The most common clinical adverse events (*i.e.*, those observed at incidences of ≥5%) in patients taking rizatriptan 10mg were dizziness, somnolence, and asthenia/fatigue. No AE's reached a ≥5% incidence in the rizatriptan 5mg treatment group.

8.5.3.2 AE's After Repeated Doses for Single Attack

In studies 022 and 025, patients were permitted to take up to 3 doses of study medication for treatment of up 2 two headache recurrences within 24 hours. In study 022, the second and third doses were identical, and were randomized to either a repeat of the first dose (5mg or 10mg), or placebo. In study 025, patients received a repeat of the first dose (10mg or placebo) in a non-randomized schedule.

Table 72 (adapted from ISS Table D-79, page D-241) shows the incidence of AE's in patients exposed to the same dose for the initial attack and subsequent recurrence(s). It does not include all patients in all studies, since not all patients took a recurrent dose, and not all patients took the same dose on each occasion.

The patients who took a second or third dose are not a randomized sample, since they are conditional upon responding and then getting a recurrence after the first dose. For rizatriptan 5mg, the incidence of any AE was roughly the same whether a patient took 1, 2, or 3 doses (32%, 37%, 33%, respectively). Patients who took rizatriptan 10mg generally had more AE's with 2 or 3 doses compared to those who took only one dose (43%, 55%, 51%, for 1, 2, 3 doses, respectively). In general, taking 2 doses was associated with more AE's than taking 3 doses and this was true of placebo patients as well.

Table 72: Adverse Events (≥1%) in Phase 3 Controlled Trials, After Multiple Doses

	% of Patients Reporting											
	Rizatriptan 5 mg Tablet Dose				Rizatriptan 10 mg Tablet Dose				Placebo Dose			
Number of Doses	1	2	3	Any	1	2	3	Any	1	2	3	Any
Total Patients	**144**	**54**	**24**	**222**	**337**	**142**	**73**	**552**	**65**	**14**	**4**	**83**
% with any AE	32	37	33	33	43	55	51	47	23	50	25	28
Dizziness	4	6	0	4	9	11	7	9	5	14	0	6
Somnolence	5	4	0	4	9	10	12	10	3	14	0	5
Nausea	8	4	8	7	6	11	7	7	3	7	0	4
Asthenia/ fatigue	1	2	0	1	6	11	6	7	0	7	0	1
Pain, chest	2	2	4	2	4	4	4	4	2	0	0	1
Paresthesia	4	2	0	3	4	6	4	4	0	0	0	0
Headache	1	4	0	2	3	4	1	3	0	7	0	1
Dry mouth	5	2	4	4	3	5	7	4	0	7	0	1
Hypesthesia	0	2	0	<1	2	<1	0	1	2	0	0	1
Vomiting	4	2	0	3	2	2	8	3	2	7	0	2
Tachycardia	0	0	0	0	2	0	3	1	0	0	0	0
Tightness, regional	1	0	0	<1	2	<1	1	1	0	0	0	0
URI	1	0	4	1	2	3	0	2	3	0	0	2
Pain, abdominal	3	4	0	3	2	1	3	2	0	0	0	0
Mental acuity dec.	0	0	0	0	2	1	3	2	3	0	0	2
Euphoria	0	0	0	0	1	<1	0	<1	0	0	0	0

Dyspnea	0	0	4	<1	1	1	0	1	0	0	0	0
Flushing	<1	2	0	<1	1	1	3	1	2	0	0	1

8.5.3.3 AE's After Treatment of up to Four Attacks

Study 025 allowed for treatment of up to 4 consecutive migraine attacks with either rizatriptan 10mg or placebo. Each attack could be treated with up to three doses of study medication within 24 hours for recurrent headache. The average time interval between attacks was 13.1 days (±14.7 days).

Adverse events were counted and tabulated in two ways. The incidence for the term "All Attacks" represents all patients who experienced the event. For example, if a patient experienced drowsiness during any attack, then that patient is counted once towards the incidence of drowsiness. The incidence for "All Attacks Corrected" is based on the number of attacks in which a particular AE is observed in a particular patient divided by the total number of attacks treated. For example. If a patient experienced drowsiness during two attacks but not during the other two, then the incidence for drowsiness for that patient is 0.5. These corrected terms are added and then divided by the total number of patients on rizatriptan 10mg to provide a corrected incidence for comparison to placebo, which was used to treat only one attack.

The incidence of selected AE's (≥5% incidence plus chest pain) is shown in Table 73 (adapted from ISS Table D-81, page D-248, and Ref. 21, Study Report 025, Table 44, page 8635). The most common AE's seen are similar to those seen in single attack analyses.

The absolute, unadjusted incidences are higher than those seen after single attacks, as would be expected since multiple exposures allow multiple opportunities for the adverse event to occur (comparison with Rizatriptan 10mg column in Table 70, page 74), however the adjusted incidences are comparable. Chest pain still occurs at a rate substantially higher than placebo, even when adjusted for number of attacks treated.

*Table 73: Selected AE's During Treatment of Multiple Attacks (Study 025)**

	All Attacks		
Adverse Experience	Unadjusted for Exposure Riza 10 mg (N= 395)	PBO (N= 289)	Adjusted Riza 10 mg (N= 395)
% with any AE	61	25	61
Somnolence	14	5	7
Dizziness	15	4	7
Nausea	10	3	5
Asthenia/ fatigue	8	0.7	4
Chest Pain	3.8	0.7	2

* ≥5% incidence plus chest pain

8.5.4 AE's During Long Term Extensions

I discuss the long-term safety of rizatriptan in section 8.9, "Long-Term Safety" page 90. The most common AE's (≥5%) are listed below. This table is an exact copy of Table 84, page 91.

Table 74: Common AE's (≥5%) in Long-Term Extensions

nausea
dizziness
somnolence
asthenia/fatigue
chest pain
vomiting
diarrhea
headache
paresthesias
pharyngeal discomfort

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8.5.5 Common and Drug-Related Side Effects

The common and drug related side effects of rizatriptan are similar to those seen with other $5HT_{1D}$ agonists. The most common clinical adverse events (*i.e.*, those observed at incidences of ≥5%) in patients taking rizatriptan 10mg were dizziness, somnolence, and asthenia/fatigue. No AE's reached a ≥5% incidence in the rizatriptan 5mg treatment group.

In addition to these events, chest pain, vomiting, diarrhea, headache, paresthesias, and pharyngeal discomfort were commonly reported (≥5%) by patients in long term extensions (see section 8.9, page 90).

8.6 Laboratory Findings

APPEARS THIS WAY ON ORIGINAL

8.6.1 Extent of Laboratory Testing During Development

Laboratory measurements (hematology, chemistry, urinalysis) were done at baseline and at regular intervals. The earlier inpatient studies allowed collection of laboratory data shortly after dosing (within 24 hours). In the controlled phase 3 studies, lab tests were collected at screening (up 2 two months before treatment) and at post-study (within 7 days). In the case of study 025 where 4 attacks were treated, monthly lab tests were performed between attacks 1-4 if such an interval between headaches existed. The post-study lab assessment in all phase 3 controlled trials served as the baseline measurement for the extension phase. Lab data were collected during the long term extension studies at roughly 1-2 month intervals, although the actual schedule varied by protocol.

The laboratory analyses were performed locally in phase 1 studies and in Phase 2/3 studies done outside the United States. Those samples collected in Phase 2/3 studies in the U.S. were analyzed at a central laboratory (Corning SciCor). Lab abnormalities were classified by individual investigators as "laboratory

adverse experiences (LAE's)." These are reviewed in detail below. FDA Table 75 lists the extent of laboratory testing during Maxalt development.

