

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022377Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ALSUMA (sumatriptan injection) 6mg/0.5ml for subcutaneous use

Initial U.S. Approval: 1992

INDICATIONS AND USAGE

ALSUMA is a 5-HT_{1B/1D} receptor agonist (triptan) indicated for:

- the acute treatment of migraine attacks, with or without aura (1.1)
- the acute treatment of cluster headache episodes (1.1).

Important limitations:

- Use only after a clear diagnosis of migraine or cluster headache has been established (1.2)
- Not intended for the prophylactic therapy of migraine (1.2)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2)
- Single 6 mg dose administered to an injection site with adequate skin and subcutaneous thickness (e.g. lateral thigh or upper arm) (2)
- The maximum recommended dose that may be given in 24 hours is two doses separated by at least 1 hour (2)
- Benefit of second dose in patients who have failed to respond to a first dose has not been established (2)

DOSAGE FORMS AND STRENGTHS

Injection: 0.5 mL of solution containing 6 mg sumatriptan (as the succinate salt) (3).

CONTRAINDICATIONS

- Do not administer intravenously as this may cause coronary vasospasm (4.1)
- Ischemic heart disease, coronary artery vasospasm, or other significant underlying cardiovascular disease (4.2)
- Cerebrovascular syndromes (e.g. history of stroke or TIA) (4.3)
- Peripheral Vascular Disease (including Ischemic Bowel Disease) (4.4)
- Uncontrolled hypertension (4.5)
- Do not use ALSUMA within 24 hours of any ergotamine-containing or ergot-type medication or another 5-HT₁ agonist, e.g. another triptan (4.6)
- Hemiplegic or basilar migraine (4.7)
- Known hypersensitivity to sumatriptan (4.8)

WARNINGS AND PRECAUTIONS

- Serious adverse cardiac events, including acute myocardial infarction, and life-threatening disturbances of cardiac rhythm (5.1)
- It is strongly recommended that ALSUMA not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors. In very rare cases, serious cardiovascular events have been reported in association with sumatriptan use in the absence of known cardiovascular disease. If ALSUMA is considered, patients should first have a cardiovascular evaluation. If the evaluation is satisfactory, first dose should take place in a physician's office setting (5.1)
- Sensations of pain, tightness, pressure and heaviness in the chest, throat, neck and jaw: generally not associated with myocardial ischemia, but pa-

tients with signs or symptoms suggestive of angina should be evaluated for the presence of CAD (5.2)

- Cerebrovascular events, some fatal (5.3)
- Gastrointestinal ischemic events and peripheral vasospastic reactions (e.g. Raynaud's syndrome) (5.4)
- Potentially life-threatening serotonin syndrome, particularly in combination with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). Monitor patients for neurologic changes and gastrointestinal symptoms if concomitant treatment is clinically warranted (5.5, 7.4)
- Increase in blood pressure, associated with significant clinical events (4.5, 5.6)
- Hypersensitivity, life-threatening or fatal (5.8)
- Seizures (5.9)

ADVERSE REACTIONS

In controlled studies with sumatriptan injection, the most common adverse reactions ($\geq 2\%$ and $>$ placebo) were tingling, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, feeling of tightness, numbness, feeling strange, tight feeling in head, flushing, tightness in chest, discomfort in nasal cavity/sinuses, jaw discomfort, dizziness/vertigo, drowsiness/sedation, and headache (6.1).

In an open-label study with ALSUMA, the most common adverse reactions ($\geq 5\%$) were injection site bruising, injection site pain, and injection site hemorrhage (6.6).

To report SUSPECTED ADVERSE REACTIONS, contact contact US WorldMeds at 1-877-770-8796 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- MAO-A inhibitors: sumatriptan plasma levels nearly doubled; concurrent use ordinarily not recommended (5.7, 7.1)
- Do not use ALSUMA and ergotamine-containing or ergot-type medications within 24 hours of each other (4.6, 7.2)
- Do not use ALSUMA and other 5HT₁ agonists (e.g. triptans) within 24 hours of each other (4.6, 7.3)
- SSRI/SNRI: life-threatening serotonin syndrome reported during combined use with triptans (5.5, 7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. ALSUMA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (5.10; 8.1)
- Nursing Mothers: Sumatriptan is excreted in human breast milk following subcutaneous administration. Use with caution while nursing (8.3)
- Pediatric Use: The safety and effectiveness in pediatric patients under 18 years of age have not been established (8.4)
- Geriatric Use: Not recommended (8.5)

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

Revised: 6/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Acute Treatment of Migraine Attacks and Cluster Headache
- 1.2 Important Limitations

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Intravenous Administration
- 4.2 Ischemic or Vasospastic Coronary Artery Disease
- 4.3 Cerebrovascular Syndromes
- 4.4 Peripheral Vascular Disease
- 4.5 Uncontrolled Hypertension
- 4.6 Ergotamine-Containing or Ergot-Type Medications or Other 5-HT₁ Agonists (e.g. Triptans)
- 4.7 Hemiplegic or Basilar Migraine
- 4.8 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events
- 5.2 Sensations of pain, tightness, pressure in the chest and/or throat, neck and jaw
- 5.3 Drug-Associated Cerebrovascular Events and Fatalities
- 5.4 Other Vasospasm-Related Events, including Peripheral Vascular Ischemia and Colonic Ischemia
- 5.5 Serotonin Syndrome
- 5.6 Increase in Blood Pressure
- 5.7 Concomitant MAO-A inhibitors
- 5.8 Hypersensitivity
- 5.9 Seizures
- 5.10 Pregnancy
- 5.11 Corneal Opacities

6 ADVERSE REACTIONS

- 6.1 Controlled Clinical Trials in Patients with Migraine Headache
- 6.2 Controlled Clinical Trials in Patients with Cluster Headache
- 6.3 Other Events Observed in Association with the Administration of Sumatriptan Injection
- 6.4 Other Events Observed in the Clinical Development of Sumatriptan
- 6.5 Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan)
- 6.6 Adverse Reactions Observed In Association With The Administration of ALSUMA

7 DRUG INTERACTIONS

- 7.1 Monoamine Oxidase Inhibitors
- 7.2 5-HT_{1B/1D} agonists (e.g. triptans)
- 7.3 Ergot-Containing Drugs
- 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 Migraine
- 14.2 Cluster Headache

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Risk of Myocardial Ischemia and/or Infarction, Other Adverse Cardiac Events, Other Vasospasm-related Events, and Cerebrovascular Events
- 17.2 Serotonin Syndrome
- 17.3 Pregnancy
- 17.4 Nursing Mothers
- 17.5 Patient Instructions for Use of ALSUMA

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Treatment Of Migraine Attacks And Cluster Headache

ALSUMA (sumatriptan injection) 6 mg/0.5 mL is indicated for the acute treatment of migraine attacks, with or without aura, and the acute treatment of cluster headache episodes.

