

## **11. Conclusions**

1. Maxalt 5mg and 10mg are effective for the acute treatment of migraine headache, when measured by the 2 hour headache response rate.
2. Both the 5mg and 10mg are effective at providing complete relief at 2 hours, and both had higher cure rates at 24 hours compared to placebo.
3. Both 5mg and 10mg are effective in the treatment of a 1<sup>st</sup> headache recurrence within 24 hours.
4. Both 5mg and 10mg are effective in relieving nausea, photophobia, and phonophobia at 2 hours. There was no difference from placebo with respect to vomiting.
5. The 10mg dose is more effective than the 5mg dose.
6. The response rates are maintained across four consecutive migraine attacks.

7. The efficacy of rizatriptan 5mg and 10mg are comparable to that seen with sumatriptan 50mg and 100mg and there is little evidence that one drug is better than the other.
8. Rizatriptan 5mg or 10mg is generally well tolerated.
9. The most common AE's were dizziness, somnolence, asthenia/fatigue, nausea, chest pain, vomiting, diarrhea, headache, paresthesias, and pharyngeal discomfort. These are typical of AE's seen with other 5HT<sub>1B/1D</sub> agonists.
10. Rizatriptan does not exhibit systematic ECG or laboratory abnormalities.
11. Diastolic blood pressure increases only slightly with rizatriptan use.
12. There are no clinically meaningful differences in the safety profile with regard to age, race or gender. Women generally have more AE's compared to men, but this was also present in placebo patients.
13. The safety profile of rizatriptan is not affected by medications concomitantly used for migraine prophylaxis, although rizatriptan levels are increased when used with propranolol. Lower doses of Maxalt should be taken when used concomitantly with propranolol.

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## 12. Recommendations

Based on my overall review of this NDA, rizatriptan is safe and effective on an intermittent, outpatient basis for the acute treatment of migraine headache attacks.

/S/

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Armando Oliva, M.D.  
Medical Reviewer

R. Levin, M.D. /S/ (see memo)

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# Appendix A - Table of All Clinical Studies

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*Table 93: Table of All Clinical Studies*

| Protocol | Design                        | Dosage                           | Formulation        | M  | F  | Total | Dropped | Analyzed                  | Age   | Results  |
|----------|-------------------------------|----------------------------------|--------------------|----|----|-------|---------|---------------------------|-------|--|
| Phase 1  |                               |                                  |                    |    |    |       |         |                           |       |  |
| 002      | DBPC safety, tolerability, PK | 0.5,1,2,10,20,40,60,80           | tablet             | 17 | 0  | 17    | 0       | 17 (safety)<br>16 (PK)    | 18-28 | Doses >60mg not well tolerated                               |
| 003      | DBPC safety, tolerability, PK | 1,2,5,10,20                      | SL, oral soln, tab | 16 | 0  | 16    | 0       | 16                        | 19-35 | no advantage to SL administration                            |
| 006      | DBPC blood flow               | 40                               | tablet             | 10 | 0  | 33    | 0       | 10                        | 21-37 | no effect on cerebral artery velocity<br>PK further outlined |
| 007      | DBPC safety, tolerability, PK | 5,10,20,40,60 µg/mL;<br>40mg tab | IV, tablet         | 13 | 0  | 13    | 2       | 13                        | 18-30 |  |
| 009      | DBPC hemodynamic              | 10, ergot. 0.25                  | tablet             | 17 | 0  | 17    | 1       | 17 (s)<br>16 (PD)         | 21-34 | less periph constriction than ergotamine                     |
| 010      | DBPC safety, tolerability, PK | 20+20, 40+40                     | tablet             | 14 | 2  | 16    | 16      | 16                        | 23-34 | study stopped due to 2 vasovagal events (syncope)            |
| 011      | DBPC intranasal               | 2,4,6,8,10 (I.N.); 4 (I.V.)      | intranasal, I.V.   | 16 | 0  | 16    | 1       | 16 (s)<br>15 (PK)         | 20-36 | good intranasal absorption seen                              |
| 013      | OL metabolism                 | 3 (IV), 10 (oral)                |                    | 6  | 0  | 6     | 0       | 6                         | 22-37 | metabolites identified                                       |
| 015      | DBPC intranasal               | 5 (IN), 10 (tab)                 | IN, tablet         | 10 | 6  | 16    | 4       | 12                        | 19-45 | safe and well absorbed IN                                    |
| 016      | OL safety, tolerability       | 2.5,5,10,15; 4 (IV)              | tablet, IV         | 12 | 12 | 24    | 0       | 24                        | 22-41 | PK further outlined; Biovail 40%                             |
| 017      | DBPC estrogen interaction     | 10                               | tablet             | 0  | 20 | 20    | 2       | 20 (s)<br>18 (PK)         | 18-42 | no interaction seen  |
| 018      | DBPC mult oral doses          | 5mgx3, 10mgx3                    | tablets            | 8  | 5  | 13    | 0       | 13 (s)<br>12 (PK)         | 19-30 | well tolerated; no accumulation                              |
| 019      | DBPC propranolol interaction  | 10                               | tablet             | 11 | 5  | 16    | 5       | 16 (s) 11 (PK)<br>10 (PD) | 20-32 | inc rizatriptan conc by 70%                                  |
| 023      | DBPC clonidine interaction    | 10,15                            | tablet             | 11 | 0  | 11    | 2       | 11 (s)<br>10 (PD)         | 20-33 | no effect, but highly variable results                       |
| 027      | OL renal dysfunction          | 5 (oral soln), 2 (IV)            | oral soln, IV      | 11 | 7  | 18    | 0       | 18                        | 26-65 | no dosing alterations recommended                            |
| 031      | OL intranasal                 | 5,10                             | intranasal         | 16 | 0  | 16    | 0       | 16                        | 19-28 | safe, well tolerated, and well                               |

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## **Appendix B - Protocol Summaries of Pivotal Trials**

### **Study 022**

#### ***Title***

A randomized, triple-blind, double-dummy, placebo-controlled, parallel groups, outpatient study to examine the safety and efficacy of MK-0462 10 mg p.o. and MK-0462 5 mg p.o. for the treatment of acute migraine and migraine recurrence.

#### ***Study Centers***

The study was conducted in 46 centers—28 in the US and 18 in 9 other countries.

#### ***Objective***

##### ***Primary***

- To examine the safety and efficacy of rizatriptan 5mg and 10mg for the treatment of acute migraine.

##### ***Secondary***

- To examine the safety and tolerability of rizatriptan 5mg and 10mg for the treatment of a first migraine recurrence developing within 24 hours.
- To examine the safety and tolerability of rizatriptan 5mg and 10mg when administered up to 3 times in a 24 hour period.
- To examine efficacy of rizatriptan 5mg and 10mg in patients with severe headache at baseline.

#### ***Design***

Randomized, double-blind, double-dummy, placebo-controlled, parallel groups, multicenter, outpatient study. A single dose for initial treatment of a 2/3 grade migraine headache, followed by up to 2 additional doses within 24 hours for recurrence.

#### ***Duration***

One migraine attack. The study was conducted 3/95 - 1/96.

#### ***Setting***

This was an outpatient study.

#### ***Sample Size***

1218 migraine patients.

#### ***Selection***

##### ***Key Inclusion Criteria***

- male or non-pregnant female, 18-65 years old, with at least a 6 month history of migraine (IHS criteria), with 1-8 migraines per month

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**Key Exclusion Criteria**

- basilar or hemiplegic migraine
- significant medical illnesses (including heart, kidney, liver, neurological, endocrine, gastrointestinal, hypertension)
- pregnancy or nursing

**Concomitant Medications**

Not allowed:

within 2 weeks: MAO inhibitors, methysergide, propranolol, metoprolol, or lithium

within 48 hours: any ergot derivative or Midrin

within 24 hours: any opiate

within 6 hours: antiemetics or any other form of analgesia

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**Dosage**

Rizatriptan 5mg, 10mg, and placebo

**Schedule**

Patients were randomized to 3 treatment arms, shown in Table 94. The ratio was 3:2:2 for 5mg:10mg:placebo as initial treatment. Randomization of the second and third dose was 1:1. Patients were instructed to take the initial treatment at the onset of a moderate to severe migraine headache. Rescue medication was permitted anytime 2 hours post dose.

Patients were instructed to take study medication for their first and second recurrence, if necessary. Rescue was again permitted 2 hours post dose. The treatments were all separated by at least 2 hours.

**Table 94: Study 022, Treatment Assignment**

| <b>Initial Treatment</b> | <b>First Recurrence</b> | <b>Second Recurrence</b> |
|--------------------------|-------------------------|--------------------------|
|                          | (1:1)                   | (1:1)                    |
|                          | 5mg                     | 5mg                      |
| PBO (n=304)              | 10mg                    | 10mg                     |
|                          | PBO                     | PBO                      |
| 5mg (n=458)              | 5mg                     | 5mg                      |
|                          | PBO                     | PBO                      |
| 10mg (n=456)             | 10mg                    | 10mg                     |

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**Study 025**

**Title**

A randomized, triple blind, placebo-controlled, outpatient study to examine the safety and efficacy of MK-462 10 mg p.o. in the treatment of multiple attacks of migraine headache.

### **Study Centers**

The study was conducted in 23 centers in the United States.

### **Objective**

#### **Primary**

- To confirm the efficacy of rizatriptan 10mg in the treatment of a first migraine attack.

#### **Secondary**

- To examine the safety and tolerability of rizatriptan after treatment of multiple migraine attacks.

### **Design**

Multicenter, triple blind, placebo-controlled, randomized, multiple dose design. Patients were assigned to one of 5 random treatment sequences (Table 95).

**Table 95: Study 025, Treatment Assignment**

| <b>Group (N)<sup>1</sup></b> | <b>Attack 1</b> | <b>Attack 2</b> | <b>Attack 3</b> | <b>Attack 4</b> |
|------------------------------|-----------------|-----------------|-----------------|-----------------|
| 1 (83)                       | Placebo         | 10 mg           | 10 mg           | 10 mg           |
| 2 (82)                       | 10 mg           | Placebo         | 10 mg           | 10 mg           |
| 3 (84)                       | 10 mg           | 10 mg           | Placebo         | 10 mg           |
| 4 (77)                       | 10 mg           | 10 mg           | 10 mg           | Placebo         |
| 5 (81)                       | 10 mg           | 10 mg           | 10 mg           | 10 mg           |

<sup>1</sup>Number of patients in group who treated at least the first attack

Patients in the first 4 groups received active treatment for 3 of the 4 attacks. The last group received active treatment for all 4 attacks. The design allowed treatment by period interactions to be evaluated. Assessment of headache severity, functional disability, and associated symptoms were performed up to 4 hours post dose during each attack.