Table 75: Extent of Laboratory Testing

	Total	Rizatriptan	Placebo	Other*
Phase 1	406	285	121	
Phase 2	1137	961	87	89
Phase 3 (Acute)	3553	2210	606	737
Phase 3 (Long-Term)	1841	1513		328

* Sumatriptan or Standard Care

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8.6.1.1.1 PHASE 1

In phase 1 studies, 21 out of 285 subjects (7%) on rizatriptan tablets and 12 out of 121 subjects (10%) on placebo had one or more laboratory adverse event. The abnormalities reported for phase 1 patients are listed in FDA Table 76. Not all patients in all studies had the same lab tests recorded at all times, which explains why the denominator changes. There were no clinically substantial differences between the two groups.

Table 76: Laboratory Adverse Events in Phase 1 Studies

	Rizatriptan	Placebo
Dec. Hematocrit	10/277 (3.6%)	4/121 (3.3%)
Dec. WBC	4/277 (1.4%)	0
Inc. AST	3/278 (1.1%)	2/121 (1.7%)
Inc. ALT	0	1/99 (1.0%)
Dec. Hemoglobin	3/277 (1.1%)	2 (1.7%)
Inc. Glucose	0	1/90 (1.1%)

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8.6.1.1.2 PHASE 2

The number of patients in phase 2 studies with LAE's were generally low and comparable for rizatriptan, sumatriptan, and placebo. Ten (10) patients on rizatriptan (10/961, 1%), two patients on placebo (2/87, 2.3%), and six patients on sumatriptan (6/89, 6.7%) reported LAE's. None were serious and none led to discontinuation. The rates of reporting among the three groups fail to suggest that LAE's are increased in patients taking rizatriptan.

The most common abnormalities reported on rizatriptan were decreased WBC in 3 patients, increased ALT in 2 patients, and increased eosinophils in 2 patients. The WBC abnormalities were noted in three patients who had post-treatment (day 4, 4, 3, respectively) values of 2600, 3360, and 3200. No additional follow-up information was available for the first two patients, but the third patient had a normal WBC count one month after treatment of 5670.

8.6.1.1.3 PHASE 3 (ACUTE)

One or more LAE occurred in 62 out of 2210 patients (2.8%) on rizatriptan (17/986, 2% on rizatriptan 5mg, and 45/1224, 3.7% on rizatriptan 10mg), compared with 15/606 or 2.5% on placebo and 17/737 or 2.3% on sumatriptan. Because patients in study 025 took multiple doses of rizatriptan and had multiple

laboratory assessments, the opportunity to report and detect an abnormality was increased in this group.

None of the LAE's were serious nor did any result in a discontinuation. The most common LAE's reported were ALT/AST increases. The incidences of LAE's due hepatic enzyme elevations were in the rizatriptan treated patients, whereas they were 0.7% in both placebo and sumatriptan indicating they were comparable in all groups.

As in phase 1 studies, a small number (2/973, or 0.2% on rizatriptan 5mg, and 6/1211, or 0.5% on rizatriptan 10mg) reported LAE's due to decreased WBC count. The incidences for placebo and sumatriptan were 2/598 (0.3%) and 1/737 (0.1%), respectively. A list of the rizatriptan associated WBC LAE's are shown in sponsor Table 77 (ISS Table D-96, page D-313). Follow-up WBC were reported for only 2 of the rizatriptan patients (6058 and 6057) and both were normal.

The other LAE's reported in acute phase 3 studies occurred in very small numbers and were comparable among all other treatment groups. A complete listing of LAE's reported in phase 3 studies is listed in Appendix E, page 148.

Table 77: Laboratory Adverse Events associated with Decreased WBC (Phase 3-Acute)

Dose	Alloc No.	Study No.	Baseline Value $10^3/mm^3$	Laboratory Adverse Experience Value $10^3/mm^3$
Rizatriptan 5 mg	4248	022- 008	4.33	
Rizatriptan 5 mg	4604	022- 019	4.72	
Rizatriptan 10 mg	6058	025- 003	7.82	
Rizatriptan 10 mg	6057	025- 003	6.78	
Rizatriptan 10 mg	6022	025- 002	5.14	
Rizatriptan 10 mg	4385	022- 013	3.88	
Rizatriptan 10 mg	7563	030- 032	4.20	
Rizatriptan 10 mg	6043	025- 003	11.51	

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8.6.1.1.4 PHASE 3 EXTENSIONS

Of the patients who had laboratory tests in phase 3 extensions studies, 696 received rizatriptan 5mg, 817 received rizatriptan 10mg, and 328 received "standard care" (often sumatriptan).

The number of LAE's reported were generally low and comparable among all three groups. Laboratory adverse events were reported in 37 (5%) patients who treated 16,250 attacks with rizatriptan 5mg, 76 (9%) of patients who treated 24,043 attacks with rizatriptan 10mg, and in 27 (9%) patients who treated 8.126 attacks with standard care. This indicates there is little evidence that long term use of rizatriptan leads to an increased in LAE's compared to standard therapy.

A complete listing of LAE's reported in phase 3 extension studies is listed in Appendix E, page 148.

The most common LAE reported was elevated liver enzymes (ALT and/or AST) which was present in 1.4%, 2.6%, and 2.7% in the 5mg, 10mg, and standard care group, respectively. Decreased WBC counts were seen in 0.3%, 1.3%, and 0%, respectively. I reviewed individual cases and in the patients either had low WBC at baseline, had normal follow-up labs, or the actual WBC count reported was normal but the investigator reported it as an LAE for other reasons. None were serious.

Although not reported as a LAE, a 57 y/o male patient with prostatitis also being treated with rizatriptan developed agranulocytosis secondary to an immune reaction to sulfonamides. This case was reported as a serious adverse event and I reviewed it on page 70 of this review (Serious Adverse Events in Phase 3 Extensions). The agranulocytosis was not reasonably related to rizatriptan use.

8.6.1.2 Dropouts for Laboratory Abnormalities

A total of seven individuals were discontinued due to a laboratory abnormality. Two were in phase 1 studies and the patients did not receive rizatriptan (placebo, and propranolol 240mg). The remaining 5 patients were enrolled in phase 3 extensions. Four of the five were on rizatriptan and the fifth was on standard care. The patient on standard care experienced elevated AST/ALT. The four patients on rizatriptan experienced decreased WBC (1), elevated AST/ALT (3, one of which was hepatitis C antibody positive). These numbers are very small and it appears unlikely that rizatriptan use leads to increased dropouts due to laboratory abnormalities.

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8.6.2 Summary

In conclusion, rizatriptan use appears not to have any clinically relevant effect on clinical laboratory parameters.

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8.7 Vital Signs

The sponsor analyzed blood pressure and heart rate abnormalities. They did not analyze temperature and respiratory rates.

8.7.1 Blood Pressure

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The clinical pharmacology studies provide the best insight on the effects of rizatriptan on vital signs since many of these studies took vital signs measurements shortly after dosing. The best study to review is study 035 (N=36), which I briefly mentioned in section 6.7.1 Blood Pressure and Heart Rate, page 19. Study 035 is informative because it exposed healthy volunteers to the maximum recommended dose of rizatriptan, 10mg orally every 2 hours for three doses on four consecutive days. Vital signs were measured at baseline, 30 minutes, and every hour for six hours. On the last day, additional vital sign measurements at 7, 8, 10, 2, 16, and 24 hours were recorded. There was no significant change in systolic blood pressure seen between treatment and

placebo. However, diastolic blood pressures did increase a maximum of 4.7 mm Hg for the rizatriptan group compared to placebo. This was statistically significant and most notable on days 1 and 2 of the four day multiple dose period.

Higher increases in diastolic blood pressure were seen in other clinical pharmacology studies (10-15mm Hg) but at higher doses not recommended for marketing (60mg).