1.2 Important Limitations

ALSUMA should only be used where a clear diagnosis of migraine or cluster headache has been established. Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or cluster headache or who experience a headache that is atypical for them.

For a given attack, if a patient does not respond to the first dose of ALSUMA, the diagnosis of migraine or cluster headache should be reconsidered before administration of a second dose.

ALSUMA is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. *[see Contraindications (4.7)]*

2 DOSAGE AND ADMINISTRATION

ALSUMA is only for subcutaneous use.

The maximum single recommended adult dose of ALSUMA is 6 mg injected subcutaneously. The maximum recommended dose that may be given in 24 hours is two doses of ALSUMA separated by at least 1 hour. Controlled clinical trials have failed to show that clear benefit is associated with the administration of a second 6 mg dose in patients who have failed to respond to a first dose.

Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery must be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle. ALSUMA is for single use only. Discard unused portions. *[see Patient Counseling Information (17.5)]*

3 DOSAGE FORMS AND STRENGTHS

ALSUMA contains 6 mg of sumatriptan (as 8.4 mg sumatriptan succinate), which is delivered as a subcutaneous injection in a single dose. ALSUMA is supplied as a single-use auto-injector pre-filled with sumatriptan succinate drug solution and fully-assembled for use.

4 CONTRAINDICATIONS

4.1 Intravenous Administration

ALSUMA is not designed to administer sumatriptan intravenously. Do not administer intravenously since sumatriptan may cause coronary vasospasm.

4.2 Ischemic or Vasospastic Coronary Artery Disease

Do not use ALSUMA in patients with ischemic heart disease (e.g. angina pectoris, history of myocardial infarction, or documented silent ischemia), or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina or other significant underlying cardiovascular disease. *[see Warnings and Precautions (5.1)]*

4.3 Cerebrovascular Syndromes

Do not use ALSUMA in patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks. *[see Warnings and Precautions (5.3)]*

4.4 Peripheral Vascular Disease

Do not use ALSUMA in patients with peripheral vascular disease including (but not limited to) ischemic bowel disease. *[see Warnings and Precautions (5.4)]*

4.5 Uncontrolled Hypertension

Because ALSUMA may increase blood pressure, do not use in patients with uncontrolled hypertension. *[see Warnings and Precautions (5.6)]*

4.6 Do Not Use Within 24 Hours of Treatment with Ergotamine-Containing or Ergot-Type Medications Or Other 5-HT₁ Agonists (e.g. Triptans)

Do not use ALSUMA and any ergotamine-containing or ergot-type medication (such as dihydroergotamine or methysergide) within 24 hours of each other; do not use ALSUMA and another 5-HT₁ agonist (e.g. triptan) within 24 hours of each other. *[See Drug Interactions (7.3)]*

4.7 Hemiplegic Or Basilar Migraine

Do not use ALSUMA in patients with hemiplegic or basilar migraine.

4.8 Hypersensitivity

ALSUMA is contraindicated in patients with known hypersensitivity to sumatriptan or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Myocardial Ischemia and Infarction and Other Adverse Cardiac Events

Cardiac Events and Fatalities with 5-HT₁ Agonists

Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

Sumatriptan can cause coronary vasospasm. Some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD with close proximity of the events to sumatriptan use.

Because ALSUMA may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following ALSUMA administration should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur.

Premarketing Experience With Sumatriptan

Among the more than 1,900 patients with migraine who participated in reported premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, without accompanying clinical symptoms or signs. Of these 8

patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Of 6,348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience with Sumatriptan

Serious cardiovascular events, some resulting in death, have been reported in association with the use of subcutaneous sumatriptan injection. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan and the onset of the clinical event, the less likely the association is to be causative. Interest has focused on events beginning within 1 hour of the administration of sumatriptan.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports of serious cardiac events within 1 hour of sumatriptan administration, the majority had risk factors predictive of CAD, and the presence of significant underlying CAD was established in most cases. *[See Contraindications (4.2)]*

Patients with Documented Coronary Artery Disease

Because of the potential of this class of compound (5-HT₁ agonists) to cause coronary vasospasm, ALSUMA should not be given to patients with documented ischemic or vasospastic coronary artery disease. *[see Contraindications (4.2)]*

Patients with Risk Factors for CAD

It is strongly recommended that ALSUMA not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, ALSUMA should not be administered. *[See Contraindications (4.2)]*

For patients with risk factors predictive of CAD who have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of ALSUMA take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical

symptoms, consideration should be given to obtaining, on the first occasion of use, an electrocardiogram (ECG) during the interval immediately following use of ALSUMA in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of ALSUMA and who have or acquire risk factors predictive of CAD, as described above, undergo cardiovascular evaluation periodically as they continue to use sumatriptan. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

5.2 Sensations of Pain, Tightness, Pressure in the Chest and/or Throat, Neck and Jaw

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw are relatively common after treatment with sumatriptan. Only rarely have these symptoms been associated with ischemic ECG changes.

However, because sumatriptan may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms occur. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT₁ agonists. *[See Contraindications (4.2) and Warnings and Precautions (5.1)]*

Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome, following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm. *[see Contraindications (4.4) and Warnings and Precautions (5.4)]*

5.3 Cerebrovascular Events and Fatalities

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with subcutaneous sumatriptan, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief 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, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack) *[see Contraindications (4.3)]*.

5.4 Other Vasospasm-Related Events, including Peripheral Vascular Ischemia and Colonic Ischemia

5-HT₁ agonists, including ALSUMA, may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported.

Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

Patients who experience other symptoms or signs suggestive of decreased arterial flow following the use of any 5-HT₁ agonist, such as ischemic bowel syndrome or Raynaud's syndrome, are candidates for further evaluation *[see Contraindications (4.4)]*.