Those who received 10mg for the initial attack were allowed to take 10mg for each of up to 2 recurrences within 24 hours. Those who received placebo for the initial attack also received placebo for recurrences. The repeat doses were not randomized and therefore did not provide information regarding efficacy of a second or third dose. Distinct attacks had to be at least 24 hours apart.

Patients who completed the blinded portion of the study were allowed to enroll in the open-label controlled extension for up to 1 year.

### **Duration**

Four (4) migraine attacks, each separated by at least 24 hours. The study was conducted between 4/95 - 1/96.

### **Setting**

This was an outpatient study.

### **Sample Size**

407 migraine patients.

**Selection**

**Key Inclusion Criteria**

- male or non-pregnant female, \_\_\_\_\_ years old, with at least a 6 month history of migraine (IHS criteria), with 1-8 migraines per month

**Key Exclusion Criteria**

- basilar or hemiplegic migraine
- significant medical illnesses (including heart, kidney, liver, neurological, endocrine, gastrointestinal, hypertension)
- pregnancy or nursing

**Concomitant Medications**

Not allowed:

within 2 weeks: MAO inhibitors, methysergide, propranolol, metoprolol, or lithium

within 48 hours: any ergot derivative or Midrin

within 24 hours: any opiate

within 6 hours: antiemetics or any other form of analgesia

**Dosage**

Rizatriptan 10mg, and placebo.

**Schedule**

The study had three periods: pretreatment, treatment, and post-treatment. The pretreatment period included screening and baseline evaluations, and study medication was dispensed in 4 bottles, one for each migraine attack.

The treatment period began when the patient developed a grade 3 or 4 migraine. He/she ingested one tablet from bottle one. The patient rated efficacy measures at 0, 0.5, 1, 1.5, 2, 3, and 4 hours post-dose. The procedure was repeated for each of the next 3 attacks, separated by at least 24 hours.

Escape medication was allowed for non-responders beginning 2 hours after the initial dose, and consisted of analgesics. Treatment with ergot derivatives or Midrin was not allowed for 24 hours.

There was a follow-up visit after the first attack to ensure that patients understood the study procedures. They also returned in one month whether or not they treated any migraine attacks during that period.

The post-treatment period began following the treatment of the 4<sup>th</sup> attack. Patients returned to the clinic within 7 days for a post-treatment evaluation.

**Study 029**

**Title**



A Randomized, Placebo-controlled, Parallel-Groups, Outpatient Study to Compare the Efficacy and Safety of MK-0462 5 mg p.o. and Sumatriptan 50 mg p.o. for the Acute Treatment of Migraine

**Study Centers**

56 Centers internationally (31 UK, 9 Norway, 2 Switzerland, 14 Sweden)

**Objective**

- To compare rizatriptan 5mg p.o. to sumatriptan 50 mg p.o. in terms of time to headache relief (*i.e.*, response)
- To compare the efficacy of rizatriptan 5 mg p.o. to that of placebo at 2 hours post-dose

**Design**

This was a randomized, double-blind, double-dummy, placebo-controlled, parallel groups outpatient study.

**Duration**

1 day. The study was conducted between 8/95 - 5/96.

**Setting**

This was an outpatient study.

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**Sample Size**

792 migraine patients

**Selection**

**Key Inclusion Criteria**

- male or non-pregnant female, 18 years old, with at least a 6 month history of migraine (IHS criteria), with 1-8 migraines per month

**Key Exclusion Criteria**

- basilar or hemiplegic migraine
- significant medical illnesses (including heart, kidney, liver, neurological, endocrine, gastrointestinal, hypertension)
- pregnancy or nursing

**Concomitant Medications**

Not allowed:

within 2 weeks: MAO inhibitors, methysergide, or lithium

within 48 hours: any ergot derivative or Midrin

within 24 hours: any opiate or analgesic

within 6 hours: antiemetics

**Dosage**

Rizatriptan 5mg (+ placebo)

Sumatriptan 50mg (+placebo)

Placebo x 2

**Schedule**

After screening, eligible patients were randomized to receive rizatriptan 5mg, sumatriptan 50mg or placebo for initial treatment of a grade 2 or 3 migraine headache. Patients rated headache severity, functional disability, and associated migraine symptoms at baseline and again at 0.5, 1, 1.5, 2,3, and 4 hours post dose. A "satisfaction with medication" questionnaire was filled out at 2 hours.

Escape medication was permitted after 2 hours for persistent headache and/or recurrence. A second dose of study medication was not given. The time to recurrence was also recorded.

Patients returned to the-clinic within 7 days of treatment for a follow-up assessment.

**Study 030**

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**Title**

A Randomized, Placebo-controlled, Parallel-Groups, Outpatient Study to Compare the Safety, Tolerability, and Efficacy of single oral doses of MK-0462 5 mg, of MK-0462 10 mg and Sumatriptan 100 mg for the Acute Treatment of Migraine

**Study Centers**

47 Centers internationally (Canada, South America, Europe, Middle East, South Africa, Australia)

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**Objective**

- To compared rizatriptan 10mg p.o. to sumatriptan 100 mg p.o. in terms of time to headache relief (*i.e.*, response)
- To compare the efficacy of rizatriptan 5mg and 10 mg p.o. to that of placebo at 2 hours post-dose

**Design**

This was a randomized, double-blind, triple-dummy, placebo-controlled, parallel groups outpatient study.

**Duration**

1 day. The study was conducted between 9/95 - 5/96.

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**Setting**

This was an outpatient study.

**Sample Size**

1099 migraine patients

**Selection**

**Key Inclusion Criteria**

- male or non-pregnant female, \_\_\_\_\_ years old, with at least a 6 month history of migraine (IHS criteria), with 1-8 migraines per month

**Key Exclusion Criteria**

- basilar or hemiplegic migraine
- significant medical illnesses (including heart, kidney, liver, neurological, endocrine, gastrointestinal, hypertension)
- pregnancy or nursing

**Concomitant Medications**

Not allowed:

within 2 weeks: MAO inhibitors, methysergide, or lithium

within 48 hours: any ergot derivative, sumatriptan, or Midrin

within 24 hours: any opiate

within 6 hours: analgesic, antiemetics

**Dosage**

Rizatriptan 5mg

Rizatriptan 10mg

Sumatriptan 100mg

Placebo

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**Schedule**

After screening, eligible patients were randomized to receive rizatriptan 5mg, rizatriptan 10mg, sumatriptan 100mg or placebo for initial treatment of a grade 2 or 3 migraine headache. Patients rated headache severity, functional disability, and associated migraine symptoms at baseline and again at 0.5, 1, 1.5, 2,3, and 4 hours post dose. A "satisfaction with medication" questionnaire was filled out at 2 hours.

Escape medication was permitted after 2 hours for persistent headache and/or recurrence. A second dose of study medication was not given. The time to recurrence was also recorded.

Patients returned to the clinic within 7 days of treatment for a follow-up assessment.

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## Appendix C - Serious Adverse Events

Table 96: Serious Adverse Events

| Study Drug       | WAES Ref. [113] | WMA Ref. No. | Study No. | Albo. No. | Day of Onset† | Number of Days/ Attacks Treated | Total Daily Dose Of Therapy Prior to Onset | Other Test Therapy Dose Prior to AE | Gender/ Age | Duration                              | Intensity                        | Relation to Drug Y/N | Recover- ed              | Action Taken‡    | Event  |
|------------------|-----------------|--------------|-----------|-----------|---------------|---------------------------------|--|-------------------------------------|-------------|---------------------------------------|----------------------------------|----------------------|--------------------------|------------------|--|
| <b>Phase I</b>   |                 |              |           |           |               |                                 |  |                                     |             |                                       |                                  |                      |                          |                  |  |
| Riza 10 mg       | 96070904        | [36]         | 042-001   | 0122      | 26            | 1                               | 10 mg/1 mg I.V.                            | Rizatriptan 1 mg I.V.               | F19         | 1 Day                                 | N/A                              | N                    | Yes                      | 1                | Elasto vs abortion                           |
| Riza 15 mg       | 94047524        | [14]         | 016-001   | 0023      | 1             | 1                               | 15 mg                                      | None                                | F27         | 3 Days                                | Severe                           | N                    | Yes                      | 1                | Irritable bowel syndrome                     |
| Riza 40 mg       | 93105012        | [9]          | 010-001   | 0015      | 1             | 1                               | 80 mg                                      | None                                | M75         | 0.5 Min                               | Severe                           | Y                    | Yes                      | 2                | Syncope                                      |
| Riza 40 mg       | 93105016        | [9]          | 010-001   | 0016      | 1             | 1                               | 80 mg                                      | Placebo                             | F29         | 5 Min                                 | Severe                           | Y                    | Yes                      | 2                | Bradycardia, Hypotension                     |
| Placebo          | 96011554        | [29]         | 035-001   | 0023      | 1             | 6                               | 13 tabs                                    | None                                | F21         | 4 Days                                | Mild                             | Y                    | No                       | 1                | Agitation                                    |
| <b>Phase II</b>  |                 |              |           |           |               |                                 |  |                                     |             |                                       |                                  |                      |                          |                  |  |
| Riza 10 mg       | 94110766        | [18]         | 020-002   | 2051      | 1             | 1                               | 10 mg                                      | None                                | M26         | 4 Hours<br>20 Min<br>10 Min<br>26 Min | Mild<br>Severe<br>Mild<br>Severe | Y<br>Y<br>Y<br>Y     | Yes<br>Yes<br>Yes<br>Yes | 1<br>2<br>1<br>2 | Dizziness, Chest pain, Arm pain, Tachycardia |
| <b>Phase III</b> |                 |              |           |           |               |                                 |  |                                     |             |                                       |                                  |                      |                          |                  |  |
| Riza 5 mg        | 95066738        | [19]         | 022-091   | 5419      | 1             | 1                               | 10 mg<br>15 mg                             | None                                | F54         | 14 Hours<br>9 Hours                   | Severe<br>Severe                 | N<br>N               | Yes<br>Yes               | 1                | Syncope<br>Dehydration                       |
| Riza 5 mg        | 95070001        | [19]         | 022-015   | 4452      | 6             | 1                               | 5 mg                                       | None                                | F40         | 15 Days                               | Moderate                         | N                    | Yes                      | 1                | Nauseum, Ang. malignant                      |
| Riza 5 mg        | 95127901        | [19]         | 022-096   | 5246      | 2             | 1                               | 5 mg                                       | None                                | F40         | 21 Days                               | Severe                           | N                    | No                       | 1                | Migraine headache                            |