The phase 2 and phase 3 studies are less helpful since vital signs measurement were performed, in most cases, several days after the last dose of study medication was taken. In these studies, the sponsor used the Agency's recommended cutoffs for reporting a clinically significant change in blood pressure. This was defined as a diastolic blood pressure ≥105mm with a ≥15mm increase from baseline or a ≤50mm with a ≤15mm decrease from baseline. For systolic BP, the cutoffs were ≥180mm increase with ≥20mm increase from baseline or a SBP ≤90mm and ≤20mm decrease from baseline.

8.7.1.1 Diastolic Blood Pressure

In phase 2 studies, five patients had clinically significant decreases in diastolic blood pressure. Four took rizatriptan 10mg and 1 took placebo. No clinically significant increases in DBP were seen in any patient in phase 2 studies.

In phase 3 acute studies, the number of patients with significant DBP increases were: 2/975 (0.2%) on rizatriptan 5mg, 1/1228 (0.1%) on rizatriptan 10mg, and 1/384 (0.3%) on sumatriptan 100mg. The two patients on rizatriptan 5mg had elevations from 75mm to 110mm. The 1 patient on rizatriptan 10mg had an elevation from 90mm to 100mm.

Clinically significant decreases in diastolic BP were seen in 5/975 (05%) on rizatriptan 5mg, and 1/1228 (0.1%) on rizatriptan 10mg.

In phase 3 extensions, 3/550 (0.5%) patients on rizatriptan 5mg, 1/675 (0.1%) on rizatriptan 10mg, and 2/260 (0.8%) patients on standard care had significant increases in DBP. Significant decreases in DBP were seen in 3 (0.5%), 9 (1.3%), and 4 (1.5%) patients on 5mg, 10mg, and standard care, respectively. None was considered an adverse experience by investigators.

8.7.1.2 Systolic Blood Pressure

In phase 2 studies, no patients had clinically significant increases in systolic blood pressure (SBP). A significant drop in SBP was seen in 1 out of 187 (0.5%) patients on rizatriptan 10mg. This was a drop from 140mm to 92mm and was asymptomatic and not serious.

In phase 3 acute studies, no patients had clinically significant increases in SBP. A clinically significant drop in SBP was seen in 5/975 patients on 5mg, 5/1228 patients on rizatriptan 10mg, and 1/547 patients on placebo. None was seen in the sumatriptan patients. All were asymptomatic and not serious.

In phase 3 extensions, clinically significant increases were seen in 5/550 patients (0.9%) on 5mg, and 1/765 (0.1%) on rizatriptan 10mg. None was observed in the 260 patients on standard care. Clinically significant drop in SBP was seen in 9/550 (1.6%) on 5mg, 22/675 (3.3%) on 10mg and 9/260 (3.5%) on standard care. None of these cases was serious and all were asymptomatic.

8.7.2 Heart Rate

Clinically significant changes in pulse were defined as ≥120/min and ≥15/min increase from baseline or ≤50/min and ≤15/min decrease from baseline. The sponsor only analyzed heart rate in the phase 3 studies.

In the phase 3 acute studies, a significant increase in heart rate was seen in only 1 out of 1228 (0.1%) patients on rizatriptan 10mg. No significant increases were seen with 5mg, placebo, or sumatriptan. Significant decreases in heart rate were seen in 1/547 (0.2%) patients on placebo, 1/355 (0.3%) on sumatriptan 50mg, and 2/385 (0.5%) on sumatriptan 100mg. None was accompanied by clinical symptoms. In the phase 3 extensions, a significant increase in heart rate was seen in 2/675 (0.3%) patients on 10mg and in none of the patients on standard care or 5mg. Significant decreases were seen in 2/550 (0.4%) of patients on 5mg, 2/675 (0.3%) on 10mg, and 4/260 (1.5%) on standard care. All were asymptomatic and none was serious.

8.7.3 Other Analysis - Pooled Vital Sign Data from Studies 029, 030

As a separate analysis, I pooled vital signs data from studies 029 and 030 to evaluate blood pressure and heart rate. I did not use data from 022 and 025 since in those studies, patients took both drug and placebo and it's difficult to sort out which vital signs measurement is associated with which treatment.

The data recorded baseline BP and HR measurements, along with any post-treatment values. The sponsor also provided a change from baseline for each variable. I analyzed all post-treatment change from baseline values. These are displayed in FDA Table 78. The post-treatment changes seen in all dose groups were very small. SBP went up with rizatriptan 10mg and down with placebo, but the pairwise comparison was not significant (p=0.26, t-test). Similarly, the changes seen between placebo and rizatriptan 10mg in diastolic BP and heart rate were not significant, (p=0.12, and p=0.43, respectively). The changes seen were also similar in the sumatriptan treated patients.

Table 78: Vital Signs - Changes from Baseline in Studies 029 and 030

Rx*	Measure-ments	Δ in SBP		Δ in DBP		Δ in HR	
		Mean	SD	Mean	SD	Mean	SD
PBO	347	-0.59	8.23	-0.70	6.94	-0.55	8.93
5	752	-1.00	10.18	-0.41	7.63	0.22	8.26
10	538	0.27	10.24	0.28	8.27	0.04	9.29
50	512	-0.88	8.90	-0.54	6.33	0.86	8.36
100	546	-0.10	9.71	0.39	8.29	0.09	7.88

* 5, 10 represent rizatriptan 5mg, 10mg; 50 and 100 represent sumatriptan 50mg, 100mg

8.7.4 Summary

In summary, treatment with rizatriptan 10mg is associated with a slight increase (<5mm) in diastolic blood pressure when three doses were given two hours apart to normal healthy volunteers. In clinical trials, rizatriptan 5mg and 10mg did not appear to cause any clinically significant changes in blood pressure and heart rate when measured several days post-treatment.

8.8 ECG

ECG's were routinely obtained during the rizatriptan clinical development program. As is the case with the laboratory and vital signs data, ECG's obtained during the phase 3 program were usually performed many days after the last dose of medication. The best ECG data come from earlier inpatient studies which recorded ECG's within the first few hours of treatment. The phase 2 study 020 was an inpatient cardiovascular safety study in 157 patients and provides the best ECG data. I review this study below. I also discuss ECG adverse events seen throughout rizatriptan clinical development. Finally, I analyze ECG data in all ECG's recorded in study 030.

8.8.1 Study 020 - Inpatient ECG Study

This was an inpatient cardiovascular safety study in 115 young and elderly (56-75) migraineurs. Each received oral rizatriptan 10mg or placebo. A second randomized dose of 10mg or placebo was given after 2 hours. The primary safety endpoint was ECG evidence of myocardial ischemia.

Patients underwent single lead telemetry between 0-6 hours. The monitor was checked at least every 15 minutes for ST or other changes. It included an alarm for heart rate <60 or >100. Twelve lead ECG's were obtained every fifteen minutes until 2.5 hours, every 30 minutes until 4 hours and every hour until 6 hours. Vitals signs were recorded every 30 minutes until 4 hours and every hour until 6 hours. Post-study ECG, vital signs were recorded 2-4 days after dosing.

One hundred fifty-seven (157) patients received study medication and were included in the safety analysis. There were 132 patients in the young group, with a mean age of 37.4 years. Of these, 99 received 10mg and 33 received placebo as the initial dose. In the elderly group, 25 patients had a mean age of 61.8 years. Among them, 20 received 10mg and 5 received placebo. The youngest patient in the study was 18 and the oldest was 72. Eighty-three (83%) were female. The majority, 90%, were Caucasian. About two-thirds had a moderate headache at baseline (grade 2).

Overall, 11 patients, 7 in the young group and 4 in the elderly group, had ECG adverse experiences during the study. Nine of these occurred in the rizatriptan 10mg group (5 or 5.1% in the young group, and 4 or 20% in the elderly group). Of these 9 AE's, 5 occurred prior to the second dose and 4 after the second dose. Eight of the 9 were considered drug related.