5.5 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including ALSUMA, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. 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). *[See Drug Interactions (7.4)]*

5.6 Increase in Blood Pressure

ALSUMA is contraindicated in patients with uncontrolled hypertension. Sumatriptan should be administered with caution to patients with controlled hypertension, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. *[See Contraindications (4.5)]*

5.7 Concomitant MAO-A inhibitors

The coadministration of ALSUMA and an MAO-A inhibitor is not generally recommended. In patients taking MAO-A inhibitors, sumatriptan plasma levels are nearly doubled. If such therapy is clinically warranted, however, suitable dose adjustment (e.g. using a different sumatriptan product, as ALSUMA only exists as a 6mg sumatriptan auto-injector) and appropriate observation of the patient are advised. *[See Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

5.8 Hypersensitivity

Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. *[see Contraindications (4.8)]*

5.9 Seizures

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

5.10 Pregnancy

ALSUMA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. *[See Use in Specific Populations (8.1)]*

5.11 Corneal Opacities

Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes. *[See Nonclinical Toxicology (13.2)]*

6 ADVERSE REACTIONS

This section provides a summary of adverse reactions reported in subjects in clinical studies conducted with

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

Serious cardiac reactions, including myocardial infarction, have occurred following the use of sumatriptan. These reactions are extremely rare and most have been reported in patients with risk factors predictive of CAD. Reactions reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. *[see Contraindications (4.2) and Warnings and Precautions (5.1)]*

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension. *[see Warnings and Precautions (5.6)]*

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

Sensations of Chest Pain and Tightness *[see Warnings and Precautions (5.2)]*

Cerebrovascular Events and Fatalities *[see Warnings and Precautions (5.3)]*

Other Vasospasm related Events including Peripheral Vascular Ischemia and Colonic Ischemia *[see Warnings and Precautions (5.4)]*

Serotonin Syndrome *[see Warnings and Precautions (5.5)]*

Among patients in clinical trials of subcutaneous sumatriptan succinate injection (n=6,218), up to 3.5% of patients withdrew for reasons related to adverse reactions.

6.1 Controlled Clinical Trials in Patients with Migraine Headache

Table 1 lists adverse reactions that occurred in 2 large placebo-controlled clinical trials in migraine patients following either a single 6 mg sumatriptan injection or placebo. Only adverse reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg and occurred at a frequency greater than in the placebo group are included in Table 1.

Table 1. Treatment-Emergent Adverse Reactions Incidence in 2 Large, Placebo-Controlled Clinical Trials in Patients with Migraine: Events Reported by at Least 2% of Patients Treated with Sumatriptan Injection 6 mg*

	Percent of Patients Reporting	
	Sumatriptan 6 mg SC (n = 547)	Placebo (n = 370)
Adverse Reactions		
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling strange	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction	59	24
Miscellaneous		
Jaw Discomfort	2	0
Musculoskeletal		
Weakness	5	<1
Neck pain/stiffness	5	<1
Myalgia	2	<1
Neurological		
Dizziness/vertigo	12	4
Drowsiness/sedation	3	2
Headache	2	<1

* The sum of the percentages cited is greater than 100% because patients could have experienced more than 1 type of adverse event. Only events that occurred at a frequency of 2% or more in groups treated with sumatriptan injection and that occurred at a frequency greater than that in the placebo group are included.

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

6.2 Controlled Clinical Trials in Patients with Cluster Headache

In the controlled clinical trials assessing sumatriptan injection as a treatment for cluster headache, no new significant adverse reactions associated with the use of sumatriptan were detected that had not already been identified in association with the drug's use in migraine.

Overall, the frequency of adverse events reported in studies of cluster headache was generally lower. Exceptions include reports of paresthesia (5% sumatriptan, 0% placebo), nausea and vomiting (4% sumatriptan, 0% placebo), and bronchospasm (1% sumatriptan, 0% placebo).

6.3 Other Adverse Reactions Observed in Association with the Administration of Sumatriptan Injection

The frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan injection in their causation cannot be reliably determined. Furthermore, variability associated with adverse reactions reporting, the terminology used to describe adverse reactions limits the value of the quantitative frequency estimates provided.

Adverse reactions frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N = 6,218) exposed to subcutaneous sumatriptan. All reported adverse reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients, infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients, and rare adverse reactions are those occurring in fewer than 1/1,000 patients.

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient ECG changes (nonspecific ST or T-wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and syncope. Rare were pallor, arrhythmia, abnormal pulse, vasodilation, and Raynaud syndrome.

Endocrine and Metabolic: Infrequent was thirst. Rare were polydipsia and dehydration.

Eye: Frequent were vision alterations. Infrequent was irritation of the eye.

Gastrointestinal: Frequent were abdominal discomfort and dysphagia. Infrequent were gastroesophageal reflux and diarrhea. Rare were peptic ulcer, retching, flatulence/eructation, and gallstones.

Musculoskeletal: Frequent were muscle cramps. Infrequent were various joint disturbances (pain, stiffness, swelling, ache). Rare were muscle stiffness, need to flex calf muscles, backache, muscle tiredness, and swelling of the extremities.

Neurological: Frequent was anxiety. Infrequent were mental confusion, euphoria, agitation, relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling sensations, paresthesia, stinging

sensations, facial pain, photophobia, and lacrimation. Rare were transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia, monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell, hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria, yawning, reduced appetite, hunger, and dystonia.

Respiratory: Infrequent was dyspnea. Rare were influenza, diseases of the lower respiratory tract, and hiccoughs.

Skin: Infrequent were erythema, pruritus, and skin rashes and eruptions. Rare was skin tenderness.

Urogenital: Rare were dysuria, frequency, dysmenorrhea, and renal calculus.

Miscellaneous: Infrequent were miscellaneous laboratory abnormalities, including minor disturbances in liver function tests, “serotonin agonist effect,” and hypersensitivity to various agents. Rare was fever.

6.4 Other Adverse Reactions Observed in the Clinical Development of Sumatriptan

The following adverse reactions occurred in clinical trials with sumatriptan tablets and sumatriptan nasal spray. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Breasts: Breast swelling, cysts, disorder of breasts, lumps, masses of breasts, nipple discharge, primary malignant breast neoplasm, and tenderness.

Cardiovascular: Abdominal aortic aneurysm, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis, and transient myocardial ischemia.

Ear, Nose, and Throat: Allergic rhinitis; disorder of nasal cavity/sinuses; ear, nose, and throat hemorrhage; ear infection; external otitis; feeling of fullness in the ear(s); hearing disturbances; hearing loss; Meniere disease; nasal inflammation; otalgia; sensitivity to noise; sinusitis; tinnitus; and upper respiratory inflammation.

Endocrine and Metabolic: Elevated thyrotropin stimulating hormone (TSH) levels; endocrine cysts, lumps, and masses; fluid disturbances; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; weight gain; and weight loss.

Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye hemorrhage, eye itching, eye pain, keratitis, mydriasis, and visual disturbances.

