that no more than two ZECUITY TDS should be used in a 24 hour period, and that a second ZECUITY TDS should not be applied until at least 2 hours after activation of the first ZECUITY TDS *[see Dosage and Administration (2)]*.

Instruct patients to apply the ZECUITY TDS to the upper arm or thigh and not to other areas of the body. Instruct patients to apply the ZECUITY TDS to dry intact, non-irritated skin on a site that is relatively hair free and without scars, tattoos, abrasions, or other skin conditions (i.e., generalized skin irritation or disease including eczema, psoriasis, melanoma, contact dermatitis).

Advise patients that the ZECUITY TDS should not be applied to a previous application site until the site remains erythema free for 3 days *[see Dosage and Administration (2)]*.

Inform patients that the safety of using more than 4 ZECUITY in one month has not been established.

Risk of Injury during Magnetic Resonance Imaging (MRI) procedure

Inform patients that Zecuity contains metal parts and must be removed before an MRI procedure.

Potential for Allergic Contact Dermatitis

Caution patients about the potential for developing allergic contact dermatitis (ACD) after use of ZECUITY. Inform patients of the signs and symptoms of ACD, and instruct patients to seek medical advice if they develop skin lesions suggestive of ACD. Inform patients that it is possible that some patients who develop ACD with sumatriptan by exposure to ZECUITY may not be able to take sumatriptan in any form.

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

Inform patients that the medication in ZECUITY or other triptans may cause serious cardiovascular side effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, advise patients that they should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should seek medical advice when observing any indicative sign or symptoms. Apprise patients of the importance of this follow-up *[see Warnings and Precautions (5.3, 5.4, 5.5, and 5.6)]*.

Anaphylactic/Anaphylactoid Reactions

Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan. 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 Warnings and Precautions (5.11)]*.

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 (5.8)]*.

Pregnancy

Inform patients that ZECUITY 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

Advise patients to notify their physician if they are breast-feeding or plan to breast-feed *[see Use in Specific Populations (8.3)]*.

Ability To Perform Complex Tasks

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

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of ZECUITY or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.9) and Drug Interactions (7.4)]*.

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FDA Approved Text Mar 2014

Patient Information
ZECUITY® (zeh-CUE-eh-tee)
(sumatriptan succinate)
Iontophoretic Transdermal System (TDS)
for topical use

Read this Patient Information before you start using ZECUITY and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about ZECUITY?

ZECUITY can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop using ZECUITY 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

ZECUITY 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

What is ZECUITY?

ZECUITY is a prescription medicine used for the acute treatment of migraine headaches with or without aura in adults. ZECUITY comes in an iontophoretic transdermal system (TDS) that uses a mild electrical current to deliver the medicine sumatriptan through your skin.

ZECUITY is used for people who have been told by a healthcare provider that they have migraine headaches.

ZECUITY is not used to prevent or decrease the number of migraine headaches you have.

It is not known if ZECUITY is safe and effective in children under 18 years of age.

Who should not use ZECUITY?

Do not use ZECUITY if you have:

- heart problems or a history of heart problems
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider
- taken any of the following medicines in the last 24 hours:
  - almotriptan (AXERT®)
  - eletriptan (RELPAX®)
  - frovatriptan (FROVA®)
  - naratriptan (AMERGE®)
  - rizatriptan (MAXALT®, MAXALT-MLT®)
  - sumatriptan and naproxen (TREXIMET®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)

Ask your healthcare provider if you are not sure if your medicine is listed above.

- severe liver problems
- an allergy to sumatriptan, the medicine in ZECUITY, or any of the components in ZECUITY TDS. See the end of this leaflet for a complete list of ingredients in ZECUITY.

What should I tell my healthcare provider before using ZECUITY?

Before you use ZECUITY, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- are a female who has gone through menopause
- have heart problems or family history of heart problems or stroke
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- have or have had any side effects caused by the use of electrical devices. Talk to your healthcare provider if you are not sure if you have a medical electronic device or sensitivities to electrical devices.
- are pregnant or plan to become pregnant. It is not known if ZECUITY will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicine in ZECUITY passes into your breast milk. You and your healthcare provider should decide if you will use ZECUITY or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using ZECUITY with certain other medicines can affect each other, causing serious side effects.