One of the 9 AE's was considered serious and 2 patients discontinued due to ECG adverse experiences.

In the placebo group, there were 2 ECG related AE's (6.1% for the young group, 5.3% for the total patient population). One occurred prior to and one after the second dose. They were both considered drug related. One patient discontinued due to the ECG adverse experience.

The ECG adverse experiences are listed in sponsor Table 79 (Study Report, 020, Table 5, page 5991). The serious adverse event occurred in patient 2051 and is described below.

Table 79: Study 020 - ECG Adverse Experiences

Allocation Number	Age	Sex	Time of AE*	Adverse Experience	Drug Related	Discontinued
Rizatriptan						
Young Patients						
2002	29	F	Post	T- wave abnormality	Possibly	No
2007	46	F	Post	T- wave flat	Possibly	No
2018	26	M	Post	P- wave abnormality	Possibly	No
2026	43	F	Pre	PVCs	Def not	Yes
2051	26	M	Pre	Sinus tachycardia	Definite	Yes
				Supraventricular tachycardia	Definite	
				ECG abnormality	Definite	
Elderly Patients						
3041	56	F	Pre	Tachycardia	Possibly	No
3009	72	F	Post	Premature atrial contraction	Probably	No
				Tachycardia		
3010	68	F	Pre	Sinus bradycardia	Possibly	No
3012	57	F	Pre	PVCs	Possibly	No
Placebo						
Young Patients						
2006	25	F	Post	T- wave flat	Possibly	No
2065	34	F	Pre	T- wave inversion	Probably	Yes

* in relation to the second dose at 2 hours

The incidence of ECG adverse events was similar in both treatment groups: 9/119 or 7.6% for rizatriptan and 2/38 or 5.3% for placebo, although the numbers are fairly small. There were no ECG evidence of definite myocardial ischemia in any patient, however there was one case of "possible ischemia" which is the serious adverse event describe below.

The serious adverse event occurred in patient 2051. This was a 26 y/o male with a history of moderate to severe migraine headaches. His baseline ECG was normal except for sinus bradycardia and nonspecific T wave abnormality. He had no history and no family history of cardiovascular disease.

He reported for treatment in the study after the onset of a severe migraine attack. He was randomized and received rizatriptan 10mg at 9AM. The pre-dosing ECG was unchanged from screening. Twelve lead ECG's were unchanged from baseline through 90 minutes. He then developed mild chest discomfort described as "pulse like sensations" and tachycardia. Heavy respirations were observed. Vital signs were normal . An ECG showed regular sinus rhythm, moderate right axis deviation and nonspecific T wave abnormality. The symptoms resolved within a few minutes. Oxygen was given at 5L by nasal cannula. Because of the chest pain, he was not given the second dose at 11AM. At 11:10AM he experienced a one minute episode of sinus tachycardia with intermittent hyperventilation. Blood pressure and respiration were normal. Between 11:10AM and 1:05PM, the following were observed:

- 11:30AM: left arm pain, intermittent chest tightness, heavy sighs, normal vital signs.
- 11:45AM: moderate headache, normal BP, heart rate normal respiration. Toradol 10mg was given for headache recurrence.
- 12:00 PM: mild chest discomfort, left arm tingling, vital signs normal except heart rate
- 12:30 PM: mild chest discomfort continues. Cardiac monitor showed sinus bradycardia of with nonspecific conduction delay, nonspecific T wave abnormality.
- 12:40 PM: severe chest pain reported, left arm tingling, heart rate BP with
- 12:42 PM: heart rate dropped
- 12:45 PM: intermittent moderate to severe chest pain with increased heart rate to lasting 30 seconds.
- 1:00 PM: continued mild chest discomfort, felt to be musculoskeletal. Vital signs BP heart rate , respirations
- 1:05 PM: severe chest pain lasting 5 minutes. Heart rate was with sinus tachycardia and supraventricular tachycardia. At 1:10PM, BP remained normal and heart rate was . Nitroglycerin was given with relief of chest pain. Oxygen was continued.
- 1:10-4:30 PM: no recurrence of chest pain, vitals remained stable. Tylenol 500mg was given for discomfort.
- 4:30 PM: patient admitted to overnight cardiac care unit to rule out MI. Serial LDH and CK values remained in the normal range. ECG the next day showed sinus arrhythmia with a rate of

The cardiologist felt that, although the ECG changes did not meet the criteria for myocardial infarction, the 12 lead ECG's at 12:54, 1:05, 1:06, 2:51, 3:05 on the treatment day showed minor inferior ST-T wave changes consistent with "possible myocardial ischemia." The patient subsequently underwent a negative treadmill stress test up to a heart rate of 179 (93% predicted).

Three patients discontinued due to an ECG adverse event—two on rizatriptan and one on placebo. One was the patient just described above. The other rizatriptan patient discontinued due to premature ventricular contractions, which was not felt to be drug related, and the third (placebo) patient discontinued due to T wave inversion.

In summary, there was no evidence of definite myocardial ischemia in any patient in the study and the incidences of ECG adverse events were similar in both groups. However, there was one case of "possible myocardial ischemia" associated with chest pain in an otherwise healthy 26 y/o male who had no previous history of cardiovascular disease. It appears possible to this reviewer that rizatriptan may produce coronary vasospasm in some individuals.

8.8.2 Phase 1 ECG Adverse Events

A total of six (6) subjects in phase 1 studies had ECG adverse events (EAE's). Two patients experienced ECG adverse events (EAE's in study 038, the beta-blocker drug interaction study. Both were associated with rizatriptan 10mg (supraventricular tachycardia and 1st degree AV block. Two (2) other EAE's were reported in an i.v. rizatriptan study and are included here for completeness (supraventricular tachycardia and PVC). The remaining 2 patients did not take rizatriptan (propranolol, and placebo). None of the six EAE's was classified as serious.

8.8.3 Phase 2 ECG Adverse Events

There were 1095 patients who had post-treatment ECG's in phase 2 studies. ECG adverse events were observed in 1.2% of these patients. The incidence in rizatriptan treated patients was 1.3% (11/816) and in placebo patients was 1% (2/207). Except for patient AN 2051 from study 20 (described above in section 8.8.1, page 84) who experienced a serious EAE and resulted in an admission and discontinuation from the study, the EAE's reported were mostly common variants, nonspecific, of no clinical significance, were not serious, and were not accompanied with clinical cardiovascular signs or symptoms. The EAE's were not related to type or doses of study drug or duration of treatment.

8.8.4 Phase 3 (Acute Studies) ECG Adverse Events

There were 3,392 patients in acute phase 3 studies who underwent post-treatment ECG recordings. A total of 10 patients reported EAE's (0.3%). None was reported in patients taking rizatriptan 5mg or placebo. Eight of the 10 took rizatriptan 10mg (0.7%) or 8/1178) and the other 2 took sumatriptan 100mg (0.3% or 2/720). None of the EAE's on rizatriptan was serious and none resulted in discontinuation. Only one of the eight (AN 6128, Study 025) was considered possibly related to dosing with rizatriptan 10mg. The event was nonspecific QRS changes (early transition) and occurred in a 44 year old male. However, the finding was noted 118 days after the patient treated his first migraine with 10mg, therefore it is unlikely the EAE was drug related. The other seven patients were considered either "definitely not" or probably not" drug related by investigators.

Of the two patients on sumatriptan who experienced EAE's, neither was serious or caused discontinuation. The listing of all phase 3 EAE's are listed in sponsor Table 80 (ISS Table D-103, page D-335).