Gastrointestinal: Abdominal distention, colitis, constipation, dental pain, dyspeptic symptoms, feelings of gastrointestinal pressure, gastric symptoms, gastritis, gastroenteritis, gastrointestinal bleeding, gastrointestinal pain, hematemesis, hypersalivation, hyposalivation, intestinal obstruction, melena, nausea and/or vomiting, oral itching and irritation, pancreatitis, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Anemia.

Mouth and Teeth: Disorder of mouth and tongue (e.g., burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, arthritis, intervertebral disc disorder, muscle atrophy, muscle tightness and rigidity, musculoskeletal inflammation, and tetany.

Neurological: Apathy, aggressiveness, bad/unusual taste, bradylogia, cluster headache, convulsions, depressive disorders, detachment, disturbance of emotions, drug abuse, facial paralysis, hallucinations, heat sensitivity, incoordination, increased alertness, memory disturbance, migraine, motor dysfunction, neoplasm of pituitary, neuralgia, neurotic disorders, paralysis, personality change, phobia, phonophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, rigidity, stress, syncope, suicide, and twitching.

Respiratory: Asthma, breathing disorders, bronchitis, cough, and lower respiratory tract infection.

Skin: Dry/scaly skin, eczema, herpes, seborrheic dermatitis, skin nodules, tightness of skin, and wrinkling of skin.

Urogenital: Abnormal menstrual cycle, abortion, bladder inflammation, endometriosis, hematuria, increased urination, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, urethritis, and urinary infections.

Miscellaneous: Contusions, difficulty in walking, edema, hematoma, hypersensitivity, fever, fluid retention, lymphadenopathy, overdose, speech disturbance, swelling of extremities, swelling of face, and voice disturbances.

Pain and Other Pressure Sensations: Chest pain and/or heaviness, neck/throat/jaw pain/tightness/pressure, and pain (location specified).

6.5 Postmarketing Experience Reports for Subcutaneous or Oral Sumatriptan

The following adverse reactions have been identified during postapproval use of Sumatriptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. However, systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia [see *Warnings and Precautions* (5.5)], Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.

Gastrointestinal: Ischemic colitis with rectal bleeding [see *Warnings and Precautions* (5.5)], xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, serotonin syndrome,

subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death [see *Warnings and Precautions (5.3)*], temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see *Warnings and Precautions (5.8)*]), photosensitivity. Following subcutaneous administration of sumatriptan, pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding, and, on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) has been reported.

Urogenital: Acute renal failure.

6.6 Adverse Reactions Observed In Association With The Administration of ALSUMA

The safety of ALSUMA was evaluated in an open-label clinical trial evaluating the usability of ALSUMA during a migraine attack. Adverse reactions that occurred at a frequency of 5% or higher were injection site bruising (16%), injection site pain (6%), and injection site hemorrhage (6%).

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan in patients receiving MAO-A inhibitors is not ordinarily recommended. If the clinical situation warrants the combined use of sumatriptan and an MAOI, the dose of sumatriptan employed should be reduced. [see *Warnings and Precautions (5.7)* and *Clinical Pharmacology (12.3)*]

7.2 5-HT_{1B/1D} agonists (e.g. triptans)

Concomitant use of other 5-HT_{1B/1D} agonists within 24 hours of sumatriptan treatment is not recommended. [see *Contraindications (4.6)*]

7.3 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Since these effects may be additive, use of ergotamine containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided. [See *Contraindications (4.6)*]

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

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with sumatriptan injection is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. [see *Warnings and Precautions (5.5)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Sumatriptan produced evidence of developmental toxicity (embryo lethality and increased incidences of fetal abnormalities) in rabbits. Embryo lethality was observed at a dose less than the maximum recommended human dose (MRHD) of 12 mg/day on a body surface area (mg/m^2) basis. There are no adequate and well-controlled studies of ALSUMA in pregnant women. ALSUMA 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, embryo lethality was observed at doses at or close to those producing maternal toxicity. These doses were less than the MRHD of 12 mg/day on a mg/m^2 basis. 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 at doses that are approximately 10 times the MRHD on a mg/m^2 basis, did not produce evidence of embryo lethality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryo lethality or teratogenicity.

8.3 Nursing Mothers

Sumatriptan is excreted in human breast milk following subcutaneous administration. Therefore, caution should be exercised when considering the administration of ALSUMA to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of sumatriptan injection in pediatric patients under 18 years of age have not been established; therefore, sumatriptan injection is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray 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.

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.

Postmarketing 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.

8.5 Geriatric Use

The use of ALSUMA in elderly patients is not recommended because they are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly. [See Warnings and Precautions (5.1, 5.6)]

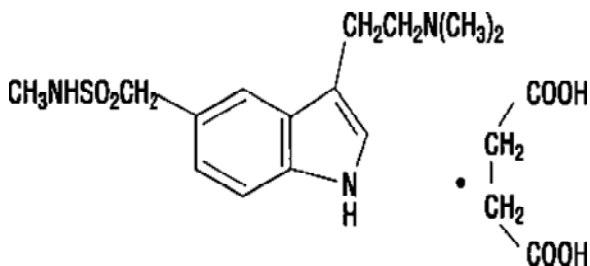
10 OVERDOSAGE

Patients (N = 269) have received single injections of 8 to 12 mg sumatriptan without significant adverse effects. Volunteers (N = 47) have received single subcutaneous doses of up to 16 mg without serious adverse events.

No gross overdoses in clinical practice have been reported. The half-life of elimination of sumatriptan is about 2 hours [see Clinical Pharmacology (12.3)], and therefore monitoring of patients after overdose with subcutaneous sumatriptan should continue while symptoms or signs persist, and for at least 10 hours. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

Sumatriptan is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT₁) agonist. Sumatriptan delivered as the succinate salt is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The empirical formula is C₁₄H₂₁N₃O₂S • C₄H₆O₄, representing a molecular weight of 413.5.

ALSUMA is a clear, colorless to pale yellow, sterile, non-pyrogenic solution for subcutaneous injection. Each 0.5 mL of ALSUMA 12 mg/mL solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in Water for Injection, USP. The pH range of the solution is approximately 4.2 to 5.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sumatriptan is the active component of ALSUMA. Sumatriptan is a selective agonist for the 5-HT_{1B} and 5-HT_{1D} receptors. Sumatriptan presumably exerts its antimigrainous effect through binding to vascular 5-HT₁-type receptors, which have been shown to be present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of the isolated dura mater of humans. In these tissues, sumatriptan activates this receptor to cause vasoconstriction, an action in humans correlating with the relief of migraine and cluster headache.

