

## 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<sub>1</sub> 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](http://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: 01/2013

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Risk of Injury During Magnetic Resonance Imaging (MRI) Procedure
- 5.2 Allergic Contact Dermatitis
- 5.3 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina
- 5.4 Arrhythmias
- 5.5 Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure
- 5.6 Cerebrovascular Events
- 5.7 Other Vasospasm Reactions
- 5.8 Medication Overuse Headache
- 5.9 Serotonin Syndrome
- 5.10 Increase in Blood Pressure
- 5.11 Anaphylactic/Anaphylactoid Reactions
- 5.12 Seizures
- 5.13 Electrically-active Implantable or Body-worn Medical Devices

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

### 7 DRUG INTERACTIONS

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

### 7.1 Ergot-Containing Drugs

### 7.2 Monoamine Oxidase-A Inhibitors

### 7.3 Other 5-HT<sub>1</sub> Agonists

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

#### 8.3 Nursing Mothers

#### 8.4 Pediatric Use

#### 8.5 Geriatric Use

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

#### 12.2 Pharmacodynamics

#### 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### 13.2 Animal Toxicology and/or Pharmacology

### 14 CLINICAL STUDIES

#### 14.1 Acute Migraine Attack – Placebo Controlled Efficacy Study

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

1

---

2 **FULL PRESCRIBING INFORMATION**

3 **1 INDICATIONS AND USAGE**

4 ZECUITY is indicated for the acute treatment of migraine with or without aura in adults.

5 Limitations of Use:

- 6 • Use only if a clear diagnosis of migraine has been established.
- 7 • If a patient has no response to the first migraine attack treated with ZECUITY reconsider  
8 the diagnosis of migraine before ZECUITY is administered to treat any subsequent  
9 attacks.
- 10 • ZECUITY is not intended for the prevention of migraine attacks.

11 **2 DOSAGE AND ADMINISTRATION**

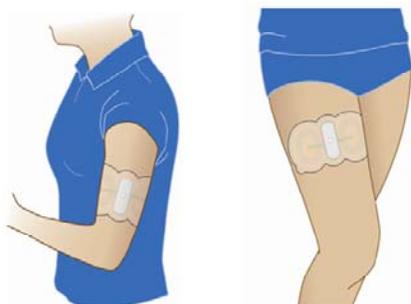
12 ZECUITY is for transdermal use only and is designed for patient self-administration to the upper  
13 arm or thigh (see Figure 1). ZECUITY should not be applied to other areas of the body.  
14 ZECUITY should not be cut.

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

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

25

26 **Figure 1: Applied Transdermal System**



27

28

29 ZECUITY delivers 6.5 mg of sumatriptan over 4 hours. Once applied, the activation button must  
30 be pushed, and the red light emitting diode (LED) will turn on. ZECUITY TDS must be applied  
31 and activated within 15 minutes of initiation of assembly. When dosing is completed, the system  
32 stops operating and the activation light turns off, signaling that the system can be removed. Once  
33 dosing is completed, the system cannot be reactivated. If the light turns off before 4 hours,  
34 dosing has stopped and ZECUITY can be removed. If headache relief is incomplete, a second  
35 ZECUITY TDS can be applied to a different site. [see Patient Counseling Information (17)].

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

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

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

### 42 **3 DOSAGE FORMS AND STRENGTHS**

43 Iontophoretic transdermal system: 6.5 mg over 4 hours.

### 44 **4 CONTRAINDICATIONS**

45 ZECUITY is contraindicated in patients with:

- 46 • Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial  
47 infarction, or documented silent ischemia) or coronary artery vasospasm, including  
48 Prinzmetal's angina [see Warnings and Precautions (5.3)].
- 49 • Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory  
50 conduction pathway disorders [see Warnings and Precautions (5.4)].
- 51 • History of stroke, transient ischemic attack (TIA), or history of hemiplegic or basilar  
52 migraine because these patients are at a higher risk of stroke [see Warnings and  
53 Precautions (5.6)].
- 54 • Peripheral vascular disease [see Warnings and Precautions (5.7)].
- 55 • Ischemic bowel disease [see Warnings and Precautions (5.7)].
- 56 • Uncontrolled hypertension [see Warnings and Precautions (5.10)].
- 57 • Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type  
58 medication (such as dihydroergotamine or methysergide), or another 5-  
59 hydroxytryptamine<sub>1</sub> (5-HT<sub>1</sub>) agonist [see Drug Interactions (7.1, 7.3)].
- 60 • Concurrent administration of an MAO-A inhibitor or recent (within 2 weeks) use of a  
61 MAO-A inhibitor [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].
- 62 • Known hypersensitivity to sumatriptan or components of ZECUITY [see Warnings and  
63 Precautions (5.2, 5.11)].