Table 80: Phase 3 (Acute) ECG Associated Adverse Events

	Study	PTID	Onset Day	Dose	Gen	Age	Disc ?	SAE ?	Causal	Event
Riza 10 mg	025	6138	44	10 mg	F	43	N	N	Probably not	Axis disturbance
Riza 10 mg	025	6137	103	10 mg	F	30	N	N	Probably not	Axis disturbance
Riza 10 mg	025	6128	119	10 mg	M	44	N	N	Possibly	Nonspecific QRS change
Riza 10 mg	022	4805	6	20 mg	F	40	N	N	Probably not	Nonspecific ST- T change
Riza 10 mg	022	4502	9	10 mg	F	37	N	N	Probably not	Premature ventricular contraction
Riza 10 mg	025	6378	21	20 mg	F	44	N	N	Probably not	Premature ventricular contractions, arrhythmia
Riza 10 mg	030	7253	4	10 mg	F	38	N	N	Definitely not	Premature atrial contraction
Riza 10 mg	030	8007	4	10 mg	F	61	N	N	Probably not	Sinus tachycardia
Suma 100 mg	030	7757	5	Suma 100 mg	F	19	N	N	Definitely not	Sinus tachycardia
Suma 100 mg	030	8099	8	Suma 100 mg	F	30	N	N	Possibly	Nonspecific ST- T change, possible cardiac ischemia,

8.8.5 Phase 3 (Extensions) ECG Adverse Events

A total of 1,769 patients in phase 3 extensions had one or more post-treatment ECG. Eighteen (18) patients experienced 19 EAE's. Of these 18, 2/663 (0.3%) were on rizatriptan 5mg, 13/788 (1.6%) were on rizatriptan 10mg, and 3/318 (0.9%) were on standard care. Three additional patients randomized to receive rizatriptan had minor EAE's prior to receiving any treatment in an extensions study.

Seven of the 18 EAE patients came from one center. This site, which only included patients on rizatriptan 10mg and standard care, was very conservative in its reporting and reported any minor change from baseline as "clinically significant" and as an ECG adverse event.

No EAE was considered serious. One patient on 10mg was discontinued due to a nonspecific T wave abnormality that occurred 2 days after treatment of a thirty third attack and was not considered to be drug related. Sponsor Table 81 (ISS Table D-104, page D-338) lists the 18 patients who experienced an ECG related adverse event in an extension study.

Table 81: Phase 3 (Extensions) ECG Adverse Events

	Study-Center	PTID	Onset Day	Attack No.	Dose	Gen.	Age	Disc ?	SAE ?	Causal	Event
Riza 5 mg	022-004	4103	4	59	5 mg	F	45	N	N	Possibly	Right bundle branch block
Riza 5 mg	029-013	9448	2	4	5 mg	F	52	N	N	Definitely not	Nonspecific QRS change
Riza 10 mg	022-030	5163	45	8	10 mg	M	41	N	N	Definitely not	Right bundle branch block
Riza 10 mg	022-036	5233	6	19	10 mg	M	28	N	N	Probably not	Right bundle branch block
Riza 10 mg	025-017	6338	10	8	10 mg	M	50	N	N	Probably not	Right bundle branch block
Riza 10 mg	025-015	6297	1	33	10 mg	F	42	N	N	Probably not	First degree AV block
Riza 10 mg	025-017	6329	2	44	30 mg	F	49	N	N	Possibly	First degree AV block
Riza 10 mg	025-001	6002	20	24	10 mg	F	30	N	N	Probably not	Sinus arrhythmia
Riza 10 mg	025-007	6122	1	1	10 mg	M	23	N	N	Possibly	Sinus arrhythmia
Riza 10 mg	025-007	6121	8	3	10 mg	F	41	N	N	Probably not	Axis disturbance
Riza 10 mg	025-007	6138	6	8	30 mg	F	43	N	N	Probably not	Axis disturbance
Riza 10 mg	025-017	6326	66	7	20 mg	F	33	N	N	Probably not	Axis disturbance
Riza 10 mg	025-003	6042	9	50	10 mg	F	37	N	N	Probably not	Prolonged QT interval
Riza 10 mg	025-014	6269	2	33	10 mg	M	55	Y	N	Probably not	T-wave abnormality
Riza 10 mg	025-015	6287	6	13	10 mg	F	45	N	N	Probably not	Left atrial hypertrophy
Standard Care	022-019	4594	14	20	1 dose	F	35	N	N	Possibly	Premature ventricular contraction
Standard Care	025-007	6130	1	0	1 dose	F	49	N	N	Probably not	T-wave abnormality
Standard Care	025-009	6161	1 10	0	2 doses	F	49	N	N	Probably not	AV conduction disorder, atrial disorder
Randomized but not treated											
Riza 10 mg	025-007	6128	27	1	None	M	44	N	N	Probably not	Arrhythmia
Riza 10 mg	025-007	6127	31	1	None	F	38	N	N	Probably not	Premature ventricular contractions
Riza 10 mg	025-007	6123	28	0	None	F	51	N	N	Probably not	Axis disturbance

8.8.6 ECG Analysis from Study 030

As an additional analysis, I chose to analyze the sponsor provided ECG data from study 030. Study 030 exposed patients to rizatriptan 5mg, 10mg, sumatriptan 100mg, and placebo. It has the advantage over studies 022 and 025 in that patients were either exposed to drug or placebo, therefore it is easy to associate any ECG changes with a particular treatment. Study 029 also has the same advantage except that only the low dose (5mg) was used and the sponsor did not provide that data. I did not feel a strong need to request it since we have data from 030.

In study 030, there were 1138 post-treatment ECG's in 1109 patients. Of these, 163 patients took placebo, 162 took 5mg, 390 took 10mg, and 394 took

sumatriptan 100mg. The ECG measurements recorded were atrial rate, ventricular rate, PR interval, QRS interval, QTc interval, axis, and all changes from baseline. An ECG interpretation is also included in text form. I analyzed all changes from baseline for the numerical parameters recorded according to treatment. The results are shown in FDA Table 82.

Table 82: Study 030 - Change from Baseline in Key ECG Parameters

Dose (mg)	No. ECG Tracings	Δ H.R. (bpm)	Δ PR (sec)	Δ QRS (sec)	QTc (sec)	Δ QTc (sec)	Δ Axis (deg)
0	166	0.31	-0.00025	0.001233	0.38	-0.00256	-0.33
5	166	0.66	-0.00134	-0.00088	0.38	-0.00158	0.57
10	404	-0.99	0.000937	-0.00053	0.38	0.000443	1.05
100*	402	-0.10	0.001591	-0.00034	0.38	0.003726	1.31

* sumatriptan 100mg

This analysis shows that there were no clinically significant systematic changes in post-treatment ECG parameters.

8.9 Long-Term Safety

Patients in studies 022, 025, and 029 were eligible to enter into long-term extension studies using open label treatment. A total of 1512 patients treated a total of 40,293 attacks with rizatriptan (5mg or 10mg), and 329 patients treated a total of 8126 attacks with standard care. Additional information regarding exposures to long-term therapy has already been discussed in section 5.1.7, "Exposures in Phase 3 Uncontrolled Studies," page 16.

A total of 695 patients treated an average of 23.4 headaches (approximately 16,250 attacks) each with rizatriptan 5mg, and 817 patients treated an average of 29.4 headaches each with rizatriptan 10mg (approximately 24,043 attacks. Patients in both treatment groups treated 25% of attacks with two doses, and 11% with three doses.

Table 93 below is a adapted from Table 14 on page 16 (ISS Table D-58, page D-169). It summarizes the number of patients exposed to rizatriptan and standard care. It only includes patients who had an average of ≥2 migraines per month, which explains why the numbers for the >0 months row are lower than the ones described above. It serves to show that the long-term extension program does meet and exceed ICH guidelines for long-term exposures. Six hundred thirty-five (635) patients experiencing ≥2 migraines/month were exposed to rizatriptan for at least six months, and 228 patients were exposed for over 12 months.