12.2 Pharmacodynamics

Blood Pressure: ALSUMA is contraindicated in patients with uncontrolled hypertension. [see Contraindications (4.5)] It should be administered with caution to patients with controlled hypertension. [See Warnings and Precautions (5.6)]

Peripheral (Small) Arteries: In healthy volunteers (N = 18), a study 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 patients in clinical studies carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

Respiratory Rate: Experience gained during the clinical development of sumatriptan as a treatment for migraine failed to detect an effect of the drug on respiratory rate.

12.3 Pharmacokinetics

Absorption and Elimination

Pharmacokinetic parameters following a 6 mg subcutaneous injection into the deltoid area of the arm in 9 males (mean age, 33 years; mean weight, 77 kg) were systemic clearance: $1,194 \pm 149$ mL/min (mean $\pm$ S.D.), distribution half-life: 15 ± 2 minutes, terminal half-life: 115 ± 19 minutes, and volume of distribution central compartment: 50 ± 8 liters. Of this dose, $22\% \pm 4\%$ was excreted in the urine as unchanged sumatriptan and $38\% \pm 7\%$ as the indole acetic acid metabolite.

After a single 6 mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (age, 24 ± 6 years; weight, 70 kg), the maximum serum concentration (C_{max}) was (mean $\pm$ standard deviation) 74 ± 15 ng/mL and the time to peak concentration (T_{max}) was 12 minutes after injection (range, 5 to 20 minutes). In this study, the same dose injected subcutaneously in the thigh gave a C_{max} of 61 ± 15 ng/mL by manual injection versus 52 ± 15 ng/mL by auto-injector techniques. The T_{max} or amount absorbed was not significantly altered by either the site or technique of injection.

The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was $97\% \pm 16\%$ of that obtained following intravenous injection. Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated.

Drug Interactions

Monoamine Oxidase Inhibitors

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of sumatriptan, resulting in a two-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life.

Migraine Prophylactic Medications

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy of sumatriptan. In 2 clinical trials in the United States, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil, n = 63; amitriptyline, n = 57; propranolol, n = 94; for 45 other drugs, n = 123) were compared to those who had not used prophylaxis (n = 452). There were no differences in relief rates at 60 minutes postdose for sumatriptan injection, whether or not prophylactic medications were used.

Special Populations

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls.

Age: The pharmacokinetics of sumatriptan in the elderly (mean age, 72 years, 2 males and 4 females) and in patients with migraine (mean age, 38 years, 25 males and 155 females) were similar to those in healthy male subjects (mean age, 30 years).

Race: The systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 weeks). There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Sumatriptan was not mutagenic when tested in the Ames test or the *in vitro* mammalian Chinese hamster V79/HGPRT assay. Sumatriptan was not clastogenic when tested in the *in vitro* human lymphocyte assay or the *in vivo* rat micronucleus assay.

Subcutaneous administration of sumatriptan to male and female rats prior to and throughout the mating period at doses approximately 50 times the maximum recommended human dose (MRHD) of 12 mg/day on a body surface area (mg/m²) basis produced no evidence of adverse effects on 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.

14 CLINICAL STUDIES

14.1 Migraine

In US controlled clinical trials enrolling more than 1,000 patients during migraine attacks who were

experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 3, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Smaller doses of sumatriptan may also prove effective, although the proportion of patients obtaining adequate relief is decreased and the latency to that relief is greater.

In one well-controlled study in which placebo (n = 62) was compared to 6 different doses of sumatriptan injection (n = 30 each group) in a single-attack, parallel-group design, the dose response relationship was found to be as shown in Table 2.

Table 2. Dose-Response Relationship for Efficacy

Sumatriptan Succinate Dose (mg)	% of Patients with Relief* at:				% of Adverse Reaction Incidence
	10 Minutes	30 Minutes	1 Hour	2 Hours	
Placebo	5	15	24	21	55
1	10	40	43	40	63
2	7	23	57	43	63
3	17	47	57	60	77
4	13	37	50	57	80
6	10	63	73	70	83
8	23	57	80	83	93

* Relief is defined as the reduction of moderate or severe pain to no pain or mild pain after dosing without use of rescue medication.

In two US well-controlled clinical trials in 1,104 migraine patients with moderate or severe migraine pain, the onset of relief was rapid (less than 10 minutes) with a 6 mg subcutaneous dose of sumatriptan injection. Headache relief, as evidenced by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the patients within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Headache relief was achieved in approximately 82% of patients within 2 hours, and 65% of all patients were pain-free within 2 hours. Table 3 shows the 1- and 2-hour efficacy results for subcutaneous sumatriptan 6 mg.

Table 3. Efficacy Data from US Clinical Efficacy Trials with Sumatriptan Injection in Patients with Migraine

1-Hour Data	Study 1		Study 2	
	Placebo (n=190)	Suma- triptan Succi- nate 6 mg (n=384)	Placebo (n=180)	Suma- triptan Succinate 6 mg (n=350)
Patients with pain relief (grade 0/1)	18%	70%*	26%	70%*
Patients with no pain	5%	48%*	13%	49%*
Patients without nausea	48%	73%*	50%	73%*
Patients without photophobia	23%	56%*	25%	58%*
Patients with little or no clinical disability ^a	34%	76%*	34%	76%*
2-Hour Data^b				
Patients with pain relief (grade 0/1)	31%	81%*	39%	82%*
Patients with no pain	11%	63%*	19%	65%*
Patients without nausea	56%	82%*	63%	81%*
Patients without photophobia	31%	72%*	35%	71%*
Patients with little or no clinical disability ^a	42%	85%*	49%	84%*

* p<0.05 versus placebo.

^a A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.

^b Includes patients who may have received an additional injection of the assigned treatment (placebo or sumatriptan 6 mg) 1 hour after the initial injection.

Subcutaneous sumatriptan also relieved photophobia, phonophobia (sound sensitivity), nausea, and vomiting associated with migraine attacks.

The efficacy of subcutaneous sumatriptan injection is unaffected by whether or not migraine is associated with aura, duration of attack, gender or age of the patient, or concomitant use of common migraine prophylactic drugs (e.g., beta blockers).

14.2 Cluster Headache

The efficacy of sumatriptan injection in the acute treatment of cluster headache was demonstrated in 2 randomized, double-blind, placebo-controlled, 2-period crossover trials. Patients age 21 to 65 were enrolled and were instructed to treat a moderate to very severe headache within 10 minutes of onset. Headache relief was defined as a reduction in headache severity to mild or no pain. In both trials, the proportion of individuals gaining relief at 10 or 15 minutes was significantly greater among patients receiving 6 mg of sumatriptan injection compared to those who received placebo (see Table 4). One study evaluated a 12 mg dose; there was no statistically significant difference in outcome between patients randomized to the 6 and 12 mg doses.