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| Study Drug                  | WAES Ref. [113] | WMA Ref. No. | Study No. | Alloc. No. | Day of Onset† | Number of Days/ Attacks Treated | Total Daily Dose Of Therapy Prior to Onset | Other Test Therapy/ Dose Prior to A/E | Gender/ Age | Duration | Intensity | Relation to Drug Y/N | Recover- ed | Action Taken† | Event                        |
|-----------------------------|-----------------|--------------|-----------|------------|---------------|---------------------------------|--|---------------------------------------|-------------|----------|-----------|----------------------|-------------|---------------|------------------------------|
| <b>Phase III (Cont.)</b>    |                 |              |           |            |               |                                 |  |                                       |             |          |           |                      |             |               |                              |
| Riza 5 mg                   | 96079605        | [19]         | 022-040   | 5376       | 1             | 1                               | 5 mg                                       | None                                  | F/42        | 9 Days   | Severe    | N                    | Yes         | 2             | Migraine headache            |
| Riza 5 mg                   | 96049451        | [25]         | 030-021   | 7976       | 6             | 1                               | 5 mg                                       | None                                  | F/34        | 5 Hours  | Severe    | N                    | Yes         | 1             | Epidemioliosis               |
| Riza 10 mg                  | 95112023        | [21]         | 025-020   | 6483       | 10            | 2                               | 10 mg                                      | (Riza 10 mg in 1 previous attack)     | F/34        | 5 Days   | Moderate  | N                    | Yes         | 1             | Culitibis                    |
| Placebo                     | 95100627        | [34]         | 025-010   | 6181       | 8             | 3                               | 2 tabs                                     | (Riza 10 mg in 2 previous attacks)    | F/55        | 1 Day    | Severe    | N                    | Yes         | 1             | Anaphylaxis                  |
| <b>Phase III—Extensions</b> |                 |              |           |            |               |                                 |  |                                       |             |          |           |                      |             |               |                              |
| Riza 5 mg                   | 96035033        | [70]         | 029-008   | 9202       | 4             | 18                              | 15 mg                                      | None                                  | F/51        | 76 Days  | Severe    | N                    | No          | 1             | Neoplasm, thyroid, malignant |
| Riza 5 mg                   | 96037914        | [70]         | 022-094   | 5290       | 1             | 23                              | 5 mg                                       | None                                  | F/59        | 2 Days   | Moderate  | N                    | Yes         | 1             | Retrocilia                   |
| Riza 5 mg                   | 96017919        | [70]         | 022-037   | 5257       | 5             | 12                              | 5 mg                                       | None                                  | F/27        | 3 Days   | Severe    | N                    | Yes         | 1             | Gastroenteritis              |
| Riza 5 mg                   |                 | [70]         | 022-026   | 0587       | 3             | 16                              | 10 mg                                      | None                                  | F/45        | 23 Hours | Moderate  | N                    | Yes         | 1             | Burnin, §                    |
|                             |                 |              |           |            |               |                                 |  |                                       |             | 17 Days  | Moderate  | N                    | No          |               | Pain, shoulder §             |
|                             |                 |              |           |            |               |                                 |  |                                       |             | 23 Hours | Moderate  | N                    | Yes         |               | Eosinosis §                  |

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| Study Drug                   | WABS<br>[113] | WMA<br>Ref.<br>No. | Study<br>No. | Allo-<br>No. | Day of<br>Onset† | Number of<br>Days/<br>Attacks<br>Treated | Total Daily<br>Dose Of<br>Therapy<br>Prior to<br>Onset | Other Test<br>Therapy/<br>Dose Prior<br>to A/E | Gender/<br>Age | Duration | Intensity | Relation<br>to Drug<br>Y/N | Recov-<br>ered | Action<br>Taken† | Event   |
|------------------------------|---------------|--------------------|--------------|--------------|------------------|--|--|--|----------------|----------|-----------|----------------------------|----------------|------------------|---|
| Phase III—Extensions (Cont.) |               |                    |              |              |                  |  |  |  |                |          |           |                            |                |                  |   |
| Riza 5 mg                    | 96010770      | [70]               | 022-027      | 4836         | 31               | 23                                       | 10 mg  | None   | M/38           | 2 Days   | Severe    | N                          | Yes            | 1                | Pain, neck  |
| Riza 5 mg                    | 96075148      | [70]               | 028-002      | 9178         | 6                | 4  | 10 mg  | None   | F/51           | 1 Day    | Severe    | N                          | Yes            | 1                | Fracture, hip   |
| Riza 5 mg                    | 96057933      | [70]               | 022-037      | 5266         | 4                | 79                                       | 10 mg  | None   | M/46           | 2 Days   | Severe    | N                          | Yes            | 1                | Trauma (sprain,<br>hand)                                    |
| Riza 9 mg                    | 96097000      | [79]               | 029-014      | 9639         |                  |  | Not treated  | None   | F/26           | 23 Hours | Severe    | N                          | Yes            | 1                | Trauma, cartilage   |
| Riza 5 mg                    | 9511435       | [70]               | 022-014      | 4443         | 2                | 3  | 10 mg  | None   | F/51           | 6 Days   | Severe    | N                          | Yes            | 1                | Migraine headache   |
| Riza 5 mg                    | 96049607      | [70]               | 022-040      | 5385         | 2                | 13                                       | 5 mg   | None   | F/28           | 30 Days  | Severe    | N                          | Yes            | 1                | Anxiety   |
| Riza 9 mg                    |               | [79]               | 022-031      | 5439         |                  |  | Not treated  | None   | F/52           | 36 Days  | Severe    | N                          | Yes            | 2                | Depression  |
| Riza 10 mg                   | 96072699      | [70]               | 022-026      | 4989         | 11               | 29                                       | 20 mg  | None   | F/62           | 1 Day    | Moderate  | N                          | Yes            | 1                | Surgery, breast<br>(excise breast<br>reduction)§            |
| Riza 10 mg                   | 95070557      | [70]               | 022-027      | 4835         | 1                | 5  | 10 mg  | None   | F/37           | 92 Days  | Severe    | N                          | Yes            | 1                | Neoplasm, skin,<br>malignant                                |
| Riza 10 mg                   |               | [70]               | 025-003      | 6044         | 6                | 17                                       | 30 mg  | None   | F/37           | 1 Day    | Mild      | N                          | Yes            | 1                | Neoplasm, skin,<br>malignant                                |
| Riza 10 mg                   | 96027255      | [70]               | 028-026      | 9968         | 6                | 10                                       | 10 mg  | None   | F/45           | 23 Days  | Severe    | N                          | No             | 2                | Neoplasm, uterine,<br>benign§                               |
| Riza 10 mg                   | 96047923      | [70]               | 022-037      | 5262         | 9                | 61                                       | 10 mg  | None   | F/46           | 5 days   | Severe    | N                          | Yes            | 2                | Embolicism,<br>infarction,<br>pulmonary<br>Thrombocytopenia |

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| Study Drug                    | WAES [113] | WMA Ref. No. | Study No. | Alloc. No. | Day of Onset† | Number of Days/Attacks Treated | Total Daily Dose Of Therapy Prior to Onset | Other Test Therapy/ Dose Prior to AE | Gender/ Age | Duration          | Intensity | Relation to Drug Y/N | Recover- ed | Action Taken† | Event                 |
|-------------------------------|------------|--------------|-----------|------------|---------------|--------------------------------|--|--------------------------------------|-------------|-------------------|-----------|----------------------|-------------|---------------|-----------------------|
| Phase III—Evaluations (Cont.) |            |              |           |            |               |                                |  |                                      |             |                   |           |                      |             |               |                       |
| Riza 10 mg                    | 93121621   | [70]         | 025-006   | 6107       | 2             | 8                              | 10 mg<br>20 mg                             | None                                 | M/57        | 3 Days<br>12 Days | Severe    | N                    | Yes         | 1             | Prostatitis           |
| Riza 10 mg                    | 96045142   | [70]         | 029-008   | 9301       | 2             | 11                             | 10 mg<br>20 mg                             | None                                 | F/38        | 12 Days           | Severe    | N                    | Yes         | 2             | Agarucyolysis         |
| Riza 10 mg                    | 96092400   | [70]         | 025-006   | 6113       | 5             | 7                              | 10 mg<br>10 mg                             | None                                 | F/30        | 3 Days            | Severe    | N                    | Yes         | 1             | Pain, abdominal       |
| Riza 10 mg                    | 96020412   | [70]         | 025-012   | 6228       | 5             | 17                             | 10 mg<br>10 mg                             | None                                 | F/49        | 4 Days            | Severe    | N                    | Yes         | 1             | Appendicitis          |
| Riza 10 mg                    | 96077941   | [70]         | 022-035   | 5183       | 6             | 26                             | 10 mg<br>10 mg                             | None                                 | F/49        | 2 Days            | Moderate  | N                    | Yes         | 1             | Pain, back            |
| Riza 10 mg                    | 95100814   | [70]         | 022-017   | 4542       | 17            | 45                             | 10 mg<br>10 mg                             | None                                 | M/55        | 2 Days            | Severe    | N                    | Yes         | 1             | Cholelithiasis        |
| Riza 10 mg                    | 93126752   | [70]         | 022-031   | 5422       | 8             | 4                              | 10 mg<br>10 mg                             | None                                 | F/29        | 2 Days            | Severe    | N                    | Yes         | 1             | Fracture, elbow       |
| Riza 10 mg                    | 96026752   | [70]         | 022-031   | 5422       | 38            | 4                              | 10 mg<br>10 mg                             | None                                 | F/29        | 2 Days            | Severe    | N                    | Yes         | 1             | Fracture, elbow       |
| Riza 10 mg                    | 95105532   | [70]         | 022-045   | 5463       | 38            | 40                             | 10 mg<br>10 mg                             | None                                 | F/50        | 21 Days           | Severe    | N                    | Yes         | 2             | Migraine              |
| Riza 10 mg                    | 95081222   | [70]         | 022-026   | 4803       | 2             | 10                             | 10 mg<br>10 mg                             | None                                 | F/38        | 11 Days           | Severe    | N                    | Yes         | 1             | Migraine              |
| Riza 10 mg                    | 96059607   | [70]         | 022-041   | 5401       | 6             | 13                             | 10 mg<br>20 mg<br>20 mg                    | None                                 | F/40        | 16 Days           | Severe    | N                    | Yes         | 2             | Migraine              |
|                               |            |              |           |            | 1             | 15                             | 20 mg                                      | None                                 |             | 4 Days            | Severe    | N                    | Yes         | 1             | Headache              |
|                               |            |              |           |            | 1             | 15                             | 20 mg                                      | None                                 |             | 10 Hours          | Severe    | Y                    | Yes         | 1             | Pain, musculoskeletal |
|                               |            |              |           |            | 5             | 18                             | 10 mg                                      | None                                 | F/52        | 7 Days            | Severe    | N                    | No          | 1             | Pain, chest           |
|                               |            |              |           |            | 6             | 18                             | 10 mg                                      | None                                 |             | 6 Days            | Moderate  | N                    | Yes         | 1             | Whooping Cough        |
|                               |            |              |           |            |               |                                |  |                                      |             |                   |           |                      |             |               | Asthma                |