Especially tell your healthcare provider if you take anti-depressant medicines called:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider 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 healthcare provider or pharmacist when you get a new medicine.

How should I use ZECUITY?

- **Read the Instructions for Use in the package that comes with your ZECUITY TDS for information about the right way to use ZECUITY TDS.**
- Certain people should apply their first dose of ZECUITY in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should use your first dose in a medical setting.
- ZECUITY is for use on the skin only.
- Use ZECUITY exactly as your healthcare provider tells you to.
- Apply 1 ZECUITY to your upper arm or thigh.
- **Do not** apply ZECUITY to other areas of your body. Talk to your healthcare provider if you are not sure where to apply ZECUITY.
- If your headache comes back or you only get some relief from your headache, you may apply a second ZECUITY to your other arm or thigh, no sooner than 2 hours after the activation of the previously applied ZECUITY.
- Do not apply more than 2 ZECUITY in 24 hours.
- If you use too much ZECUITY, call your healthcare provider or go to the nearest hospital emergency room right away.
- It is not known if using more than 4 ZECUITY in 1 month is safe.

What should I avoid while using ZECUITY?

- Do not bathe, shower, or swim while wearing ZECUITY.
- ZECUITY 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.

- You should remove ZECUITY before you have a Magnetic Resonance Imaging (MRI) procedure.

What are the possible side effects of ZECUITY?

See "What is the most important information I should know about ZECUITY?"

ZECUITY may cause serious side effects including:

- **injury during a Magnetic Resonance Imaging (MRI).** The ZECUITY TDS contains metal parts and must be removed before an MRI.
- **allergic contact dermatitis (ACD).** Some people have had a serious skin reaction called allergic contact dermatitis (ACD) where ZECUITY is applied. Symptoms of ACD include:
    - itching, redness, or irritation of skin
    - blistering or peeling of your skin
    - warmth or tenderness of skin
    - blisters that ooze, drain, or crust over

  You should stop using ZECUITY and call your healthcare provider if you have any of the symptoms of ACD. If you have or have had ACD while using ZECUITY and need to take sumatriptan by mouth or injection, your first dose of sumatriptan should be given in your healthcare provider's office or in another medical setting.
- **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 use too many ZECUITY may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with sumatriptan.
- **serotonin syndrome.** Serotonin syndrome is a rare but serious problem that can happen in people using ZECUITY, especially if ZECUITY is used with anti-depressant medicines called SSRIs or SNRIs.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Call your healthcare provider 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

- **increases in blood pressure.** You should not use ZECUITY if you have uncontrolled high blood pressure.
- **serious allergic reactions.** Get medical help right away if you have any of these symptoms of a serious allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - severe itching
  - skin rash, redness, or swelling
  - dizziness or fainting

  - fast heartbeat or pounding in your chest (tachycardia)
  - sweating
- **seizures.** Seizures have happened in people taking sumatriptan who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take ZECUITY.

The most common side effects of ZECUITY include pain, tingling, itching, warmth, discomfort or a change in the skin color at the application site of ZECUITY.

Most people have some skin redness after removal of ZECUITY. This redness will usually go away in 24 hours.

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

These are not all the possible side effects of ZECUITY. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZECUITY?

- Store ZECUITY at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not store ZECUITY in the refrigerator or freezer.

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

General information about the safe and effective use of ZECUITY

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

This Patient Information leaflet summarizes the most important information about ZECUITY. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZECUITY that is written for healthcare professionals.

For more information, go to www.ZECUITY.com or call 1-855-ZECUITY.

What are the ingredients in ZECUITY?