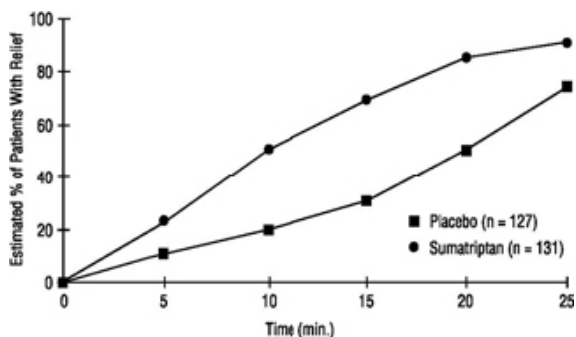
Table 4. Efficacy Data from the Cluster Headache Efficacy Trials with Sumatriptan Injection

Patients with Pain Relief (no/mild)	Study 1		Study 2	
	Placebo (n=39)	Sumatriptan Succinate 6 mg (n=39)	Placebo (n=88)	Sumatriptan Succinate 6 mg (n=92)
5 minutes post-injection	8%	21%	7%	23%*
10 minutes post-injection	10%	49%*	25%	49%*
15 minutes post-injection	26%	74%*	35%	75%*

* p<0.05 (n = Number of headaches treated)

The Kaplan-Meier (product limit) Survivorship Plot (Figure 1) provides an estimate of the cumulative probability of a patient with a cluster headache obtaining relief after being treated with either sumatriptan or placebo.

Figure 1. Time to Relief from Time of Injection*



*Patients taking rescue medication were censored at 15 minutes.

The plot was constructed with data from patients who either experienced relief or did not require (request) rescue medication within a period of 2 hours following treatment. As a consequence, the data in the plot are derived from only a subset of the 258 headaches treated (rescue medication was required in 52 of the 127 placebo-treated headaches and 18 of the 131 sumatriptan-treated headaches).

Other data suggest that sumatriptan treatment is not associated with an increase in early recurrence of headache, and that treatment with sumatriptan has little effect on the incidence of later-occurring headaches (i.e., those occurring after 2, but before 18 or 24 hours).

16 HOW SUPPLIED/STORAGE AND HANDLING

ALSUMA contains sumatriptan (base) as the succinate salt and is supplied as a clear, colorless to pale yellow, sterile, nonpyrogenic solution in a single-dose pre-filled autoinjector.

Injection Strength	Package Contents	NDC#
6 mg	Two 6 mg single dose ALSUMA (sumatriptan injection) 6 mg/0.5 mL Auto- Injectors	xxxxxx-xxx-xx
	ALSUMA Physician Insert	
	Patient Instructions for Use	

Store at 25°C, excursions permitted 15° to 30°C (59° to 86° F). Protect from light. Do not refrigerate.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling]

17.1 Risk of Myocardial Ischemia and/or Infarction, Other Adverse Cardiac Events, Other Vasospasm-related Events, and Cerebrovascular Events

Inform patients that ALSUMA 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, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Apprise patients of the importance of this follow-up. [see Warnings and Precautions (5.1, 5.2, 5.3,

5.4)]

17.2 Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of ALSUMA or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). *[See Warnings and Precautions (5.5)]*

17.3 Pregnancy

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

17.4 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)]*

17.5 Patient Instructions for Use of ALSUMA

ALSUMA is a pre-filled, fully-assembled, single-use device intended to deliver a 6 mg dose of sumatriptan.

Instruct patients on the proper use of the product prior their first use in a medically unsupervised situation. Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery must be avoided. Direct patients to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle (e.g. lateral thigh or upper arms)

Manufactured by:

Meridian Medical Technologies™, Inc., Columbia, MD 21046

A wholly-owned subsidiary of King Pharmaceuticals®, Inc.

Distributed by:

US WorldMeds, LLC, Louisville, KY 40207

FOOD AND DRUG ADMINISTRATION

Patient Information ALSUMA™ (Awl-SOO'-mah) (sumatriptan injection) Auto-Injector

Read the patient information that comes with ALSUMA before you start taking it 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 treatment. You and your healthcare provider should talk about ALSUMA when you start taking it and at regular checkups.

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

ALSUMA, which contains sumatriptan, may increase your chance of getting a heart attack or stroke that can lead to death. This chance is higher in people who have heart disease.

ALSUMA is not for people with risk factors for heart disease unless a heart exam is done and shows no problem.

The risk factors for heart disease include:

- high blood pressure
- high cholesterol levels
- smoking
- obesity
- diabetes
- family history of heart disease
- female who has gone through menopause
- male over age 40

“Serotonin syndrome” is a serious and life-threatening problem that can be caused by ALSUMA, especially if used with anti-depressant medicines called: selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs).

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

Call your healthcare provider if you have symptoms of serotonin syndrome, which include:

- mental changes (seeing things that are not there, unusual tension and restlessness)
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles

- trouble walking
- nausea, vomiting, diarrhea

What is ALSUMA?

The ALSUMA auto-injector is a prescription medicine injection used to treat people who have been diagnosed with migraine or cluster headaches.

ALSUMA is not used to prevent or lessen the number of migraine or cluster headaches you have.

ALSUMA is not used to treat other types of headaches.

It is not known if ALSUMA is safe or effective in people under 18 years of age.

Who should not take ALSUMA?

Do not take ALSUMA if you have:

- narrowing of blood vessels to the legs, arms, stomach or kidneys (peripheral vascular disease)
- heart disease or a history of heart disease
- uncontrolled high blood pressure
- migraines that cause temporary paralysis (unable to move) on one side of your body or basilar migraine. If you are not sure about this, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs) or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
 - o almotriptan (AXERT)
 - o eletriptan (RELPAX)
 - o frovatriptan (FROVA)
 - o naratriptan (AMERGE)
 - o rizatriptan (MAXALT)
 - o sumatriptan (IMITREX)
 - o sumatriptan and naproxen (TREXIMET)
 - o ergotamines like ERGOMAR, CAFERGOT OR MIGERGOT
 - o dihydroergotamine (D.H.E. 45, MIGRANAL)
- are allergic to sumatriptan or any of the other ingredients in ALSUMA. See the end of this leaflet for a complete list of ingredients in ALSUMA.

What should I tell my healthcare provider before taking ALSUMA?

Before taking ALSUMA, tell your healthcare provider about all your medical conditions, including if you:

- have high cholesterol
- have diabetes
- smoke
- have gone through menopause
- have heart disease or a family history of heart disease or stroke
- are pregnant or plan to become pregnant. It is not known if ALSUMA will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast feeding or plan to breast feed. ALSUMA passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take ALSUMA.
- have had epilepsy or seizures

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

Using ALSUMA 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)
- Monoamine Oxidase Inhibitors (MAO-A)

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

How should I take ALSUMA?