Table 83: Exposures in Open Label Extensions, by Dose and Time; ≥2 migraines/mo.

Extension (Months)	Rizatriptan 5mg N	Rizatriptan 10mg N	Total N	Standard Care N
>0	449	601	1050	215
≥6	245	390	635	140
≥12	93	135	228	59

On rizatriptan 5mg, rizatriptan 10mg, or standard care, 67, 80 and 78% of the patients had one or more adverse experiences, respectively.

The most common AE's (≥5%) were included those which were observed in acute studies: nausea, dizziness, somnolence, and asthenia/fatigue. In addition to these, chest pain, vomiting, diarrhea, headache, paresthesias, and pharyngeal discomfort were also reported by ≥5% of patients in extensions (Table 84).

Table 84: Common AE's (≥5%) in Long-Term Extensions

nausea
dizziness
somnolence
asthenia/fatigue
chest pain
vomiting
diarrhea
headache
paresthesias
pharyngeal discomfort

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In general, the incidence of most clinical AE's were higher by about threefold in the long-term extension compared with the acute studies. The types of individual AE's reported during long term therapy were similar to those in studies of individual attacks. The only new AE's not previously seen were dyspepsia, neck pain, stiffness, vertigo, nervousness, ataxia, pruritus, blurred vision, and thirst. The incidence of these events were generally one percent or less, without a clear dose-response relationship and equally present in patients on standard care. They are not likely drug related. No new serious AE's were reported in this population.

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8.10 Summary of Cardiovascular Safety Data

The cardiovascular safety data consist of data from adverse events, vital signs, and ECG. These have been reviewed separately in previous sections. As a member of the therapeutic class of $5HT_{1B/1D}$ agonists, rizatriptan has the potential to cause coronary vasospasm in humans and contribute, if not cause cardiovascular adverse events.

The actual cardiovascular safety data presented in the NDA have demonstrated the following:

1. Adverse Events: Chest pain does occur in patients with rizatriptan at an incidence higher than seen in placebo (acute phase 3 studies), although the incidence appears to be less than that seen with sumatriptan in these same studies. Chest pain was also one of the most commonly reported adverse events in phase three extensions (≥5%). There are no documented cases of definite myocardial ischemia or infarction.
2. Vital Signs: Rizatriptan appears to have little effect, if any, on heart rate or systolic blood pressure. However, diastolic pressure is increased mildly. In

one study, subjects taking rizatriptan 10mg orally every two hours experienced a <5mm increase in diastolic blood pressure on average.

3. ECG: There was one document serious adverse event with ECG changes consistent with "possible myocardial ischemia" accompanied with clinical chest pain. In general, however, rizatriptan appears to have little effect on the ECG.

In summary, although no definite evidence for cardiac ischemia is present in the rizatriptan clinical development program, the pharmacological action of the compound, as well as the presence of chest pain and the ECG changes seen in one patient in study 020 indicate that the potential for serious cardiovascular events similar to those seen with sumatriptan exists and rizatriptan should contain class labeling for $5HT_{1B/1D}$ compounds.

8.11 Drug-Drug Interactions

From the clinical pharmacology drug interaction studies, the MAO inhibitor moclobemide doubled the mean AUC for rizatriptan and the mean AUC for the active N-monodesmethyl-rizatriptan increased nearly 5 fold. In the presence of propranolol (240 mg/day), the mean AUC for rizatriptan increased by 70%. Plasma N-monodesmethyl rizatriptan did not change. There were no demonstrable changes when rizatriptan was co-administered with paroxetine, or an oral contraceptive.

In the phase 3 extension studies, some patients were also exposed to migraine prophylactic medications (some of which may have also been prescribed for a coexisting depression). Table 85 (adapted from ISS Table D123, page D-402) lists the incidence of clinical adverse events which occurred in patients exposed to rizatriptan 5mg at an incidence of ≥10% in any subgroup in phase 3 extension studies. Similar tables are present for rizatriptan 10mg and for standard care but are not reproduced here.

Across all treatment groups (*i.e.*, rizatriptan 5mg, 10mg, standard care), the incidences of clinical AE's in patients on medications commonly used for migraine prophylaxis were higher than those in patients on no prophylaxis. The difference appeared to be greatest in the standard care group. This suggests that the increase in observed AE's were due to the adjunctive medications themselves, or to the underlying co-morbid diseases that prompted their prescription (*e.g.*, depression in patients on SSRI's), rather than to concomitant therapy with rizatriptan. Of note, despite the known pharmacokinetic interaction between propranolol and rizatriptan, the incidences of AE's were comparable to those in patients receiving other medications for migraine prophylaxis.

Table 85: Incidence of Clinical AE's (≥10%) According To Prophylaxis Use

Rizatriptan 5 mg				Specific Prophylaxis				
AE	All Pts N= 700	No Prophylaxis N= 501	Any Prophylaxis N= 199	SSRIs N= 34	CCBs* N= 23	Propranolol N= 96	Other β-Blockers N= 124	Tricyclics N= 46

Nausea	15	14	18	21	17	19	19	15
URI	10	9	14	15	9	15	15	9
Asthenia/ fatigue	9	9	11	9	9	5	8	13
Dizziness	9	9	11	18	9	9		107
Somnolence	7	6	9	9	13	13	10	4

* CCB = calcium channel blockers

As migraine is prevalent in younger females, incidences of clinical adverse experiences in women in Phase III extensions on rizatriptan both on and off "Oral Contraceptives or Estrogen Replacement Therapy" (OC/ERT) were examined. The incidences of adverse experiences were generally slightly higher for patients on OC/ERT compared with those not on OC/ERT for all three treatment groups. No unusual adverse experiences, particularly cerebro- or cardiovascular, were observed in patients in whom OC/ERT and rizatriptan therapies were used concomitantly. Overall, these clinical data suggest that the adverse experience profile for rizatriptan is not changed by the concomitant use of oral contraceptives or estrogen replacement therapies.

8.12 Drug-Disease Interactions

Patients with known clinically significant diseases were excluded from phase 2/3 studies. However, some patients with active secondary diagnoses did manage to get treated in clinical studies: 2 with angina, 28 with cardiac arrhythmias, 35 with mitral valve prolapse and other valvular disorders, and 100 with hypertension. The drug experience and discontinuation profiles of these patients suggests there was no evidence that rizatriptan interacted in a clinically meaningful manner with these or other underlying disease conditions.

From the clinical pharmacology studies performed in renal or hepatic impaired patients, plasma clearance in renal insufficiency patients was similar to normal patients except in those with severe disease on hemodialysis (creatinine clearance ≤ 10 mL/min/1.73 m^2), in which rizatriptan clearance averaged 830 mL/min. The plasma half-life averaged in all groups. AUC, C_{max}, T_{max}, and $T_{1/2}$ were all similar to healthy subjects.

In mild to moderate hepatic disease, the plasma clearance was similar to healthy subjects, averaging . $T_{1/2}$ was also similar (2 hours). Following a single oral dose, mean AUC and C_{max} were not clinically significantly different. However, the bioavailability of rizatriptan in mild to moderate hepatic impairment was 44-69%, respectively, suggesting reduced first pass metabolism.

8.13 Drug-Demographic Interactions

Adverse experiences were analyzed by age (<40, ≥40, ≥65), gender, and race (Caucasian vs. other).

8.13.1 Age

There were few elderly patients who participated in phase 2/3 studies (only 21 with ages ≥ 65 years). Eleven elderly patients participated in phase 3 trials. Four had a total of five adverse events (somnolence-2, nausea-1, dizziness-1,

decreased mental acuity-1). All were mild in intensity except one somnolence report which was moderate. They were similar to those observed in younger patients.

The incidence of common adverse events in patients <40 or ≥40 were almost identical (Table 86, ISS Table D-118, page D-391). One exception was dizziness was somewhat higher in older patients treated with rizatriptan 10mg. Overall, the incidences of the common clinical adverse events are representative of both older and younger patients.