Active ingredient: sumatriptan succinate

Inactive ingredients:

- **Sumatriptan Reservoir Card and pad:** purified water, basic butylated methacrylate copolymer (polyamine), lauric acid, adipic acid, methylparaben, and non-woven viscose pad.
- **Salt Reservoir Card and pad:** purified water, hydroxypropylcellulose, sodium chloride, methylparaben, and non-woven viscose pad.
- **Iontophoretic device:** medical grade adhesive fabric, foam and plastic dome containing an activation button, coin cell lithium batteries, and electronics.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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S/001 & S/002
FDA Approved Text Mar 2014

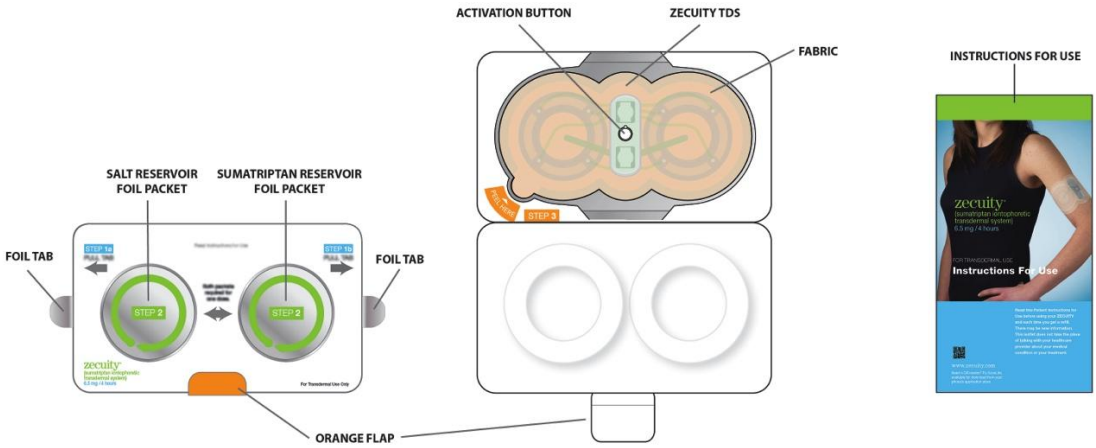
Instructions for Use

ZECUITY (zeh-CUE-eh-tee)
(sumatriptan succinate)
Iontophoretic Transdermal System (TDS)
For topical use

Read this Patient Instructions for Use before using your ZECUITY and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

Your ZECUITY Transdermal System (TDS): See Figure A

Figure A

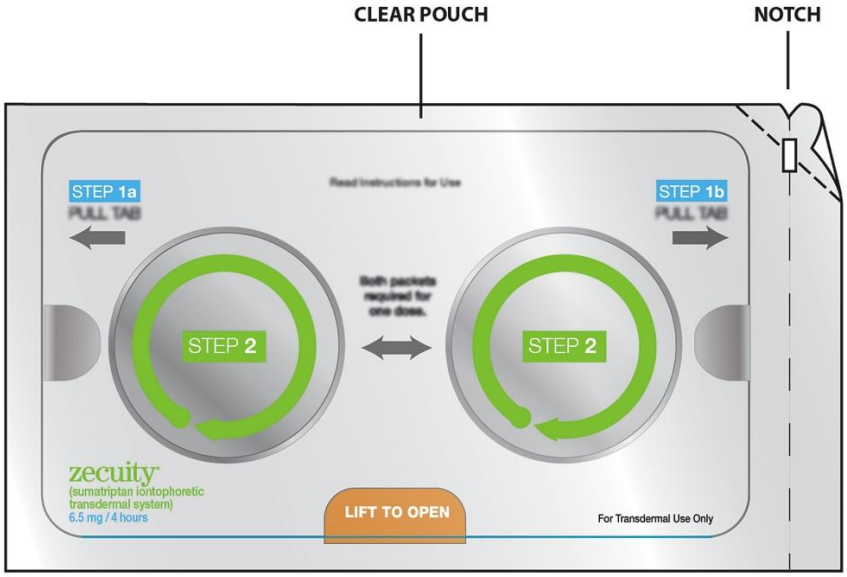


Preparation

ZECUITY is a single-use Transdermal System (TDS) or patch.