| Study Drug                    | WAES [113] | WMA Ref. No. | Study No. | Alloc. No. | Day of Onset† | Number of Days/Attacks Treated | Total Daily Dose Of Therapy Prior to Onset | Other Test Therapy/ Dose Prior to AE | Gender/ Age | Duration                    | Intensity                    | Relation to Drug Y/N | Recover- ed | Action Taken† | Event                        |
|-------------------------------|------------|--------------|-----------|------------|---------------|--------------------------------|--|--------------------------------------|-------------|-----------------------------|------------------------------|----------------------|-------------|---------------|------------------------------|
| Phase III—Evaluations (Cont.) |            |              |           |            |               |                                |  |                                      |             |                             |                              |                      |             |               |                              |
| Riza 10 mg                    | 95061225   | [70]         | 022-012   | 4354       | 34            | 1                              | not treated                                | None                                 | F/53        | 5 Days                      | Moderate                     | N                    | Yes         | 1             | Asthma, bronchitis (chronic) |
| Riza 10 mg                    | 96075126   | [70]         | 023-003   | 9398       |               |                                | not treated                                | None                                 | F/19        | 54 Days<br>14 Days<br>1 Day | Severe<br>Severe<br>Moderate | N                    | Yes         | 1             | Vomiting                     |
| Riza 10 mg                    |            | [70]         | 025-013   | 6251       | 4             | 10                             | 20 mg                                      | None                                 | F/41        | 23 Hours                    | Moderate                     | N                    | Yes         | 1             | Dehydration                  |
| Standard Care                 | 96082394   | [70]         | 022-009   | 4280       | 36            | 15                             | 1 dose                                     | None                                 | M/29        | 5 Days                      | Moderate                     | N                    | Yes         | 1             | Abortion                     |
| Standard Care                 | 96011798   | [70]         | 025-005   | 6085       | 2             | 17                             | 1 dose                                     | None                                 | F/52        | 1 Day                       | Moderate                     | N                    | Yes         | 1             | Menstruation disorder        |
| Standard Care                 | 96037906   | [70]         | 022-038   | 5208       | 8             | 12                             | 1 dose                                     | None                                 | F/45        | 2 Days                      | Moderate                     | N                    | Yes         | 1             | Hernia, inguinal             |
| Standard Care                 | 96090427   | [70]         | 022-026   | 4834       | 89            | 19                             | 1 dose                                     | None                                 | F/43        | 4 Days                      | Moderate                     | N                    | Yes         | 1             | Cholelithiasis               |
| Standard Care                 | 96052792   | [70]         | 022-013   | 4403       | 2             | 60                             | 1 dose                                     | None                                 | M/44        | 5 Days                      | Severe                       | N                    | Yes         | 1             | Joint disorder (bursitis)    |
| Standard Care                 | 96036754   | [70]         | 022-031   | 5417       | 2             | 21                             | 1 dose                                     | None                                 | F/24        | 4 Days                      | Severe                       | N                    | Yes         | 1             | Cystocele                    |
|                               |            |              |           |            |               |                                |  |                                      |             |                             |                              |                      |             |               | Menagitis                    |
|                               |            |              |           |            |               |                                |  |                                      |             |                             |                              |                      |             |               | Migraine                     |

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| Study Drug                     | WARS Ref. No. [113] | WMA Ref. No. | Study No. | Allo. No. | Day of Onset† | Number of Days/Attacks Treated | Total Daily Dose Of Therapy Prior to Onset | Other Test Therapy/ Dose Prior to A/E | Gender/ Age | Duration | Intensity | Relation to Drug Y/N | Recoy-ered | Action Taken† | Event      |
|--------------------------------|---------------------|--------------|-----------|-----------|---------------|--------------------------------|--|---------------------------------------|-------------|----------|-----------|----------------------|------------|---------------|------------|
| Phase III — Extensions (Cont.) |                     |              |           |           |               |                                |  |                                       |             |          |           |                      |            |               |            |
| Standard Care                  | 96126752            | [70]         | 022-031   | 5423      | 4             | 17                             | 1 dose                                     | None                                  | F49         | 2 Days   | Severe    | N                    | Yes        | 1             | Migraine   |
| Standard Care                  | 96036752            | [70]         | 022-031   | 5426      | 1             | 54                             | 1 dose                                     | None                                  | F34         | 2 Days   | Severe    | N                    | Yes        | 1             | Migraine   |
| Standard Care                  | 96060402            | [70]         | 025-009   | 6165      | 18            | 16                             | 1 dose                                     | None                                  | M57         | 25 Days  | Severe    | N                    | Yes        | 1             | Depression |

† Day of onset relative to last dose.

‡ Action Taken: 1—none; 2—discontinued.

§ The specific term on the case report form is "head and neck pressure." The preferred term mapping will be corrected in the Safety Update Report.

¶ The investigator has confirmed that this was not a serious adverse experience. The adverse experience will be deleted for the Safety Update Report.

Note: Patients in bold are those who had a serious adverse experience after they entered extension, but did not yet treat with study drug in extension at the time of the adverse experience.

Rules of placement of event in one of the above columns:

If the event occurred on a day in which Riza was taken in addition to placebo, the event is listed under Riza unless it occurred prior to Riza administration.

Events in Protocol 025—Multiple Attack Study—are listed under the study medication used in the present attack, or, if in between attacks, that used in the most recent attack.

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Appendix D - Adverse Dropouts

Table 97: Dropouts Due To Adverse Events

| Study Number     | AN   | Gender | Age (Yrs) | Treatment      | Study Day | Adverse Experience                 | Duration | Intensity | Serious | Drug Related   | Recovered |
|------------------|------|--------|-----------|----------------|-----------|------------------------------------|----------|-----------|---------|----------------|-----------|
| <b>Phase I</b>   |      |        |           |                |           |                                    |          |           |         |                |           |
| 010-001          | 0016 | F      | 29        | Riza 40 mg     | 1         | Headache                           | 25 Min   | Moderate  | No      | Probably       | Yes       |
|                  |      |        |           |                | 1         | Somnolence                         | 9 Hours  | Moderate  | No      | Probably       | Yes       |
|                  |      |        |           |                | 1         | Vomiting                           | 10 Min   | Severe    | No      | Possibly       | Yes       |
|                  |      |        |           |                | 1         | Bradycardia                        | 5 Min    | Severe    | Yes     | Probably       | Yes       |
|                  |      |        |           |                | 1         | Hypotension                        | 5 Min    | Severe    | Yes     | Probably       | Yes       |
|                  |      |        |           |                | 1         | Pallor                             | 5 Min    | Severe    | No      | Probably       | Yes       |
|                  |      |        |           |                | 1         | Bradycardia                        | 5 Min    | Moderate  | Yes     | Probably       | Yes       |
|                  |      |        |           |                | 1         | Pallor                             | 5 Min    | Moderate  | No      | Probably       | Yes       |
| 010-001          | 0015 | M      | 25        | Riza 40 mg     | 1         | Syncope                            | 0.5 Min  | Severe    | Yes     | Possibly       | Yes       |
|                  |      |        |           |                | 1         | Sinus bradycardia                  | 0.5 Min  | Moderate  | No      | Possibly       | Yes       |
|                  |      |        |           |                | 1         | Urinary incontinence               | 0.5 Min  | Moderate  | No      | Possibly       | Yes       |
|                  |      |        |           |                | 1         | Asystole                           | 0.1 Min  | Severe    | No      | Possibly       | Yes       |
| 017-001          | 0018 | F      | 35        | Riza 10 mg     | 14        | Pain, chest                        | 21 Days  | Mild      | No      | Definitely not | Yes       |
|                  |      |        |           |                | 14        | Pain, abdominal                    | 21 Days  | Mild      | No      | Definitely not | Yes       |
|                  |      |        |           |                | 28        | Palpitation                        | 1 Hour   | Mild      | No      | Probably not   | Yes       |
| 042-001          | 0022 | F      | 28        | Riza 10 mg     | 2         | Depression                         | 2 Days   | Severe    | No      | Probably not   | Yes       |
| 2-001            | 0122 | F      | 19        | Riza 10 mg     | 8         | Pregnancy test positive            | 19 Days  | N/ A      | No      | Definitely not | Yes       |
| 007-001          | 0001 | M      | 29        | Riz iv 60mg/kg | 15        | Headache                           | 38 Min   | Moderate  | No      | Probably       | Yes       |
| 009-001          | 0013 | M      | 23        | Placebo        | 7         | Muscle/ ligament/ fascia disorders | 14 Days  | Moderate  | No      | Definitely not | No        |
| 019-001          | 0001 | M      | 20        | Propranolol    | 1         | Pancreatitis                       | 5 Days   | Moderate  | No      | Probably not   | Yes       |
| 019-001          | 0101 | M      | 27        | Propranolol    | 2         | Dizziness                          | 3 Days   | Moderate  | No      | Possibly       | Yes       |
|                  |      |        |           |                | 2         | Chest pain                         | 3 Days   | Moderate  | No      | Possibly       | Yes       |
|                  |      |        |           |                | 2         | Asthenia/ fatigue                  | 3 Days   | Moderate  | No      | Possibly       | Yes       |
| 023-001          | 0007 | M      | 33        | Clonidine      | 1         | Bradycardia                        | 10 Min   | Severe    | No      | Probably       | Yes       |
|                  |      |        |           |                | 1         | Hypotension                        | 4 Hours  | Severe    | No      | Probably       | Yes       |
|                  |      |        |           |                | 1         | Syncope                            | 0.5 Min  | Severe    | No      | Probably       | Yes       |
| 038-001          | 0010 | M      | 28        | Nadolol 80 mg  | 3         | Hypotension                        | 3 Days   | Moderate  | No      | Probably       | Yes       |
| 043-001          | 0007 | M      | 30        | Paroxetine     | 3         | Blood pressure increased           | 13 Days  | Mild      | No      | Probably       | No        |
| <b>Phase II</b>  |      |        |           |                |           |                                    |          |           |         |                |           |
| 026-001          | 0019 | F      | 30        | Riza 5 mg      | 4         | Cramp, muscle                      | 61 Days  | Severe    | No      | Definitely not | Yes       |
| 020-002          | 2049 | F      | 31        | Riza 10 mg     | 1         | Dyspnea                            | 3 Days   | Mild      | No      | Definitely     | Yes       |
|                  |      |        |           |                | 1         | Paresthesia                        | 10 Min   | Moderate  | No      | Definitely     | Yes       |
|                  |      |        |           |                | 1         | Pain, chest                        | 1.8 Hour | Moderate  | No      | Definitely     | Yes       |
| 020-002          | 2051 | M      | 26        | Riza 10 mg     | 1         | Tachycardia                        | 26 Min   | Severe    | Yes     | Definitely     | Yes       |
|                  |      |        |           |                | 1         | Pain, chest                        | 30 Min   | Severe    | Yes     | Definitely     | Yes       |
| 020-002          | 2061 | F      | 52        | Riza 10 mg     | 1         | Tachycardia                        | 3 Min    | Mild      | No      | Probably       | Yes       |
|                  |      |        |           |                | 1         | Tremor                             | 2 Hours  | Mild      | No      | Probably       | Yes       |
| 020-002          | 2065 | F      | 34        | Placebo        | 1         | Paresthesia                        | 30 Min   | Moderate  | No      | Probably       | Yes       |
| <b>Phase III</b> |      |        |           |                |           |                                    |          |           |         |                |           |
| 022-040          | 5376 | F      | 42        | Riza 5 mg      | 1         | Migraine                           | 9 Days   | Severe    | Yes     | Probably not   | Yes       |