Table 86: Incidence of Common Adverse Events (≥5%) in Phase 3 Studies, by Age

	Rizatriptan 5 mg		Rizatriptan 10 mg		Placebo	
	Age <40 (N= 451)	≥40 (N= 526)	Age <40 (N= 596)	≥40 (N= 571)	Age <40 (N= 280)	≥40 (N= 347)
Any AE	32	34	43	42	28	23
Dizziness	4	5	7	11	5	4
Somnolence	4	4	9	8	3	4
Asthenia/ Fatigue	3	5	6	8	3	2
Nausea	4	4	5	6	4	3

8.13.2 Gender

Most (85%) of the patients on rizatriptan in the development program were female. Furthermore, females tend to have higher (~20%) plasma drug concentrations than males. In general, across all treatment groups, the incidences of patients with one or more AE were slightly higher for females than for males (Table 87, ISS Table D-121, page D-396).

Table 87: Incidence of Common Adverse Events (≥5%) in Phase 3 Studies, by Gender

	Rizatriptan 5 mg		Rizatriptan 10 mg		Placebo	
	M (N= 154)	F (N= 823)	M (N= 173)	F (N= 994)	M (N= 98)	F (N= 529)
any AE	31	33	36	43	20	26
Dizziness	3	5	7	9	2	5
Somnolence	3	4	6	9	3	4
Asthenia/ fatigue	3	4	9	7	1	2
Nausea	1	5	5	6	2	4

8.13.3 Race

The clinical adverse events reported in ≥5% of Caucasians and non-Caucasians ("other") are shown in Table 88 (ISS Table D-119, page D-392).

Table 88: Incidence of Common Adverse Events (≥5%) in Phase 3 Studies, by Race

	Rizatriptan 5 mg		Rizatriptan 10 mg		Placebo	
	Cauc (N= 899)	Other (N= 78)	Cauc (N= 1010)	Other (N= 157)	Cauc (N= 562)	Other (N= 65)
Any AE	33	36	42	41	24	39
Dizziness	4	6	9	8	4	8
Somnolence	4	10	8	12	3	9
Asthenia/ Fatigue	5	0	7	3	2	3

Nausea	4	3	6	5	3	8
Dry mouth	3	0	3	5	1	2
Vomiting	2	1	2	5	2	5

In general, for patients on placebo, non-Caucasian patients higher incidences compared to Caucasians. With that in mind and given the relatively small number of non-Caucasians enrolled, the incidences between the two racial groups were comparable. Hispanics and blacks made up the largest subgroups within "Other." Within the context of the small numbers of Hispanic, Black and Oriental patients studied, no important differences clinical AE incidences were observed among these three subgroups.

8.14 Withdrawal Phenomenon and Abuse Potential

As a class, $5HT_{1D}$ agonists have not been associated with withdrawal phenomena. In three of the phase 3 controlled studies (022, 029, 030), safety evaluations were obtained days to a week after acute dosing with rizatriptan. There were no systematic abnormalities observed or reported in post-study physical examination, history, vital signs, laboratory, or ECG evaluation. These data suggest that withdrawal or rebound phenomena are not observed.

Similarly, as a class, $5HT_{1D}$ agonists have not been associated with high abuse potential. Although no specific data addressing this issue with rizatriptan exist, it is notable that during the phase 3 extensions, the mean interdose interval of rizatriptan was approximately constant over the trials. Also, there were no clinical reports of drug-seeking behavior, systematic reports of lost prescriptions or inappropriate escalations of dosing, or other signs of psychological or physical addiction, withdrawal or rebound phenomena associated with rizatriptan.

8.15 Human Reproduction Data

There were no studies conducted in pregnant women, and they were systematically excluded from clinical trials. Despite such precautions, several patients became pregnant during clinical studies. These are listed in Table 89 (ISS Table D-122, page D-399). All patients on rizatriptan presumably were exposed during the first trimester. For completeness, the spontaneously aborted pregnancy on RAPIDISC™ is included in this table.

Table 89: Pregnant Patients Who Received Rizatriptan or Control

Study Drug	WAES #	Study	ID	Age	Safety Results
Rizatriptan 5 mg	96040937	022 014	4443	31	Normal delivery
Rizatriptan 5 mg	96119113	022 029	5136	33	Ongoing, no known complications.
Rizatriptan 10 mg	96041053	022 018	4550	44	Normal delivery
Rizatriptan 10 mg	96030565	022 002	4043	26	Normal delivery
Rizatriptan 10 mg	96119112	022 029	5124	39	Ongoing, no known complications.
Rizatriptan 10 mg	95121463	025 011	6400	27	Normal delivery
Rizatriptan 10 mg	96042547	025 013	6248	24	Normal delivery
Rizatriptan 10 mg	95081921	025 019	6373	22	Normal delivery
Rizatriptan 10 mg	96081518	022 020	4623	33	Elective abortion

Rizatriptan 10 mg	96119603	022 040	5384	36	Unknown
Rizatriptan 10 mg	96067913	030 010	8168	37	Unknown
Rizatriptan 10 mg	96081518	022 020	4623	33	Elective abortion
Rizatriptan 10 mg	96075180	029 003	9398	19	Elective abortion
Rizatriptan 10 mg/1mg IV	96070904	042 001	0122	19	Elective abortion
Standard care	96110834	022 012	4367	21	Unknown
Standard care	96020409	022 009	4267	30	Lost to follow up
Standard care	96031291	022 023	0199	23	Normal delivery
5 mg RAPIDISC™	96041079	039 010	0255	44	Spontaneous miscarriage †
Blinded treatment	96121709	046 003	0049	24	Ongoing, no known complications
Blinded treatment	97010982	046 015	0454	32	Elective abortion

† This patient is discussed in the safety review for the RAPIDISC™

Six patients carried the pregnancies to term without complications. Four individuals decided to abort the fetus electively for reasons unrelated to study drug exposure, and one patient exposed to the rapidly dissolving formulation (RAPIDISC™) aborted spontaneously (discussed in the safety review for the rapidly dissolving tablet, NDA 20-865). No adverse events have been reported for the 2 patients in rizatriptan tablets in which the pregnancy continue.

No cases of male or female infertility have been reported during rizatriptan development.

8.16 Overdose

No intentional overdoses of rizatriptan were reported during clinical trials. In phase 2 trials, rizatriptan 40mg (administered as a single dose or as two 20mg doses given 2 hours apart) was generally well tolerated in 323 patients. However, somnolence and dizziness were common at this dose level and two patients experienced syncope. One syncopal episode was associated with a painful venipuncture and the second one was associated with micturition and neither was serious.

In a clinical pharmacology study, 12 subjects received 80mg. Two of the 12 experienced syncope and/or bradycardia. One of the subjects, a 29 y/o female, developed vomiting, bradycardia, and dizziness beginning 3 hours after receiving a total of 80mg rizatriptan administered over 2 hours. Bradycardia was followed by a 10 second period of AV dissociation, which was responsive to atropine. This occurred one hour after the onset of the other symptoms. The other case was a 25 y/o male who experienced transient dizziness, syncope, incontinence, and a 5 second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred 2 hours after the subject had received a total of 80mg rizatriptan administered over 4 hours.

Based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular events due to vasoconstriction (*e.g.*, angina) could occur. Since there is no known antidote for rizatriptan, standard treatment for overdoses is recommended. Based on the half-life of rizatriptan, clinical and electrocardiographic monitoring should be continued for at least 12 hours even if

clinical symptoms are not observed. The effects of hemodialysis or peritoneal dialysis on serum concentration of rizatriptan are unknown.