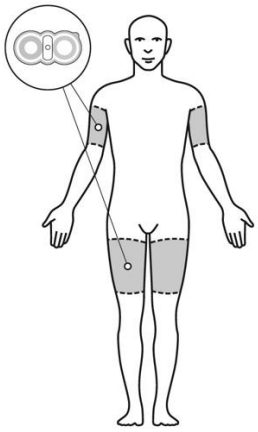
- Remove ZECUITY by folding and tearing from the notch at the corner of the clear pouch**. See Figure B**
  - ZECUITY TDS should not be cut.
  - Do not use ZECUITY TDS if the clear pouch is torn or damaged.

Figure B



- **Choose an application site: See Figure C**

Figure C



Choose an application site on your upper arm or thigh. **Do not** apply ZECUITY to any other body parts.

Choose an area of skin that is dry, clean and relatively hair free.

Do not apply ZECUITY over skin that is red or irritated. Skin should be free of redness and irritation for at least 3 days prior to application.

Do not apply ZECUITY over scars, tattoos, scratches, burns, abrasions, or broken skin.

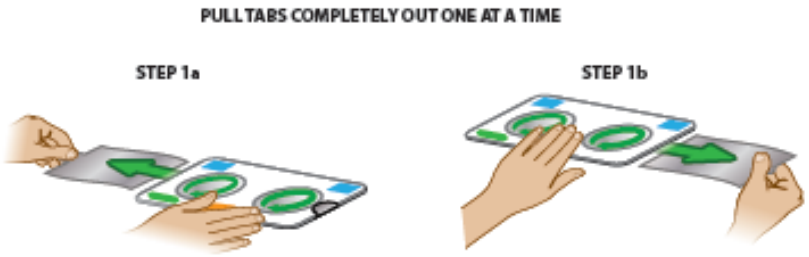
Step 1 – **Pull Tabs**

To apply the ZECUITY TDS you must pull the 2 foil tabs. These tabs are marked on the package as Step 1a and Step 1b. **See Figure D**

- Place ZECUITY on a flat surface with the foil packets facing up.
- While holding the package, pull both foil tabs out, 1 at a time, and throw the foil tabs away in the trash.

Note: You must apply and activate ZECUITY within 15 minutes of completing Step 1.

Figure D

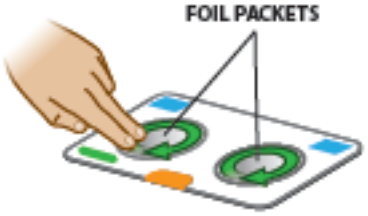


Step 2 – **Rub Foil Packets**

ZECUITY has 2 foil packets that each contain a white medication pad that **must** be properly attached to the ZECUITY TDS before use.

- To transfer and attach the medication pads to the ZECUITY TDS use 2 fingers and firmly press and rub each foil packet, tracing the green arrow 3 times around. **See Figure E**

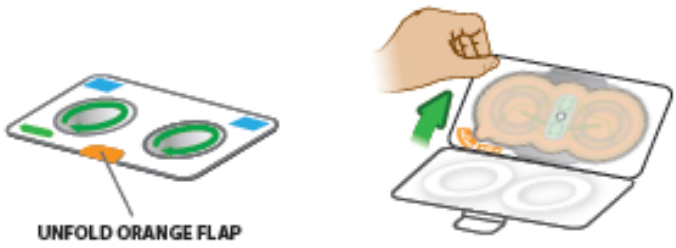
Figure E



Step 3 – Unfold and Lift Open

Unfold the orange flap, marked as Step 3 on the bottom of the packet and lift open the package. **See Figure F**

Figure F



Step 4 - Peel Pads and Check

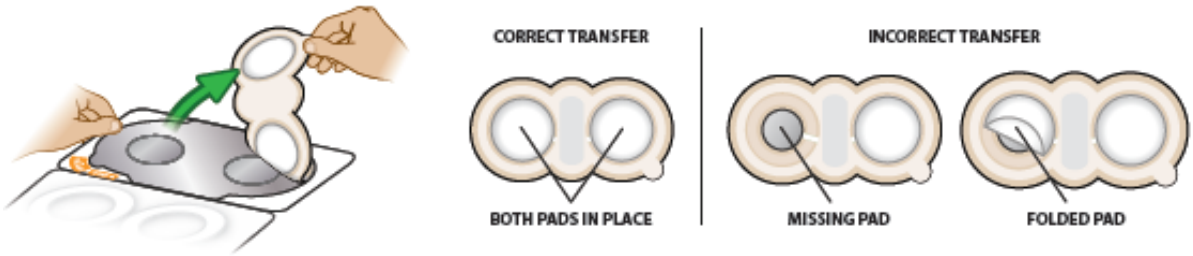
- Slowly peel the first part of the ZECUITY TDS back from the silver liner. If the medication pad is not attached, lay the ZECUITY TDS down on a hard surface and repeat Steps 2 and 3. **See Figure G**