- 64 • Severe hepatic impairment [see *Clinical Pharmacology (12.3)*].
- 65 • Allergic contact dermatitis to ZECUITY [see *Warnings and Precautions (5.2)*].

## 66 **5 WARNINGS AND PRECAUTIONS**

### 67 **5.1 Risk of Injury During Magnetic Resonance Imaging (MRI)** 68 **Procedure**

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

### 70 **5.2 Allergic Contact Dermatitis**

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

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

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

### 86 **5.3 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's** 87 **Angina**

88 The use of ZECUITY is contraindicated in patients with ischemic or vasospastic CAD. There  
89 have been rare reports of serious cardiac adverse reactions, including acute myocardial  
90 infarction, occurring within a few hours following administration of sumatriptan. Some of these  
91 reactions occurred in patients without known CAD. 5-HT<sub>1</sub> agonists, including ZECUITY, may  
92 cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of  
93 CAD.

94 Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular  
95 risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history  
96 of CAD) prior to using ZECUITY. Do not use ZECUITY if there is evidence of CAD or  
97 coronary artery vasospasm [see *Contraindications (4)*]. For patients with multiple cardiovascular  
98 risk factors who have a negative cardiovascular evaluation, consider using the first ZECUITY  
99 TDS in a medically supervised setting and performing an electrocardiogram (ECG) upon  
100 activation of ZECUITY. For such patients, consider periodic cardiovascular evaluation in  
101 intermittent long-term users of ZECUITY.

## 102 **5.4 Arrhythmias**

103 Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and  
104 ventricular fibrillation leading to death, have been reported within a few hours following the  
105 administration of 5-HT<sub>1</sub> agonists. Discontinue ZECUITY if these disturbances occur. ZECUITY  
106 is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated  
107 with other cardiac accessory conduction pathway disorders [*see Contraindications (4)*].

## 108 **5.5 Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure**

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

## 114 **5.6 Cerebrovascular Events**

115 Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated  
116 with 5-HT<sub>1</sub> agonists, and some have resulted in fatalities. In a number of cases, it appears  
117 possible that the cerebrovascular events were primary, the 5-HT<sub>1</sub> agonist having been  
118 administered in the incorrect belief that the symptoms experienced were a consequence of  
119 migraine when they were not.

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

## 124 **5.7 Other Vasospasm Reactions**

125 5-HT<sub>1</sub> agonists, including ZECUITY, may cause non-coronary vasospastic reactions, such as  
126 peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with  
127 abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients  
128 who experience symptoms or signs suggestive of a vasospastic reaction following the use of any  
129 5-HT<sub>1</sub> agonist, rule out a vasospastic reaction before using ZECUITY [*see Contraindications*  
130 *(4)*].

131 Reports of transient and permanent blindness and significant partial vision loss have been  
132 reported with the use of 5-HT<sub>1</sub> agonists. Since visual disorders may be part of a migraine attack,  
133 a causal relationship between these events and the use of 5-HT<sub>1</sub> agonists have not been clearly  
134 established.

## 135 **5.8 Medication Overuse Headache**

136 Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, combination of drugs for 10  
137 or more days per month) may lead to exacerbation of headache (medication overuse headache).  
138 Medication overuse headache may present as migraine-like daily headaches or as a marked  
139 increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the

140 overused drugs, and treatment of withdrawal symptoms (which often includes a transient  
141 worsening of headache) may be necessary.

## 142 **5.9 Serotonin Syndrome**

143 Serotonin syndrome may occur with triptans, including ZECUITY, particularly during  
144 coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine  
145 reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [*see Drug*  
146 *Interactions (7.4)*]. Serotonin syndrome symptoms may include mental status changes (e.g.,  
147 agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure,  
148 hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or  
149 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually  
150 occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication.  
151 Discontinue ZECUITY if serotonin syndrome is suspected.