|                             |            |   |    |             |     |                        |            |          |     |                |     |
|-----------------------------|------------|---|----|-------------|-----|------------------------|------------|----------|-----|----------------|-----|
| 022-040                     | 5375       | F | 23 | Riza 10 mg  | 1   | Dizziness              | 12 Hours   | Severe   | No  | Probably       | Yes |
|                             |            |   |    |             | 1   | Somnolence             | 12 Hours   | Severe   | No  | Probably       | Yes |
| 025-011                     | 6212       | F | 42 | Riza 10 mg  | 2   | Pain, chest            | 2.5 Hour   | Mild     | No  | Possibly       | Yes |
|                             |            |   |    |             | 2   | Somnolence             | 14.8 Hours | Moderate | No  | Possibly       | Yes |
| 025-014                     | 6268       | F | 30 | Riza 10 mg  | 1   | Dizziness              | 30 Min     | Moderate | No  | Probably       | Yes |
|                             |            |   |    |             | 1   | Edema                  | 10 Hours   | Moderate | No  | Probably       | Yes |
|                             |            |   |    |             | 1   | Tremor                 | 30 Min     | Mild     | No  | Probably       | Yes |
|                             |            |   |    |             | 1   | Sweating               | 30 Min     | Moderate | No  | Probably       | Yes |
| 025-017                     | 6332       | F | 52 | Riza 10 mg  | 1   | Urticaria              | 3 Days     | Severe   | No  | Probably       | Yes |
|                             |            |   |    |             | 1   | Dyspnea                | 1 Hour     | Mild     | No  | Probably       | Yes |
|                             |            |   |    |             | 1   | Dysphagia              | 1 Hour     | Mild     | No  | Probably       | Yes |
| 025-002                     | 6394       | F | 24 | Riza 10 mg  | 2   | Menstruation disorder  | 5 Min      | Mild     | No  | Possibly       | Yes |
| 025-021                     | 6404       | F | 50 | Riza 10 mg  | 1   | Dizziness              | 2 Hours    | Moderate | No  | Probably       | Yes |
| 025-017                     | 6339       | F | 37 | Placebo     | 1   | Vomiting               | 1 Day      | Moderate | No  | Probably       | Yes |
| 025-007                     | 6133       | F | 30 | Placebo     | 28  | Somnolence             | 10 Hours   | Moderate | No  | Possibly       | Yes |
| 025-010                     | 6190       | F | 45 | Placebo     | 1   | Accommodation disorder | 2 Days     | Moderate | No  | Possibly       | Yes |
|                             |            |   |    |             | 1   | Mental acuity dec.     | 2 Days     | Moderate | No  | Possibly       | Yes |
| 030-032                     | 7587       | F | 58 | Sumatriptan | 1   | Vomiting               | 5 Min      | Mild     | No  | Possibly       | Yes |
| <b>Phase III Extensions</b> |            |   |    |             |     |                        |            |          |     |                |     |
| 022-005                     | 4905       | F | 23 | Riza 5 mg   | 216 | Rash                   | 17 days    | Mild     | No  | Possibly       | No  |
| 022-008                     | 4228       | F | 46 | Riza 5 mg   | 72  | Pain, chest            | 8 Hours    | Severe   | No  | Definitely     | Yes |
|                             |            |   |    |             | 95  | Pain, chest            | 11 Hours   | Severe   | No  | Definitely     | Yes |
| 022-008                     | 4246       | F | 46 | Riza 5 mg   | 146 | Pain, back             | 3 Days     | Severe   | No  | Definitely not | No  |
| 02-017                      | 0184       | F | 46 | Riza 5 mg   | 146 | Hypertension           | 1 Day      | Moderate | No  | Probably not   | No  |
| 02-017                      | 0185       | F | 46 | Riza 5 mg   | 23  | Pain, back             | 83 Days    | Moderate | No  | Definitely not | No  |
|                             |            |   |    |             | 48  | Burn                   | 58 Days    | Moderate | No  | Definitely not | No  |
| 022-017                     | 4529       | F | 35 | Riza 5 mg   | 110 | Pain, back             | 37 Days    | Moderate | No  | Definitely not | No  |
| 022-019                     | 4604       | F | 42 | Riza 5 mg   | 39  | Pain, chest            | 20 Days    | Moderate | No  | Possibly       | No  |
| 022-020                     | 4615       | F | 50 | Riza 5 mg   | 7   | Nausea                 | 1.5 Hours  | Moderate | No  | Probably       | Yes |
|                             |            |   |    |             | 7   | Dizziness              | 30 Mins    | Moderate | No  | Probably       | Yes |
| 022-020                     | 4625       | F | 45 | Riza 5 mg   | 8   | Diarrhea               | 4 Hours    | Moderate | No  | Probably       | Yes |
|                             |            |   |    |             | 8   | Nausea                 | 15 Mins    | Moderate | No  | Probably       | Yes |
|                             |            |   |    |             | 8   | Warm sensation         | 30 Mins    | Moderate | No  | Probably       | Yes |
|                             |            |   |    |             | 8   | Dizziness              | 15 Mins    | Moderate | No  | Probably       | Yes |
| 022-023                     | 4729       | F | 34 | Riza 5 mg   | 17  | Nausea                 | 1 Hours    | Moderate | No  | Probably       | Yes |
| 022-028                     | 4890       | F | 38 | Riza 5 mg   | 141 | Pain, back             | 14 Days    | Severe   | No  | Definitely not | No  |
| 022-036                     | 5230       | F | 54 | Riza 5 mg   | 23  | Mental acuity dec.     | 14 Hours   | Moderate | No  | Definitely     | Yes |
| 022-038                     | 5220       | F | 41 | Riza 5 mg   | 115 | Depression             | 41 Days    | Moderate | No  | Probably not   | No  |
| 022-040                     | 5385       | F | 28 | Riza 5 mg   | 179 | Depression             | 36 Days    | Severe   | Yes | Definitely not | Yes |
| 022-042                     | 5008       | F | 46 | Riza 5 mg   | 38  | Diarrhea               | 12 Hours   | Moderate | No  | Prob not       | Yes |
|                             |            |   |    |             | 38  | Asthenia/ fatigue      | 12 Hours   | Severe   | No  | Prob not       | Yes |
|                             |            |   |    |             | 38  | Nausea                 | 12 Hours   | Moderate | No  | Prob not       | Yes |
| 029-002                     | 9031       | F | 53 | Riza 5 mg   | 121 | Disorientation         | 4 Hours    | Moderate | No  | Probably       | Yes |
| 029-002                     | 9096       | F | 48 | Riza 5 mg   | 28  | Somnolence             | 2 Hours    | Severe   | No  | Probably       | Yes |
| 029-002                     | 9117<br>NR | F | 56 | Riza 5 mg   | 16  | Somnolence             | 5 Hours    | Severe   | No  | Probably       | Yes |
| 029-002                     | 9139       | F | 47 | Riza 5 mg   | 31  | Psychic disturbance    | 4 Hours    | Moderate | No  | Probably       | Yes |
| -002                        | 9175       | F | 48 | Riza 5 mg   | 34  | Paresthesia            | 20 Mins    | Severe   | No  | Probably       | Yes |
|                             |            |   |    |             | 34  | Cold sensation         | 20 Mins    | Severe   | No  | Probably       | Yes |