- Take ALSUMA exactly as your healthcare provider tells you.
- Give the injection in the side of your thigh, or the upper arm just below the skin (subcutaneous). Check with your doctor if you are not sure where to inject yourself.
- See the detailed Patient Instructions for Use on the other side of this leaflet.
- Do not give ALSUMA into a vein.
- Take ALSUMA as soon as your symptoms of a migraine or cluster headache start, but it may be given at any time during an attack.
- You may take a second injection at least one hour after your first dose if your migraine or cluster headache symptoms come back.

- Do not take more than two doses of ALSUMA in 24 hours.
- If you do not feel better after the first injection, do not give a second injection for the same attack without talking with your healthcare provider.

What are the possible side effects of ALSUMA?

ALSUMA can cause serious side effects or even death. See “What is the most important information I should know about ALSUMA?”

Serious side effects include:

- heart attacks
- fast heartbeat
- increase in blood pressure
- stroke
- changes in mental status (agitation, hallucinations, coma)
- changes in color or sensation to your fingers and toes (Raynaud’s syndrome)
- poor blood flow to your arms or legs
- poor blood flow to your gastrointestinal tract

Get medical help right away, if you have:

- severe tightness, pain, pressure or heaviness in your chest, throat, neck, or jaw
- shortness of breath or wheezing
- sudden or severe stomach pain
- hives (raised bumps), swelling of your tongue, mouth, or throat
- problems seeing
- unusual weakness or numbness
- nausea or vomiting
- bloody diarrhea
- high temperature
- unusual sweating

The most common side effects of ALSUMA include:

- Bleeding, swelling, redness, bruising and pain at the injection site
- Tingling or numbness in your fingers or toes
- Dizziness
- Warm, hot, burning feeling to your face (flushing)
- Feeling of heaviness or pressure
- Discomfort or tightness in the chest, neck, throat, nose, or jaw
- Feeling weak, drowsy, or tired
- Feeling strange
- Muscle pain

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

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

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

How should I store ALSUMA?

Store ALSUMA between 59°F to 86°F (15°C-30°C).

- Keep ALSUMA out of the light.
- Do not put ALSUMA in the refrigerator.
- Keep each ALSUMA auto-injector in its storage and disposal case.
- Remove the ALSUMA auto-injector from the storage and disposal case only when you need to give yourself an injection

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

General information about the safe and effective use of ALSUMA.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ALSUMA for a condition for which it was not prescribed. Do not give ALSUMA 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 ALSUMA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ALSUMA that is written for health professionals.

For more information, go to www.ALSUMAAI.com or call 1-877-770-8796.

What are the Ingredients in ALSUMA?

Active ingredient: sumatriptan

Inactive ingredient: sodium chloride

PATIENT INSTRUCTIONS FOR USE

ALSUMA™ (Awl-SOO'-mah) (sumatriptan injection) Auto-Injector

Read the Patient Instructions for Use that come with the ALSUMA Auto-Injector before you start using it 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.

Before you use ALSUMA for the first time, make sure your healthcare provider teaches you the right way to use it.

Follow these instructions each time you use ALSUMA.

ALSUMA is a disposable one time use, prefilled auto-injector used for the treatment of acute migraine or cluster headaches.

Each ALSUMA Auto-Injector is filled with medicine and ready to use. No assembly is required.

ALSUMA is packaged with two doses to a box, with each ALSUMA dose stored in a separate storage and disposal case (see Figure 1).



[Figure 1]

ALSUMA Important Tips

- Do not remove the Blue Safety Release until you are ready to inject yourself.
- Do not place your fingers on the top or the bottom end of the ALSUMA Auto-Injector.
- Do not touch the orange needle end.
- Always point the orange needle end down.
- Do not take apart the ALSUMA Auto-Injector.
- **Keep out of the reach of children.**

The Storage and Disposal Case (see Figure 2)

- Always store and carry ALSUMA in the storage and disposal case.
- Do not remove ALSUMA from the storage and disposal case until you are ready to use it.
- **Always keep the orange needle end facing the bottom of the storage and disposal case**
- The purple cap should be screwed tightly onto the storage and disposal case before use.
- After your injection, the ALSUMA Auto-Injector should be placed back into the storage and disposal case. Throw away the case the way your healthcare provider told you.



[Figure 2]

The ALSUMA Auto-Injector

- When the Blue Safety Release is in place, ALSUMA is locked and will not inject. (see Figure 3)
- When the Blue Safety Release is taken off, ALSUMA is unlocked and ready to use. (see Figure 4)



[Figure 3]



[Figure 4]

Holding the ALSUMA Auto-Injector

- Always hold the ALSUMA Auto-Injector in the middle with the orange **needle end** pointing down. (see Figure 5)
 - **Never** hold the injector upside down. (see Figure 6)
 - **Never** put your thumb on either end of the injector. (see Figure 7 and 8)
 - **Never** touch the orange **needle end**. (see Figure 8)



[Figure 5]



[Figure 6]



[Figure 7]



[Figure 8]

How to Use ALSUMA

1. Choose an injection site.

- Ask your doctor about where you should inject yourself (usually the side of your thigh or your upper arm) See Figures 9 and 10 below.



[Figure 9]



[Figure 10]

- Do not inject through your clothes.

2. Preparing Your ALSUMA Auto-Injector

An Inside Look

ALSUMA (SUMATRIPTAN INJECTION) 6 mg/0.5mL AUTO-INJECTOR BEFORE ACTIVATION

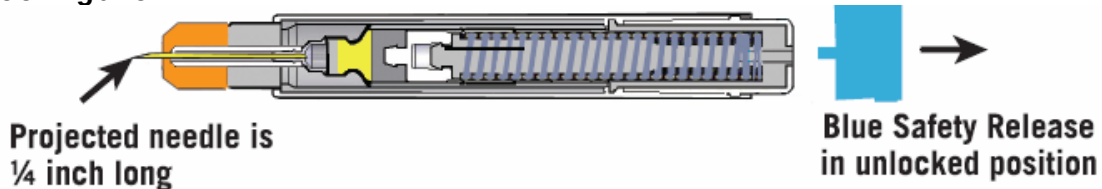
See Figure 11



[Figure 11]

ALSUMA (SUMATRIPTAN INJECTION) 6 mg/0.5mL AUTO-INJECTOR WHEN ACTIVATED

See Figure 12



[Figure 12]

- Twist off the purple cap from the storage and disposal case. See Figure 13



[Figure 13]

- Slide the ALSUMA Auto-Injector out into your hand. See Figure 14



[Figure 14]

- Hold the ALSUMA Auto-Injector in the middle. See Figure 15



[Figure 15]

- Pull off the Blue Safety Release to unlock the ALSUMA Auto-Injector. See Figure 16



[Figure 16]

3. Giving Your Injection

Give yourself the injection exactly the way your healthcare provider showed you.