## 152 **5.10 Increase in Blood Pressure**

153 Significant elevation in blood pressure, including hypertensive crisis with acute impairment of  
154 organ systems, has been reported on rare occasions in patients treated with 5-HT<sub>1</sub> agonists,  
155 including patients without a history of hypertension. Monitor blood pressure in patients treated  
156 with ZECUITY. ZECUITY is contraindicated in patients with uncontrolled hypertension [*see*  
157 *Contraindications (4)*].

## 158 **5.11 Anaphylactic/Anaphylactoid Reactions**

159 Anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan. Such  
160 reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more  
161 likely to occur in individuals with a history of sensitivity to multiple allergens. ZECUITY is  
162 contraindicated in patients with prior serious anaphylactic reaction.

## 163 **5.12 Seizures**

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

169

## 170 **5.13 Electrically-active Implantable or Body-worn Medical Devices**

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

## 174 **6 ADVERSE REACTIONS**

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

- 177 • Allergic Contact Dermatitis [see *Warnings and Precautions (5.2)*]
- 178 • Myocardial ischemia, myocardial infarction, and Prinzmetal's angina [see *Warnings and*  
179 *Precautions (5.3)*]
- 180 • Arrhythmias [see *Warnings and Precautions (5.4)*]
- 181 • Chest, throat, neck, and/or jaw pain/tightness/pressure [see *Warnings and Precautions*  
182 *(5.5)*]
- 183 • Cerebrovascular events [see *Warnings and Precautions (5.6)*]
- 184 • Other vasospasm reactions [see *Warnings and Precautions (5.7)*]
- 185 • Medication overuse headache [see *Warnings and Precautions (5.8)*]
- 186 • Serotonin syndrome [see *Warnings and Precautions (5.9)*]
- 187 • Increase in blood pressure [see *Warnings and Precautions (5.10)*]
- 188 • Anaphylactic/anaphylactoid reactions [see *Warnings and Precautions (5.11)*]

### 189 **6.1 Clinical Trials Experience**

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

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

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

#### 199 ***Controlled single dose acute migraine study***

200 [Table 1](#) lists adverse reactions that occurred at a frequency of 2% or greater in a controlled  
201 clinical study of ZECUITY in patients with acute migraine (Study 1) [see *Clinical Studies*  
202 *(14.1)*]. In that study, patients randomized to the control group used the same activated  
203 iontophoretic transdermal delivery system (TDS) as patients randomized to ZECUITY, with the  
204 only difference being the absence of sumatriptan in the drug reservoir. Therefore, patients in the  
205 control group were exposed to same TDS-related risks as patients in the ZECUITY group, minus  
206 the risks related to sumatriptan. Only reactions that occurred at a frequency of 2% or more in  
207 patients treated with ZECUITY or control are included in [Table 1](#).

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

Adverse Reaction	Percent of Subjects Reporting	
	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%

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

214 Subgroup analyses of age ( $\leq 41$  years,  $> 41$  years), race (Caucasian, non-Caucasian) and body  
 215 mass index (BMI) ( $\leq 25.7$  mg/kg<sup>2</sup>,  $> 25.7$  mg/kg<sup>2</sup>) showed no difference between subgroups for  
 216 adverse events.

217 *Skin Irritation Examination*

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

222 **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%

Time-point		ZECUITY (n = 234)	Control (n = 235)
	Intense redness	1%	0%
	Intense redness with blisters/broken skin	1%	1%

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

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

227 **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%

228

## 229 **7 DRUG INTERACTIONS**

230

### 231 **7.1 Ergot-Containing Drugs**

232 Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because  
 233 these effects may be additive, use of ergotamine-containing or ergot-type medications (like  
 234 dihydroergotamine or methysergide) and ZECUITY within 24 hours of each other is  
 235 contraindicated [see *Contraindications (4)*].

### 236 **7.2 Monoamine Oxidase-A Inhibitors**

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

240 **7.3 Other 5-HT<sub>1</sub> Agonists**

241 Because their vasospastic effects may be additive, coadministration of ZECUITY and other  
242 5-HT<sub>1</sub> agonists (e.g., triptans) within 24 hours of each other is contraindicated.