|         |            |   |    |            |     |                     |           |          |     |                |     |
|---------|------------|---|----|------------|-----|---------------------|-----------|----------|-----|----------------|-----|
|         |            |   |    |            | 35  | Paresthesia         | 1.5 Hours | Severe   | No  | Probably       | Yes |
| 29-005  | 9617       | F | 25 | Riza 5 mg  | 7   | Dizziness           | 6 Hours   | Moderate | No  | Probably not   | Yes |
|         |            |   |    |            | 7   | Hypesthesia         | 3 Hours   | Moderate | No  | Possibly       | Yes |
|         |            |   |    |            | 8   | Nausea              | 2.5 Hours | Moderate | No  | Probably not   | Yes |
|         |            |   |    |            | 16  | Dizziness           | 8 Hours   | Moderate | No  | Probably not   | Yes |
|         |            |   |    |            | 16  | Nausea              | 8 Hours   | Moderate | No  | Probably not   | Yes |
|         |            |   |    |            | 16  | Ataxia              | 4 Hours   | Moderate | No  | Possibly       | Yes |
| 029-005 | 9626       | F | 27 | Riza 5 mg  | 39  | Vomiting            | 340 Mins  | Severe   | No  | Probably       | Yes |
|         |            |   |    |            | 39  | Nausea              | 340 Mins  | Severe   | No  | Probably       | Yes |
| 029-008 | 9188<br>NR | M | 60 | Riza 5 mg  | 20  | Nausea              | 4 Hours   | Moderate | No  | Probably       | Yes |
| 029-008 | 9259       | F | 45 | Riza 5 mg  | 17  | Dizziness           | 2 Hours   | Moderate | No  | Probably       | Yes |
|         |            |   |    |            | 17  | Visual disturbance  | 2 Hours   | Moderate | No  | Probably       | Yes |
|         |            |   |    |            | 17  | Panic disorder      | 2 Hours   | Moderate | No  | Probably       | Yes |
| 022-008 | 4232       | F | 46 | Riza 10 mg | 178 | Dizziness           | 3 Hours   | Moderate | No  | Definitely     | Yes |
|         |            |   |    |            | 178 | Nausea              | 3 Hours   | Moderate | No  | Definitely     | Yes |
|         |            |   |    |            | 179 | Dizziness           | 3 Hours   | Moderate | No  | Definitely     | Yes |
|         |            |   |    |            | 179 | Nausea              | 3 Hours   | Moderate | No  | Definitely     | Yes |
| 022-010 | 4294       | F | 19 | Riza 10 mg | 19  | Vomiting            | 4.6 Hours | Moderate | No  | Probably       | Yes |
|         |            |   |    |            | 20  | Headache            | 5 Hours   | Severe   | No  | Probably       | Yes |
| 022-012 | 4355       | F | 39 | Riza 10 mg | 7   | Pain, chest         | 2.3 Hours | Moderate | No  | Possibly       | Yes |
|         |            |   |    |            | 7   | Vomiting            | 3 Days    | Moderate | No  | Definitely not | Yes |
| 022-013 | 4388       | F | 39 | Riza 10 mg | 28  | Nausea              | 2 Hours   | Severe   | No  | Probably       | Yes |
|         |            |   |    |            | 29  | Nausea              | 2.5 Hours | Severe   | No  | Probably       | Yes |
|         |            |   |    |            | 29  | Dizziness           | 2.5 Hours | Severe   | No  | Probably       | Yes |
|         |            |   |    |            | 31  | Nausea              | 3 Hours   | Severe   | No  | Probably       | Yes |
|         |            |   |    |            | 31  | Dizziness           | 3 Hours   | Severe   | No  | Probably       | Yes |
| 022-017 | 4516       | F | 51 | Riza 10 mg | 248 | Hypertension        | 6 Days    | Mild     | No  | Prob not       | No  |
| 022-017 | 4527       | F | 41 | Riza 10 mg | 174 | Blood pressure inc. | 41 Days   | Moderate | No  | Def not        | No  |
| 022-017 | 4542       | F | 29 | Riza 10 mg | 45  | Migraine            | 3 Days    | Severe   | Yes | Def not        | Yes |
| 022-019 | 4590       | F | 50 | Riza 10 mg | 153 | Urticaria           | 4 Days    | Moderate | No  | Possibly       | No  |
| 022-022 | 4690       | F | 41 | Riza 10 mg | 35  | Nervousness         | 5 Hours   | Moderate | No  | Probably       | Yes |
|         |            |   |    |            | 35  | Hypertension        | 5 Hours   | Moderate | No  | Probably       | Yes |
|         |            |   |    |            | 35  | Headache            | 5 Hours   | Moderate | No  | Probably       | Yes |
|         |            |   |    |            | 35  | Palpitation         | 2 Hours   | Moderate | No  | Probably       | Yes |
| 022-024 | 4740       | F | 42 | Riza 10 mg | 115 | Edema/ swelling     | 4 Days    | Mild     | No  | Possibly       | Yes |
| 022-027 | 4846       | F | 57 | Riza 10 mg | 7   | Orthostatic effects | 14 Days   | Moderate | No  | Possibly       | Yes |
|         |            |   |    |            | 18  | Ataxia              | 2 Days    | Moderate | No  | Possibly       | Yes |
| 022-030 | 5163       | M | 41 | Riza 10 mg | 202 | Headache            | 1.5 Hours | Moderate | No  | Possibly       | Yes |
|         |            |   |    |            | 229 | Nervousness         | 11 Hours  | Moderate | No  | Possibly       | Yes |
| 022-034 | 5283       | F | 46 | Riza 10 mg | 30  | Somnolence          | 1 Day     | Mild     | No  | Probably       | Yes |
| 022-035 | 5190       | F | 50 | Riza 10 mg | 1   | Dizziness           | 4 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 1   | Somnolence          | 4 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 2   | Dizziness           | 4 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 2   | Dizziness           | 2 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 2   | Somnolence          | 4 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 2   | Somnolence          | 2 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 7   | Dizziness           | 2 Hours   | Severe   | No  | Definitely     | Yes |
|         |            |   |    |            | 7   | Somnolence          | 2 Hours   | Severe   | No  | Definitely     | Yes |
| 022-037 | 5251       | F | 33 | Riza 10 mg | 68  | Rash                | 31 Days   | Moderate | No  | Possibly       | Yes |

|         |         |   |    |            |     |                        |           |          |     |              |     |
|---------|---------|---|----|------------|-----|------------------------|-----------|----------|-----|--------------|-----|
| 022-037 | 5262    | F | 46 | Riza 10 mg | 285 | Thrombocytopenia       | 5 Days    | Severe   | Yes | Probably not | Yes |
|         |         |   |    |            | 290 | Thrombocytopenia       | 3 Days    | Moderate | No  | Probably not | Yes |
| 022-039 | 5107    | F | 25 | Riza 10 mg | 22  | Pain, chest            | 4.3 Hours | Mild     | No  | Possibly     | Yes |
| 022-044 | 5340    | F | 54 | Riza 10 mg | 27  | Discomfort, pharyngeal | 2 Hours   | Mild     | No  | Probably     | Yes |
| 022-045 | 5463    | F | 38 | Riza 10 mg | 38  | Migraine               | 16 Days   | Severe   | Yes | Probably not | Yes |
| 025-006 | 6107    | M | 57 | Riza 10 mg | 65  | Agranulocytosis        | 20 Days   |          | No  | Probably not | Yes |
|         |         |   |    |            | 77  | Agranulocytosis        | 8 Days    |          | No  | Probably not | Yes |
| 025-009 | 6163    | F | 33 | Riza 10 mg | 2   | Anxiety                | 2 Hours   | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 2   | Insomnia               | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 2   | Paresthesia            | 2 Hours   | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 8   | Anxiety                | 17 Hours  | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 8   | Insomnia               | 17 Hours  | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 10  | Insomnia               | 1 Hour    | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 20  | Anxiety                | 11 Hours  | Moderate | No  | Probably     | Yes |
| 025-012 | 6230    | F | 37 | Riza 10 mg | 64  | Dizziness              | 1.5 Hours | Mild     | No  | Possibly     | Yes |
|         |         |   |    |            | 64  | Nausea                 | 11 Hours  | Mild     | No  | Possibly     | Yes |
|         |         |   |    |            | 64  | Discomfort, pharyngeal | 30 Mins   | Mild     | No  | Possibly     | Yes |
|         |         |   |    |            | 64  | Tightness, regional    | 30 Mins   | Mild     | No  | Possibly     | Yes |
| 025-013 | 6253    | F | 38 | Riza 10 mg | 64  | Pain, Chest            | 2 Hours   | Moderate | No  | Possibly     | Yes |
|         |         |   |    |            | 64  | Arthralgia             | 2 Hours   | Moderate | No  | Possibly     | Yes |
| 029-002 | 9020    | F | 39 | Riza 10 mg | 44  | Headache               | 1.5 Hours | Severe   | No  | Probably     | Yes |
| 029-002 | 9052    | F | 44 | Riza 10 mg | 84  | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 88  | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 89  | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 93  | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 95  | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 96  | Somnolence             | 10 Hours  | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 103 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 104 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
| 029-002 | 9052    |   |    |            | 112 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
| (Cont.) | (Cont.) |   |    |            | 113 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 126 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 128 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 130 | Dizziness              | 2 Hours   | Severe   | No  | Probably     | Yes |
|         |         |   |    |            | 130 | Somnolence             | 2 Hours   | Mild     | No  | Probably     | Yes |
|         |         |   |    |            | 130 | Disorientation         | 2 Hours   | Severe   | No  | Probably     | Yes |
|         |         |   |    |            | 130 | Flushing               | 2 Hours   | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 130 | Dizziness              | 2 Hours   | Severe   | No  | Probably     | Yes |
| 029-002 | 9092    | F | 37 | Riza 10 mg | 48  | Palpitation            | 10 Days   | Moderate | No  | Probably     | No  |
| 029-002 | 9109    | F | 43 | Riza 10 mg | 112 | Dizziness              | 4 Hours   | Severe   | No  | Probably     | Yes |
|         |         |   |    |            | 112 | Nausea                 | 4 Hours   | Mild     | No  | Probably     | Yes |
| 029-002 | 9110    | F | 35 | Riza 10 mg | 53  | Rash                   | 10 Hours  | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 55  | Rash                   | 15 Hours  | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 56  | Rash                   | 13 Hours  | Moderate | No  | Probably     | Yes |
| 029-002 | 9118    | F | 49 | Riza 10 mg | 59  | Euphoria               | 2 Hours   | Moderate | No  | Probably     | Yes |
|         |         |   |    |            | 59  | Dyspepsia              | 2 Hours   | Mild     | No  | Probably     | Yes |
| 029-002 | 9161    | M | 50 | Riza 10 mg | 28  | Somnolence             | 2 Hours   | Severe   | No  | Probably     | Yes |
|         |         |   |    |            | 28  | Nausea                 | 2 Hours   | Severe   | No  | Probably     | Yes |
| 029-002 | 9164    | F | 43 | Riza 10 mg | 21  | Bradycardia            | 8.8 Hours | Mild     | No  | Probably     | Yes |