- Place the orange needle end on your skin where you will give the injection. See Figures 17 and 18
- Push the ALSUMA Auto-Injector hard into your skin until you feel a jolt. See Figures 17 and 18
- Hold the ALSUMA Auto-Injector in place for 5 seconds to deliver the medicine. See Figures 17 and 18



[Figure 17]



[Figure 18]

4. After your injection, throw away (dispose of) the ALSUMA Auto-Injector.

- Place the uncapped, empty storage and disposal case onto a flat surface. See Figure 19
- Slowly insert the orange needle end of the used injector into the open end of the storage and disposal case. Slide the entire used injector into the case. See Figure 19



[Figure 19]

- Tilt up the open end of the storage and disposal case and screw on the purple cap. See Figure 20



[Figure 20]

Check with your healthcare provider about the right way to throw away your used ALSUMA Auto-Injector.

Each ALSUMA Auto-Injector can be used only **one** time.

Important Tips on Storing and Using Your Auto-Injector

- Store the ALSUMA Auto-Injector between 59°F to 86°F (15°C-30°C).
- Keep the ALSUMA Auto-Injector out of the light.
- Do not put the ALSUMA Auto-Injector in the refrigerator.
- Keep each ALSUMA auto-injector in its storage and disposal case.
- Remove the ALSUMA auto-injector from the storage and disposal case only when you need to give yourself an injection.

Distributed by:
US WorldMeds
Louisville, KY 40207

Manufactured by:
Meridian Medical Technologies™, Inc.,
Columbia, MD 21046
A wholly-owned subsidiary of King Pharmaceuticals®, Inc.

0001587 6/2010 Printed in U.S.A.

APPENDICES

Appendix A: Container Labeling



ALSUMA™
(sumatriptan injection, 6mg/0.5mL)
Auto-Injector

STEP 1

GRASP
then
PULL OFF
Blue Safety Release
to unlock.



NEEDLE END

STEP 2

PLACE orange
NEEDLE END
against the
injection site.
PUSH HARD
until it jolts.



STEP 3

Now **HOLD IN PLACE**
for **5 seconds**.

NEEDLE END **NEEDLE END** **NEEDLE END**

See other side for instructions

Rx only

For subcutaneous injection only.

Each 0.5 mL injection contains 6 mg sumatriptan (as the succinate salt) and 3.5 mg of sodium chloride



ALSUMA™
(sumatriptan injection, 6mg/0.5mL)
Auto-Injector

STORE AT 25°C (77°F); EXCURSIONS PERMITTED TO 15-30°C (59-86°F)
DO NOT REFRIGERATE
PROTECT FROM LIGHT

Distributed by:
US WorldMeds
Louisville, KY 40207

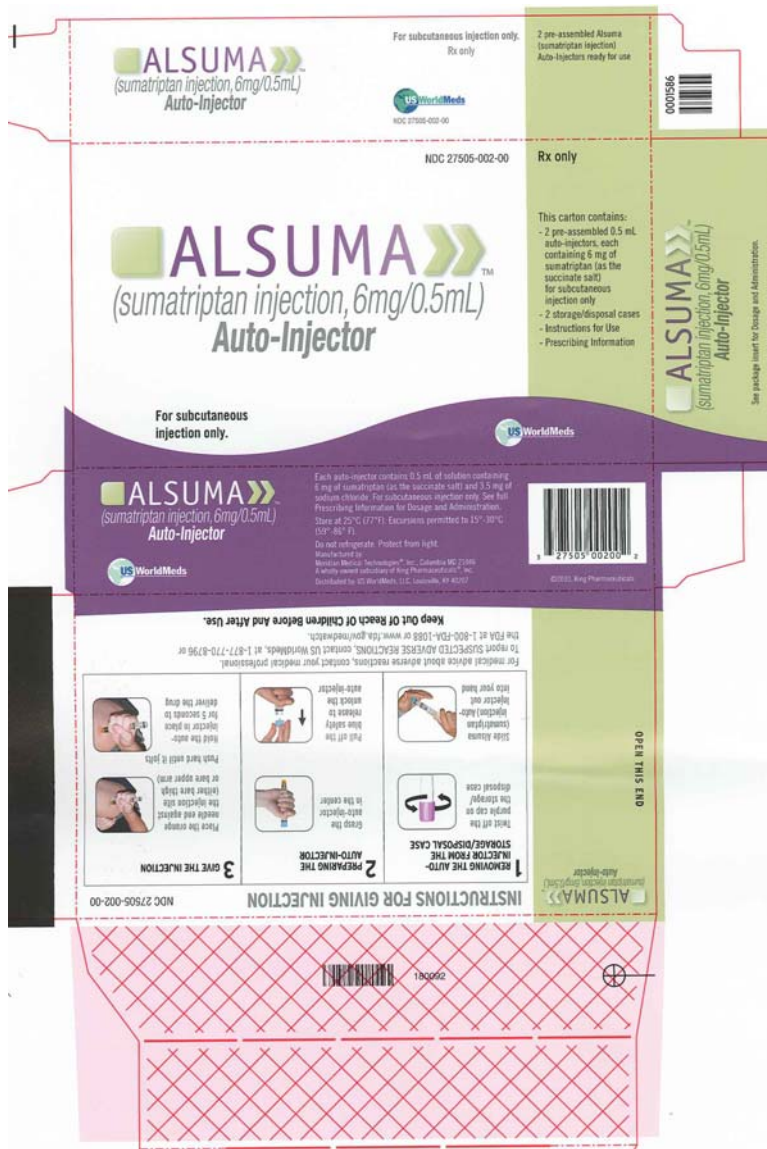
VIEWING WINDOW

APPEARS RED IF UNIT USED

Manufactured by:
Meridian Medical Technologies®, Inc.
Columbia MD 21046
A wholly-owned subsidiary of King Pharmaceuticals®, Inc.

0001585

Appendix B: Carton Labeling



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22377	ORIG-1	KING PHARMACEUTICA LS INC	SUMATRIPTAN SUCCINATE AUTO-INJECTOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LANA Y CHEN
06/29/2010

RUSSELL G KATZ
06/29/2010