243 **7.4 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine**  
244 **Reuptake Inhibitors and Serotonin Syndrome**

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

247 **8 USE IN SPECIFIC POPULATIONS**

248 **8.1 Pregnancy**

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

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

260 **8.3 Nursing Mothers**

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

266 **8.4 Pediatric Use**

267 Safety and effectiveness in pediatric patients have not been established.

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

273 Five controlled clinical trials (2 single-attack studies, 3 multiple-attack studies) evaluating oral  
274 sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701  
275 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared

276 to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical  
277 trials were similar in nature to those reported in clinical trials in adults. The frequency of all  
278 adverse events in these patients appeared to be both dose- and age dependent, with younger  
279 patients reporting events more commonly than older adolescents.

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

## 288 **8.5 Geriatric Use**

289 Clinical trials of ZECURITY did not include sufficient numbers of subjects aged 65 and over to  
290 determine whether they respond differently from younger subjects. Other reported clinical  
291 experience has not identified differences in responses between the elderly and younger subjects.  
292 In general, dose selection for an elderly patient should be cautious, usually starting at the low end  
293 of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac  
294 function and of concomitant disease or other drug therapy.

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

298 **10 OVERDOSAGE**

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

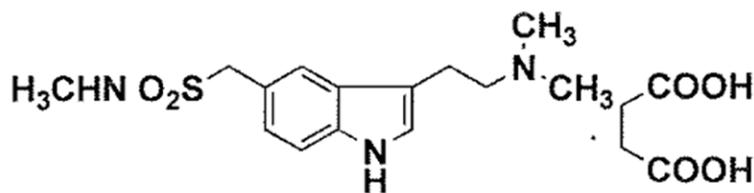
305 The apparent elimination half-life of sumatriptan after ZECUITY administration is about 3 hours  
306 [see *Clinical Pharmacology 12.3*], and therefore monitoring of patients after overdose with  
307 ZECUITY should continue for at least 15 hours or while symptoms or signs persist.

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

310 **11 DESCRIPTION**

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

316 Sumatriptan succinate, the active component of ZECUITY, is a selective 5-hydroxy-tryptamine  
317 receptor subtype 1 (5-HT<sub>1</sub>) agonist (triptan). Sumatriptan succinate is chemically designated as  
318 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and has the  
319 following structure:



320  
321 The empirical formula is C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S•C<sub>4</sub>H<sub>6</sub>O<sub>4</sub> representing a molecular weight of 413.5.

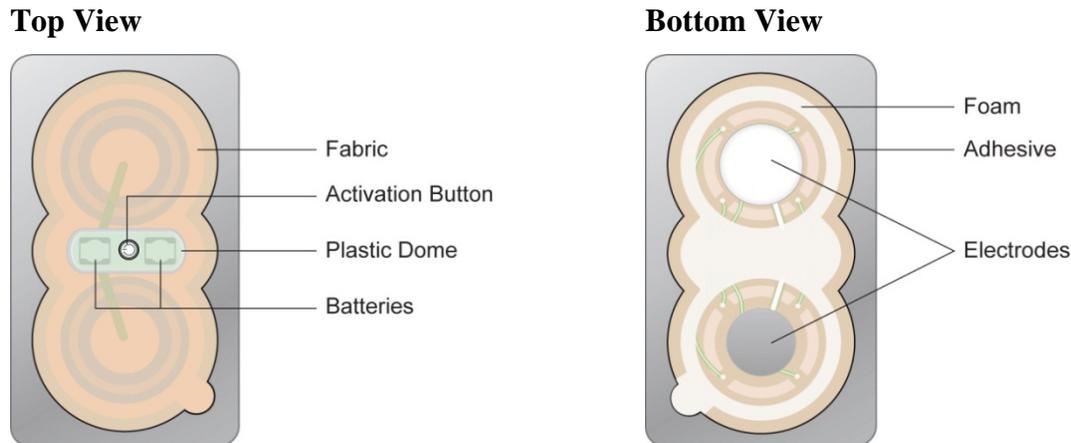
322 Sumatriptan succinate is a white to off-white powder that is freely soluble in water. Each  
323 ZECUITY iontophoretic transdermal system contains 86 mg sumatriptan (base) as the succinate  
324 salt in an aqueous formulation. ZECUITY, upon activation, delivers 6.5 mg of sumatriptan  
325 through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

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

331 methylparaben and a non-woven viscose pad. The salt formulation and pad contains: purified  
332 water, hydroxypropylcellulose, sodium chloride, methylparaben and a non-woven viscose pad.  
333 ZECUITY is a non-sterile product.