|         |      |   |    |            |     |                        |           |          |     |                |     |
|---------|------|---|----|------------|-----|------------------------|-----------|----------|-----|----------------|-----|
| 029-007 | 9317 | M | 31 | Riza 10 mg | 69  | Vomiting               | 1.5 Hours | Severe   | No  | Probably not   | Yes |
| 029-011 | 9475 | F | 33 | Riza 10 mg | 76  | Nausea                 | 11 Hours  | Moderate | No  | Probably       | Yes |
|         |      |   |    |            | 76  | Headache               | 11 Hours  | Moderate | No  | Probably       | Yes |
|         |      |   |    |            | 76  | Asthenia/ fatigue      | 11 Hours  | Moderate | No  | Probably       | Yes |
|         |      |   |    |            | 76  | Vertigo                | 11 Hours  | Moderate | No  | Probably       | Yes |
|         |      |   |    |            | 76  | Abnl Breathing pattern | 11 Hours  | Moderate | No  | Probably       | Yes |
| 029-026 | 9968 | F | 45 | Riza 10 mg | 110 | Pulmonary infarct      | 23 Days   | Severe   | Yes | Prob not       | No  |
| 029-031 | 0018 | F | 54 | Riza 10 mg | 12  | Pain, chest            | 3 Hours   | Moderate | No  | Probably       | Yes |
| 022-028 | 0168 | F | 30 | Std Care   | 86  | Trauma                 | 33 Days   | Severe   | No  | Definitely not | Yes |
| 022-042 | 5026 | F | 36 | Std Care   | 31  | Palpitation            | 2 Hours   | Moderate | No  | Probably       | Yes |
|         |      |   |    |            | 31  | Pain, chest            | 2 Hours   | Moderate | No  | Probably       | Yes |
|         |      |   |    |            | 31  | Discomfort, pharyngeal | 2 Hours   | Moderate | No  | Probably       | Yes |
| 022-042 | 5049 | F | 42 | Std Care   | 38  | Somnolence             | 3 Hours   | Moderate | No  | Probably       | Yes |
| 022-042 | 5056 | F | 38 | Std Care   | 3   | Dizziness              | 2 Hours   | Severe   | No  | Probably       | Yes |
| 029-003 | 9357 | F | 47 | Std Care   | 33  | Vomiting               | 24 Hours  | Severe   | No  | Definitely not | Yes |

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**Appendix E - Laboratory Adverse Events in Phase 3 Studies**

**Table 98: LAE's in Acute Phase 3 Studies (ISS Table D-95, page D-311)**

| Lab Test               | Rizatriptan 5-mg Tablet<br>N=986 |   |     |     | Rizatriptan 10-mg Tablet<br>N=1224 |    |     |     | Placebo<br>N=606 |   |     |     | Sumatriptan 50 mg/100 mg<br>N=737 |   |     |     |
|------------------------|----------------------------------|---|-----|-----|------------------------------------|----|-----|-----|------------------|---|-----|-----|-----------------------------------|---|-----|-----|
|                        | N                                | n | %   | % R | N                                  | n  | %   | % R | N                | n | %   | % R | N                                 | n | %   | % R |
| <b>HEMATOLOGY</b>      |                                  |   |     |     |                                    |    |     |     |                  |   |     |     |                                   |   |     |     |
| Hemoglobin ↓           | 973                              | 0 | 0.0 | 0.0 | 1212                               | 0  | 0.0 | 0.0 | 598              | 1 | 0.2 | 0.0 | 728                               | 1 | 0.1 | 0.0 |
| Hemoglobin ↓           | 973                              | 0 | 0.0 | 0.0 | 1212                               | 1  | 0.1 | 0.0 | 598              | 1 | 0.2 | 0.0 | 728                               | 2 | 0.3 | 0.0 |
| Hematocrit ↑           | 971                              | 0 | 0.0 | 0.0 | 1206                               | 0  | 0.0 | 0.0 | 597              | 1 | 0.2 | 0.0 | 727                               | 1 | 0.1 | 0.0 |
| Hematocrit ↓           | 971                              | 1 | 0.1 | 0.0 | 1206                               | 1  | 0.1 | 0.0 | 597              | 1 | 0.2 | 0.0 | 727                               | 0 | 0.0 | 0.0 |
| Platelet count ↑       | 971                              | 0 | 0.0 | 0.0 | 1211                               | 0  | 0.0 | 0.0 | 595              | 1 | 0.2 | 0.2 | 724                               | 0 | 0.0 | 0.0 |
| Platelet count ↓       | 971                              | 0 | 0.0 | 0.0 | 1211                               | 0  | 0.0 | 0.0 | 595              | 2 | 0.3 | 0.2 | 724                               | 1 | 0.1 | 0.0 |
| Leukocytes ↑           | 973                              | 1 | 0.0 | 0.0 | 1211                               | 0  | 0.0 | 0.0 | 598              | 0 | 0.0 | 0.0 | 728                               | 1 | 0.1 | 0.1 |
| Leukocytes ↓           | 973                              | 2 | 0.2 | 0.0 | 1211                               | 6  | 0.5 | 0.3 | 598              | 2 | 0.3 | 0.3 | 728                               | 1 | 0.1 | 0.1 |
| % Neutrophils ↑        | 969                              | 0 | 0.0 | 0.0 | 1202                               | 2  | 0.2 | 0.0 | 595              | 0 | 0.0 | 0.0 | 720                               | 0 | 0.0 | 0.0 |
| % Neutrophils ↓        | 969                              | 2 | 0.2 | 0.2 | 1202                               | 2  | 0.2 | 0.1 | 595              | 1 | 0.2 | 0.0 | 720                               | 0 | 0.0 | 0.0 |
| % Monocytes ↑          | 969                              | 0 | 0.0 | 0.0 | 1202                               | 1  | 0.1 | 0.0 | 595              | 0 | 0.0 | 0.0 | 720                               | 0 | 0.0 | 0.0 |
| % Lymphocytes ↑        | 969                              | 3 | 0.3 | 0.2 | 1202                               | 2  | 0.2 | 0.0 | 595              | 0 | 0.0 | 0.0 | 720                               | 0 | 0.0 | 0.0 |
| % Lymphocytes ↓        | 969                              | 0 | 0.0 | 0.0 | 1202                               | 2  | 0.2 | 0.1 | 595              | 0 | 0.0 | 0.0 | 720                               | 0 | 0.0 | 0.0 |
| % Eosinophils ↑        | 969                              | 0 | 0.0 | 0.0 | 1202                               | 3  | 0.2 | 0.2 | 595              | 0 | 0.0 | 0.0 | 720                               | 2 | 0.3 | 0.1 |
| HIV Positive           | 1                                | 1 | -   | -   | -                                  | -  | -   | -   | -                | - | -   | -   | -                                 | - | -   | -   |
| <b>BLOOD CHEMISTRY</b> |                                  |   |     |     |                                    |    |     |     |                  |   |     |     |                                   |   |     |     |
| Alkaline phosphatase ↑ | 970                              | 1 | 0.1 | 0.1 | 1198                               | 0  | 0.0 | 0.0 | 599              | 3 | 0.5 | 0.5 | 725                               | 1 | 0.1 | 0.0 |
| Serum bilirubin ↑      | 970                              | 0 | 0.0 | 0.0 | 1198                               | 1  | 0.1 | 0.0 | 598              | 1 | 0.2 | 0.0 | 725                               | 0 | 0.0 | 0.0 |
| SGOT (AST) ↑           | 974                              | 4 | 0.4 | 0.2 | 1213                               | 8  | 0.7 | 0.2 | 600              | 4 | 0.7 | 0.5 | 729                               | 6 | 0.8 | 0.7 |
| SGPT (ALT) ↑           | 972                              | 5 | 0.5 | 0.2 | 1212                               | 12 | 1.0 | 0.4 | 600              | 4 | 0.7 | 0.5 | 729                               | 5 | 0.7 | 0.7 |
| Cholesterol ↑          | 126                              | 0 | 0.0 | 0.0 | 495                                | 1  | 0.2 | 0.0 | 208              | 1 | 0.5 | 0.5 | 16                                | 0 | 0.0 | 0.0 |
| BUN ↑                  | 485                              | 0 | 0.0 | 0.0 | 348                                | 2  | 0.6 | 0.0 | 216              | 0 | 0.0 | 0.0 | 36                                | 0 | 0.0 | 0.0 |

| Lab Test                       | Rizatriptan 5-mg Tablet<br>N=986 |   |     |     | Rizatriptan 10-mg Tablet<br>N=1224 |   |     |     | Placebo<br>N=606 |   |     |     | Sumatriptan 50 mg/100 mg<br>N=737 |   |     |     |
|--------------------------------|----------------------------------|---|-----|-----|------------------------------------|---|-----|-----|------------------|---|-----|-----|-----------------------------------|---|-----|-----|
|                                | N                                | n | %   | % R | N                                  | n | %   | % R | N                | n | %   | % R | N                                 | n | %   | % R |
| <b>BLOOD CHEMISTRY (Cont.)</b> |                                  |   |     |     |                                    |   |     |     |                  |   |     |     |                                   |   |     |     |
| Glucose ↑                      | 969                              | 0 | 0.0 | 0.0 | 1208                               | 2 | 0.2 | 0.0 | 600              | 0 | 0.0 | 0.0 | 726                               | 2 | 0.3 | 0.1 |
| Potassium ↑                    | 973                              | 0 | 0.0 | 0.0 | 1204                               | 1 | 0.1 | 0.0 | 598              | 0 | 0.0 | 0.0 | 724                               | 0 | 0.0 | 0.0 |
| Potassium ↓                    | 973                              | 2 | 0.2 | 0.1 | 1204                               | 1 | 0.1 | 0.0 | 598              | 1 | 0.2 | 0.0 | 724                               | 0 | 0.0 | 0.0 |
| Chloride ↑                     | 964                              | 0 | 0.0 | 0.0 | 1185                               | 1 | 0.1 | 0.0 | 467              | 0 | 0.0 | 0.0 | 702                               | 0 | 0.0 | 0.0 |
| <b>URINAL EXAM</b>             |                                  |   |     |     |                                    |   |     |     |                  |   |     |     |                                   |   |     |     |
| Protein                        | 935                              | 1 | 0.1 | 0.0 | 1186                               | 0 | 0.0 | 0.0 | 587              | 2 | 0.3 | 0.0 | 706                               | 1 | 0.1 | 0.1 |
| Glucose                        | 928                              | 0 | 0.0 | 0.0 | 1187                               | 1 | 0.1 | 0.0 | 585              | 0 | 0.0 | 0.0 | 703                               | 0 | 0.0 | 0.0 |
| RBCs                           | 399                              | 2 | 0.2 | 0.0 | 781                                | 6 | 0.8 | 0.0 | 550              | 1 | 0.2 | 0.0 | 96                                | 0 | 0.0 | 0.0 |
| Urine WBCs                     | 399                              | 2 | 0.2 | 0.0 | 781                                | 3 | 0.4 | 0.0 | 550              | 1 | 0.2 | 0.0 | 96                                | 0 | 0.0 | 0.0 |

Values do not equal a number of patients treated, as not all lab parameters were evaluated in each patient.  
 % R = Percent possibly, probably, or definitely drug related.