Figure G

After checking to make sure that both white medication pads are securely attached, peel the ZECUITY TDS completely away from liner. **See Figure H**

- The ZECUITY TDS will not work properly if both medication pads are not attached.
- There may be gel left in the reservoirs after the ZECUITY TDS is peeled back from the silver liner.

Figure H



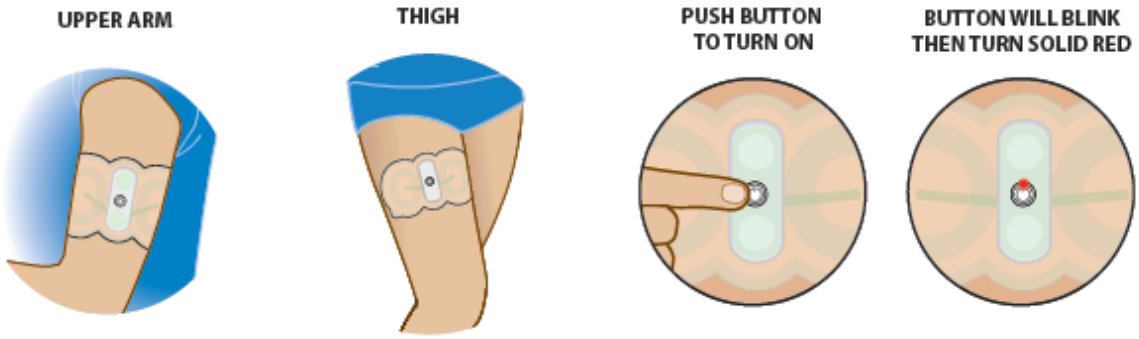
Step 5 – Apply and Activate

Apply ZECUITY to your upper arm or thigh and activate it by pressing the button to turn it on. The button will blink and then turn solid red as it releases the medicine.

See Figure I

- If the light does not turn solid red or goes off within the first 10 minutes of application this means no medicine is being delivered. The TDS should be gently removed and thrown away. See "How to safely remove and throw away ZECUITY TDS" for instructions. You can immediately apply a new TDS to a different application site.
- Wear the TDS for 4 hours or until the red light goes off.
- If the red light turns off before 4 hours, the TDS has stopped delivering your medicine and should be gently removed and thrown away. See "How to safely remove and throw away ZECUITY TDS" for instructions. If you still have migraine pain, another ZECUITY TDS can be applied to a different application site.

Figure I



Important Information about using ZECUITY TDS:

- You may feel slight tingling or a mild burning sensation within 30 seconds of activating the ZECUITY TDS after pressing the button.
- If ZECUITY begins to peel off, the ZECUITY TDS may be taped down with **medical** tape.
- You must keep ZECUITY dry. Do not bathe, shower, or swim while wearing ZECUITY.
- Do not have a Magnetic Resonance Imaging (MRI) while wearing ZECUITY.
- Remove ZECUITY if you have a painful burning sensation during use.

How to safely remove and throw away ZECUITY TDS:

- Slowly remove ZECUITY to minimize skin irritation. Gently clean the area with mild soap and water to remove any medicine that might be left on the skin.
- ZECUITY TDS contains lithium-manganese dioxide batteries. Talk to your pharmacist or healthcare provider about how to follow state and local regulations when throwing away ZECUITY.
- After use, fold your used ZECUITY TDS so the adhesive side sticks to itself and safely throw it away.
- Keep ZECUITY out of the reach of children and pets.

How should I store ZECUITY?

- Store ZECUITY TDS at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not store ZECUITY in the refrigerator or freezer.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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