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

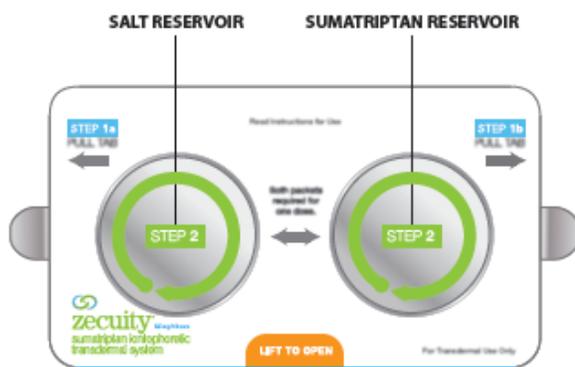
336 **Figure 2: Iontophoretic Device**



337  
338 The sumatriptan and salt pads are housed in individual reservoirs. Each reservoir is sealed by a  
339 foil strip that is removed prior to transfer of the pads to the iontophoretic device (see Figure 3).  
340 The iontophoretic device and foil reservoirs are co-packaged in a single unit pouch [see Patient  
341 Counseling Information (17)].

342 **Figure 3: Reservoir Card**

343



344  
345 For ZECUITY to function, the pads must completely cover the electrodes [see Patient  
346 Counseling Information (17)].

## 347 **12 CLINICAL PHARMACOLOGY**

### 348 **12.1 Mechanism of Action**

349 Sumatriptan is the active component of ZECUITY. Sumatriptan binds with high affinity to  
350 human cloned 5-HT<sub>1B/1D</sub> receptors. Sumatriptan presumably exerts its therapeutic effects in the  
351 treatment of migraine headache by binding to 5-HT<sub>1B/1D</sub> receptors located on intracranial blood  
352 vessels and sensory nerves of the trigeminal system.

353 Current theories proposed to explain the etiology of migraine headache suggest that symptoms  
354 are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including  
355 substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system.  
356 The therapeutic activity of sumatriptan for the treatment of migraine headaches is thought to be  
357 due to the agonist effects at the 5-HT<sub>1B/1D</sub> receptors on intracranial blood vessels (including the  
358 arterio-venous anastomoses) and sensory nerves of the trigeminal system, which result in cranial  
359 vessel constriction and inhibition of pro-inflammatory neuropeptide release.

### 360 **12.2 Pharmacodynamics**

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

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

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

### 370 **12.3 Pharmacokinetics**

371 Absorption and Bioavailability: Following ZECUITY administration to the upper arm the  
372 maximum mean sumatriptan serum concentration (C<sub>max</sub>) was 22 ng/mL, the mean total area  
373 under the curve (AUC<sub>0-inf</sub>) was 110 hr\*ng/mL, and the median t<sub>max</sub> was 1.1 hours. The mean C<sub>max</sub>  
374 and mean AUC<sub>0-inf</sub> measured after ZECUITY administration were approximately 37% and 45%  
375 of the values measured after administration of 100 mg Imitrex<sup>®</sup> tablets, respectively.

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

379 Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of  
380 10 to 1000 ng/mL, is between 14% and 21%. The effect of sumatriptan on the protein binding of  
381 other drugs has not been evaluated. The apparent volume of distribution of sumatriptan is 2.4  
382 L/kg.

383 Metabolism: *In vitro* studies with human microsomes suggest that sumatriptan is metabolized by  
384 MAO, predominantly the A isoenzyme. No new metabolites were identified in comparison with  
385 the oral sumatriptan tablets. Most of a radiolabeled sumatriptan dose that is excreted in the urine

386 is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are  
387 inactive.