**Table 99: LAE's in Phase 3 Extension Studies (ISS Table D-97, page D-315)**

| Lab Test                 | Rizatriptan 5-mg Tablet<br>N=896 |    |     |     | Rizatriptan 10-mg Tablet<br>N=817 |    |     |     | Standard Care<br>N=328 |   |     |     |
|--------------------------|----------------------------------|----|-----|-----|-----------------------------------|----|-----|-----|------------------------|---|-----|-----|
|                          | N                                | n  | %   | % R | N                                 | n  | %   | % R | N                      | n | %   | % R |
| <b>HEMATOLOGY</b>        |                                  |    |     |     |                                   |    |     |     |                        |   |     |     |
| Eosinophils ↑            | 695                              | 0  | 0.0 | 0.0 | 816                               | 1  | 0.1 | 0.0 | 327                    | 2 | 0.6 | 0.0 |
| Hematocrit ↑             | 694                              | 1  | 0.1 | 0.0 | 815                               | 1  | 0.1 | 0.0 | 327                    | 0 | 0.0 | 0.0 |
| Hematocrit ↓             | 694                              | 1  | 0.1 | 0.0 | 815                               | 2  | 0.2 | 0.0 | 327                    | 1 | 0.3 | 0.0 |
| Hemoglobin ↑             | 694                              | 1  | 0.1 | 0.0 | 816                               | 0  | 0.0 | 0.0 | 327                    | 0 | 0.0 | 0.0 |
| Hemoglobin ↓             | 694                              | 1  | 0.1 | 0.0 | 816                               | 5  | 0.6 | 0.0 | 327                    | 4 | 1.2 | 0.0 |
| Lymphocytes % ↑          | 695                              | 1  | 0.1 | 0.0 | 816                               | 2  | 0.2 | 0.0 | 327                    | 0 | 0.0 | 0.0 |
| Lymphocytes % ↓          | 695                              | 0  | 0.0 | 0.0 | 816                               | 3  | 0.4 | 0.0 | 327                    | 1 | 0.3 | 0.0 |
| Monocytes % ↑            | 695                              | 0  | 0.0 | 0.0 | 816                               | 1  | 0.0 | 0.0 | 327                    | 1 | 0.3 | 0.0 |
| Platelet count ↑         | 694                              | 0  | 0.0 | 0.0 | 816                               | 0  | 0.0 | 0.0 | 327                    | 1 | 0.3 | 0.0 |
| Platelet count ↓         | 694                              | 1  | 0.1 | 0.1 | 816                               | 6  | 0.7 | 0.2 | 327                    | 0 | 0.3 | 0.0 |
| Neutrophils % ↑          | 695                              | 1  | 0.0 | 0.0 | 816                               | 2  | 0.2 | 0.0 | 327                    | 0 | 0.0 | 0.0 |
| Neutrophils % ↓          | 695                              | 0  | 0.0 | 0.0 | 816                               | 2  | 0.2 | 0.0 | 327                    | 1 | 0.3 | 0.0 |
| Leukocyte count ↑        | 694                              | 2  | 0.3 | 0.0 | 816                               | 3  | 0.4 | 0.0 | 327                    | 5 | 1.5 | 0.3 |
| Leukocyte count ↓        | 694                              | 2  | 0.3 | 0.1 | 816                               | 11 | 1.3 | 0.5 | 327                    | 0 | 0.0 | 0.0 |
| <b>BLOOD CHEMISTRY</b>   |                                  |    |     |     |                                   |    |     |     |                        |   |     |     |
| SGPT (ALT) ↑             | 696                              | 10 | 1.4 | 1.1 | 815                               | 21 | 2.6 | 1.2 | 328                    | 9 | 2.7 | 0.6 |
| SGOT (AST) ↑             | 696                              | 9  | 1.3 | 0.7 | 815                               | 18 | 2.2 | 1.1 | 328                    | 9 | 2.7 | 0.9 |
| Hepatitis C antibody     | 0                                | 0  | 0.0 | 0.0 | 1                                 | 1  | 100 | 0.0 | 0                      | 0 | 0.0 | 0.0 |
| Serum albumin            | 696                              | 0  | 0.0 | 0.0 | 815                               | 1  | 0.1 | 0.1 | 328                    | 0 | 0.0 | 0.0 |
| Alkaline phosphatase ↑   | 696                              | 2  | 0.3 | 0.3 | 814                               | 3  | 0.4 | 0.4 | 328                    | 1 | 0.0 | 0.3 |
| Serum β-HCG              | 405                              | 1  | 0.2 | 0.0 | 441                               | 0  | 0.0 | 0.0 | 180                    | 0 | 0.0 | 0.0 |
| Chloride ↑               | 695                              | 1  | 0.1 | 0.1 | 814                               | 0  | 0.0 | 0.0 | 328                    | 1 | 0.3 | 0.0 |
| Serum Creatinine ↑       | 696                              | 1  | 0.1 | 0.0 | 815                               | 0  | 0.0 | 0.0 | 328                    | 0 | 0.0 | 0.0 |
| Creatinine Phosphokinase | 0                                | 0  | 0.0 | 0.0 | 1                                 | 1  | 100 | 0.0 | 0                      | 0 | 0.0 | 0.0 |
| Serum GOT                | 0                                | 0  | 0.0 | 0.0 | 1                                 | 1  | 100 | 0.0 | 0                      | 0 | 0.0 | 0.0 |

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| Lab Test            | Rizatriptan 5-mg Tablet<br>N=696 |   |     |     | Rizatriptan 10-mg Tablet<br>N=817 |   |     |     | Standard Care<br>N=328 |   |     |     |
|---------------------|----------------------------------|---|-----|-----|-----------------------------------|---|-----|-----|------------------------|---|-----|-----|
|                     | N                                | a | %   | % R | N                                 | a | %   | % R | N                      | a | %   | % R |
| Serum Glucose ↑     | 696                              | 3 | 0.4 | 0.1 | 814                               | 2 | 0.2 | 0.0 | 328                    | 1 | 0.3 | 0.0 |
| Serum Glucose ↓     | 696                              | 1 | 0.1 | 0.0 | 814                               | 2 | 0.2 | 0.0 | 328                    | 2 | 0.6 | 0.0 |
| Potassium ↑         | 696                              | 0 | 0.0 | 0.0 | 813                               | 1 | 0.1 | 0.0 | 328                    | 0 | 0.0 | 0.0 |
| Potassium ↓         | 696                              | 1 | 0.3 | 0.0 | 813                               | 1 | 0.1 | 0.0 | 328                    | 0 | 0.0 | 0.0 |
| Sodium ↓            | 696                              | 1 | 0.1 | 0.0 | 815                               | 1 | 0.1 | 0.1 | 328                    | 0 | 0.0 | 0.0 |
| Total Cholesterol ↑ | 130                              | 0 | 0.0 | 0.0 | 126                               | 2 | 1.6 | 0.8 | 57                     | 1 | 1.8 | 0.0 |
| Protein ↑           | 0                                | 0 | 0.0 | 0.0 | 1                                 | 1 | 100 | 100 | 0                      | 0 | 0.0 | 0.0 |
| Total Bilirubin ↑   | 696                              | 3 | 0.4 | 0.1 | 815                               | 2 | 0.2 | 0.2 | 328                    | 1 | 0.3 | 0.3 |
| Triglycerides ↑     | 0                                | 0 | 0.0 | 0.0 | 1                                 | 1 | 100 | 100 | 0                      | 0 | 0.0 | 0.0 |
| TSH ↓               | 0                                | 0 | 0.0 | 0.0 | 1                                 | 1 | 100 | 100 | 0                      | 0 | 0.0 | 0.0 |
| T4 ↑                | 0                                | 0 | 0.0 | 0.0 | 1                                 | 1 | 100 | 100 | 0                      | 0 | 0.0 | 0.0 |
| T3 uptake ↓         | 0                                | 0 | 0.0 | 0.0 | 1                                 | 1 | 100 | 100 | 0                      | 0 | 0.0 | 0.0 |
| <b>URINALYSES</b>   |                                  |   |     |     |                                   |   |     |     |                        |   |     |     |
| Bacteria            | 372                              | 0 | 0.0 | 0.0 | 333                               | 3 | 0.6 | 0.0 | 209                    | 3 | 1.4 | 0.0 |
| Epithelial Cells    | 372                              | 3 | 0.8 | 0.0 | 333                               | 0 | 0.0 | 0.0 | 209                    | 0 | 0.0 | 0.0 |
| Urine Bilirubin     | 1                                | 0 | 0.0 | 0.0 | 1                                 | 1 | 100 | 0.0 | 0                      | 0 | 0.0 | 0.0 |
| Urine Blood         | 127                              | 3 | 2.4 | 0.0 | 125                               | 0 | 0.0 | 0.0 | 61                     | 0 | 0.0 | 0.0 |
| Urine Cast          | 372                              | 1 | 0.3 | 0.0 | 333                               | 0 | 0.0 | 0.0 | 209                    | 0 | 0.0 | 0.0 |
| Urine Glucose       | 672                              | 0 | 0.0 | 0.0 | 791                               | 1 | 0.1 | 0.0 | 317                    | 0 | 0.0 | 0.0 |
| Urine Protein       | 676                              | 6 | 0.9 | 0.0 | 794                               | 2 | 0.2 | 0.0 | 317                    | 2 | 0.6 | 0.0 |
| Urine RBCs          | 372                              | 3 | 0.8 | 0.0 | 333                               | 6 | 1.1 | 0.0 | 209                    | 3 | 1.4 | 0.0 |
| Urine WBCs          | 372                              | 5 | 1.3 | 0.0 | 333                               | 6 | 1.1 | 0.0 | 209                    | 3 | 0.6 | 0.0 |

(N) varies and does not equal the number of patients treated because not all laboratory parameters were evaluated in each patient.  
 % R = Percent possibly, probably or definitely drug related.

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