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

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

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

#### 397 Special Populations:

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

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

404 *Hepatic Impairment*: The effect of mild to moderate hepatic disease on the pharmacokinetics of  
405 subcutaneously administered sumatriptan has been evaluated. There were no significant  
406 differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately  
407 hepatically impaired subjects compared with healthy controls. The pharmacokinetics of  
408 subcutaneously administered sumatriptan in patients with severe hepatic impairment has not  
409 been studied. The use of ZECUITY in this population is contraindicated [*see Contraindications*  
410 *(4)*].

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

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

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

422 **13 NONCLINICAL TOXICOLOGY**

423 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

437 **13.2 Animal Toxicology and/or Pharmacology**

438 Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in  
439 the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day,  
440 and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a  
441 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses  
442 were not established.

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

447 **14 CLINICAL STUDIES**

448 **14.1 Acute Migraine Attack – Placebo Controlled Efficacy Study**

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

451 Patients in Study 1 were predominantly female (85%) and Caucasian (82%), with a mean age of  
452 41 years. Patients were instructed to treat a migraine headache of moderate to severe pain with a  
453 single ZECUITY TDS or matching TDS with no sumatriptan in the drug reservoir. Additional  
454 medications were allowed as rescue therapy beginning 2 hours after the initial treatment.

455 The primary efficacy endpoint in Study 1 was the proportion of patients who had no headache  
456 pain at 2 hours post TDS activation. Absence of nausea, photophobia, and phonophobia at 2  
457 hours post TDS activation were assessed as secondary endpoints. Headache pain relief, defined  
458 as a reduction in migraine-related headache pain severity from moderate or severe pain to mild

459 or no pain, was also assessed. As shown in Table 4, a significantly greater proportion of patients  
460 had no headache pain, had headache pain relief, no nausea, no phonophobia, or no photophobia  
461 at two hours after TDS activation in the ZECUITY treatment group than in the control group.

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

Two Hours After ZECUITY TDS Activation			<i>p</i> value
	ZECUITY (n = 226)	Placebo (n = 228)	
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

465

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

## 468 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

475 ZECUITY is packaged individually in a sealed pouch. ZECUITY is supplied in cartons of  
476 6 systems, NDC 51759-101-06.

477

## 478 **17 PATIENT COUNSELING INFORMATION**

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

### 480 **How to Use ZECUITY**

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

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

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

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

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

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

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

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

### 501 **Risk of Injury during Magnetic Resonance Imaging (MRI) procedure**

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

### 503 **Potential for Allergic Contact Dermatitis**

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

### 509 **Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other** 510 **Vasospasm-related Events, Arrhythmias, and Cerebrovascular Events**

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

518 **Anaphylactic/Anaphylactoid Reactions**

519 Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving  
520 sumatriptan. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to  
521 drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens  
522 *[see Warnings and Precautions (5.11)]*.

523 **Medication Overuse Headache**

524 Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an  
525 exacerbation of headache and encourage patients to record headache frequency and drug use  
526 (e.g., by keeping a headache diary) *[see Warnings and Precautions (5.8)]*.

527 **Pregnancy**

528 Inform patients that ZECUITY should not be used during pregnancy unless the potential benefit  
529 justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

530 **Nursing Mothers**

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

533 **Ability To Perform Complex Tasks**

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

537 **Serotonin Syndrome**

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

541  
542  
543  
544  
545  
546  
547  
548  
549  
550

**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<sup>®</sup>)
  - eletriptan (RELPAX<sup>®</sup>)
  - frovatriptan (FROVA<sup>®</sup>)
  - naratriptan (AMERGE<sup>®</sup>)
  - rizatriptan (MAXALT<sup>®</sup>, MAXALT-MLT<sup>®</sup>)
  - sumatriptan and naproxen (TREXIMET<sup>®</sup>)
  - ergotamines (CAFERGOT<sup>®</sup>, ERGOMAR<sup>®</sup>, MIGERGOT<sup>®</sup>)
  - dihydroergotamine (D.H.E. 45<sup>®</sup>, MIGRANAL<sup>®</sup>)

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](http://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.

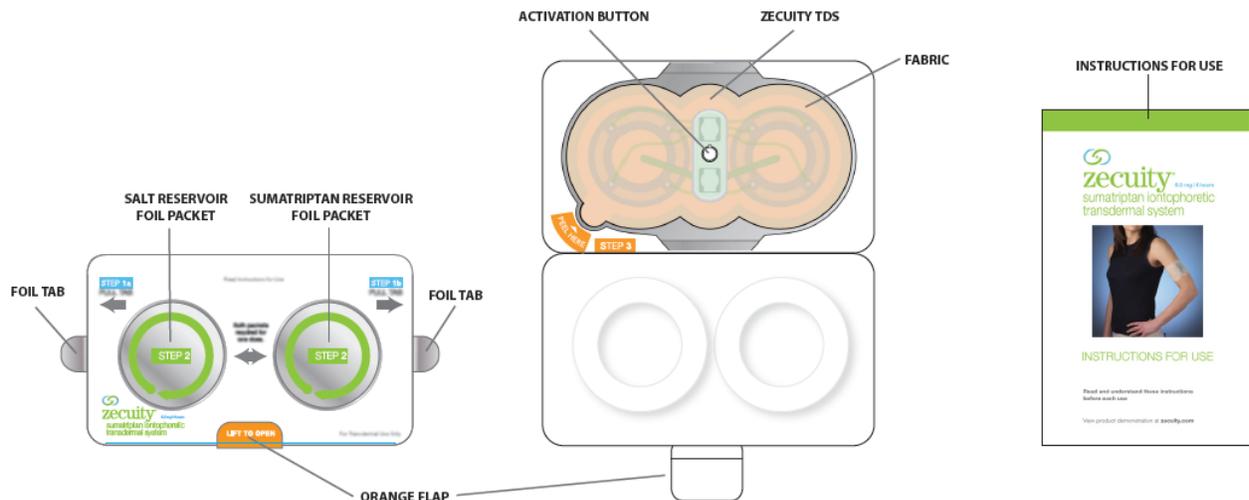
- **Salt Reservoir Card and pad:** purified water, hydroxypropylcellulose, sodium chloride, methylparaben, and non-woven viscose pad.
- **Iontophoretic device:** medical grade adhesive fabric, foam and plastic dome containing an activation button, coin cell lithium batteries, and electronics.

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

**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**

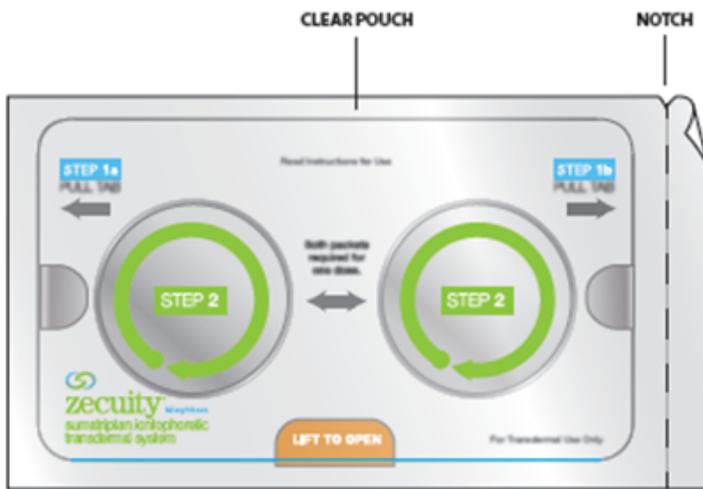
ZECUITY is a single-use Transdermal System (TDS) or patch.

- Remove ZECUITY by tearing from the notch at the corner of the clear

pouch. **See Figure B**

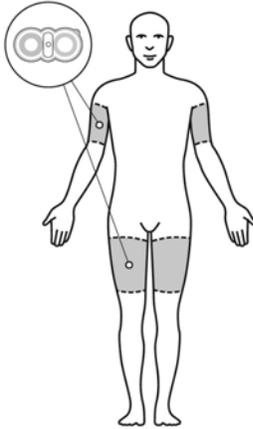
- ZECURITY TDS should not be cut.
- Do not use ZECURITY TDS if the clear pouch is torn or damaged.

**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.

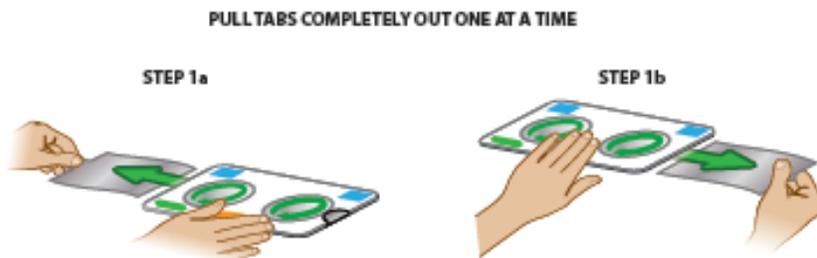
## Step 1 – Pull Tabs

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**

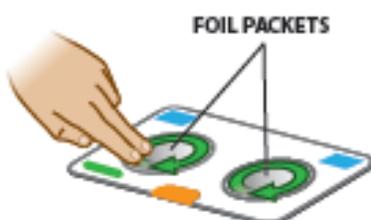


## Step 2 – Rub Foil Packets

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**

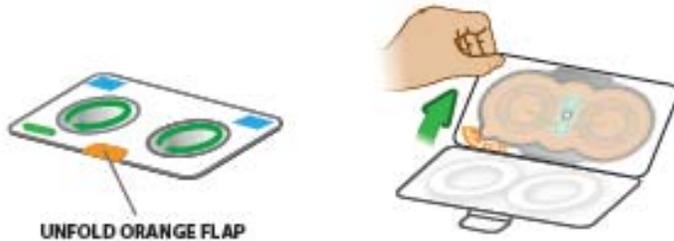
**Figure E**



### 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**

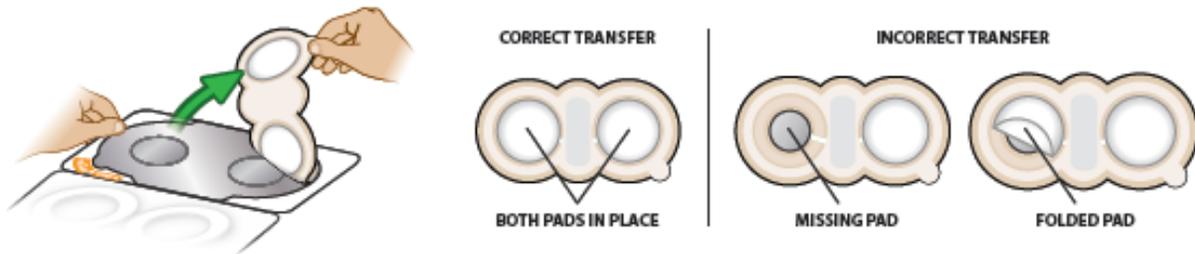
**Figure G**



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**



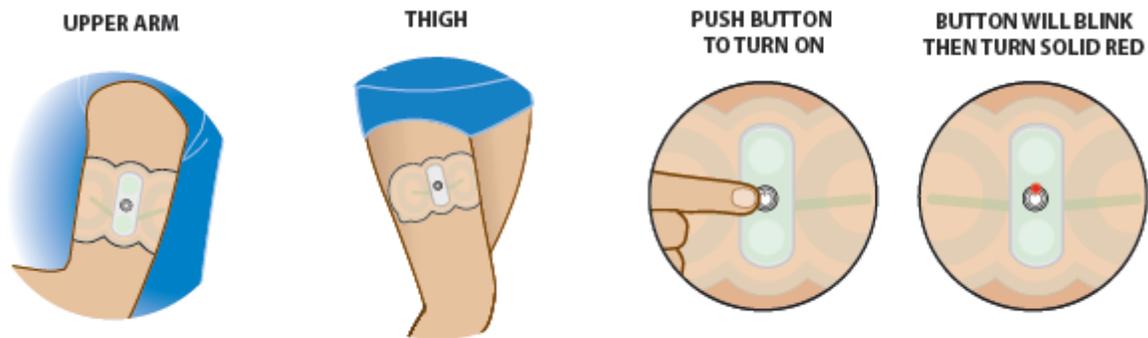
### **Step 5 – Apply and Activate**

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.

ZECUITY™ is a trademark of NuPathe Inc. The other brands listed are trademarks of their respective owners and are not trademarks of NuPathe. The makers of these brands are not affiliated with and do not endorse NuPathe or its products.

©2012 NuPathe Inc. All rights reserved.

NuPathe Inc.  
227 Washington Street  
Conshohocken, PA 19428

Approved: January 2013