8.17 Summary of Key Adverse Events

The adverse events seen with rizatriptan are typical of those seen with other $5HT_{1B/1D}$ receptor agonists, *i.e.* dizziness, asthenia, chest pain, nausea, paresthesia, heaviness, and somnolence. Most AE's were mild and transient. Chest pain occurs with rizatriptan use. The incidence was in the acute studies and ≥5% in the long term extensions. The most common AE's seen with long term use were similar to those seen in the acute studies, although the incidences were roughly three-fold higher. They are listed below.

Table 90: Common AE's (≥5%) in Long-Term Extensions

nausea
dizziness
somnolence
asthenia/fatigue
chest pain
vomiting
diarrhea
headache
paresthesias
pharyngeal discomfort

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8.18 Safety Conclusions

Based on the safety data presented,

1. Rizatriptan 5mg or 10mg is generally well tolerated.
2. 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 $5HT_{1B/1D}$ agonists.
3. Rizatriptan does not exhibit systematic ECG or laboratory abnormalities.
4. Diastolic blood pressure increases only slightly with rizatriptan use.
5. 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.
6. 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.

9. Four Month Safety Update

The four month safety update was submitted on October 30, 1997. It contains additional safety data since the NDA cutoff date 10/1/96 until 6/30/97, a period of eight months. In addition, all serious adverse events reported through 7/31/97 are also included.

The safety update, combined with the safety data from the original NDA documents the cumulative experience for 3,726 migraineurs who received rizatriptan in phase 2/3 studies. The new safety data in this report contains data from the following three sources:

- 598 migraineurs who continued treatment in the extensions of studies 022, 025, and 029, which were in progress at the time the NDA was submitted.
- two recently completed clinical pharmacology studies (044, 045).
- serious adverse event reports from 3/1/97 to 7/31/97 from ongoing blinded studies (048, 051, 046, 049)

Study 044 was a phase 1 multicenter, double-blind, placebo-controlled, two period crossover study which investigated the effects of rizatriptan on blood pressure in hypertensive patients. Twenty subjects contributed to safety data.

Study 045 was a phase 1 open label, single dose, randomized, four period crossover study which compared the plasma concentrations of 5mg and 10mg rizatriptan administered intranasally (citrate formulation) to oral 5mg and 10mg rizatriptan in 12 healthy male subjects.

Study 048 is an ongoing phase 1 single dose study to investigate the PK and safety of rizatriptan in adolescents.

Study 051 is an ongoing phase 1 double-blind, randomized, three period placebo-controlled study to investigate the effects of propranolol 60mg bid and 120 mg bid on the PK of rizatriptan in healthy male and female subjects.

Study 046 is an ongoing phase 3 two period crossover study comparing rizatriptan 5mg and 10mg p.o. to sumatriptan 25mg and 50mg p.o.

Study 049 is an ongoing phase 3 randomized, triple blind, placebo-controlled, outpatient study to examine the safety, tolerability and efficacy of rizatriptan 10mg RAPIDISC™ and 5mg RAPIDISC™ for the acute treatment of migraine.

The reports in this safety update are similar to the reports contained in the original NDA. There were few new serious adverse events; all were similar to those in the original application.

The sponsor has updated the exposure information for rizatriptan. This is shown in Table 91 (SUR, Table 3, page 14).

Table 91: Updated Exposures Table

	Tablets			RAPIDISC			Intranasal			Other		
Category	APP	SUR	CUM	APP	SUR	CUM	APP	SUR	CUM	APP	SUR	CUM
Phase I	313	32	345	36	0	36	44	12	56	188	0	188
Phase II	974	0	974				21	0	21			
Phase III	2742	10	2752	214	0	214						
Total	***4029***	***42***	***4071***	***250***	***0***	***250***	***65***	***12***	***77***	***188***	***0***	***188***

Non-unique subjects	80	0	80	0	0	0	0	0	0			
Unique subjects	***3949***	***42***	***3991***	***250***	***0***	***250***	***65***	***12***	***77***	***188***	***0***	***188***

APP = number of patients in original NDA
SUR = number of patients in the safety update report
CUM = total number of patients
Other = includes intravenous, oral solution, dry filled capsule

APPEARS THIS WAY
ON ORIGINAL

9.1 Deaths

There were no deaths reported in the safety update.

9.2 Serious Adverse Events

There were seven (7) new serious adverse events reported through 7/31/97. No new types of serious adverse experiences occurred during the safety update period. Four of the seven occurred in patients taking 5mg and 3 occurred in patients taking 10mg. None was discontinued from study. None was considered drug related.

The three SAE's on 5mg were: knee pain, breast cancer, and benign uterine cancer. The four SAE's on 10mg were: melanoma, uterine hypertrophy, anaphylaxis, anal hemorrhage, headaches. The case of anaphylaxis is described below.

A **30 y/o female (25-006)** experience a severe anaphylactic reaction immediately after exposure to rosemary. The event was life-threatening. The event occurred on study day 310, 17 days after treatment of a 39th migraine attack with rizatriptan 10mg. She recovered later that day and continued in the study.

The investigator deemed the SAE not related to rizatriptan 10mg. I agree with that assessment. After review of the other cases, I agree with the investigators that none was drug related.

An additional 4 SAE's were reported from ongoing blinded studies. The treatment assignment are not know and I don't discuss these in any detail for this reason. The reports were for suicide attempt, abdominal pain, pyelonephritis, and wound infection. All patients recovered.

APPEARS THIS WAY
ON ORIGINAL

9.3 Adverse Dropouts

Withdrawals due to AE's were infrequent and remained about 4%, as in the original application. No patients withdrew due to an SAE in the safety update. During the safety update, 7 patients withdrew due to an adverse event. All occurred in the phase 3 extension studies. The seven patients reported a total of eight AE's resulting in their discontinuation. All seven AE's were reported by others in the original application. No new AE's resulting in dropouts were observed. The seven AE's resulting in the 5 dropouts were: rash-pruritus, chest pain, migraine, headache, pharyngeal discomfort-neck pain, dizziness, paresthesia, warm sensation. Brief narratives of two key ADO's are described below.

Chest Pain: A **47 y/o F (AN 9159)** discontinued due to severe chest tightness lasting 75 minutes on study day 29. The chest pain occurred one hour after treatment of an initial attack with rizatriptan 5mg. She also experience burning of the face, heavy feeling of the body, moderate tingling, and severe nausea, all lasting 75 minutes. None of the AE's were considered serious but they were probably drug related according to the investigator.

Neck Pain: A **25 y/o M (AN 9688)** discontinued due to severe pharyngeal discomfort and neck pain lasting 50 minutes. These AE's occurred on study day 122 about 30 minutes after treating a migraine attack with rizatriptan 10mg (total number of attacks treated=16). Neither the neck pain or the pharyngeal discomfort was serious but were considered probably drug related.

These cases illustrate typical rizatriptan-related adverse events which are also seen with the other 5-HT_1 agonists.

9.4 Adverse Events

The new 1% table of clinical adverse experiences from the long term extension is shown in Table 91 (SUR, Table 13, page 43). The overview of the new clinical adverse experiences reported in phase 3 extensions were comparable to those documented in the original application. In the NDA, 67% percent of patients on 5mg and 80% of patients on 10mg reported at least one AE. With the update, the incidences are now 69% and 81%, respectively. The new data provided by this update do not appreciably change any category.

Table 92: Clinical Adverse Events (≥1%) in Phase 3 Extensions

	Percent of Patients Reporting (% Drug-Related)					
	Rizatriptan 5 mg			Rizatriptan 10 mg		
	(N=700)†	(N=244)	(N=711)	(N=825‡)	(N=354)	(N=834)
	APP	SUR	CUM	APP	SUR	CUM
Average number of attacks treated per patient	23.4	12.5	26.9	29.4	14.7	34.6
Patients with any clinical adverse experience	67 (39)	44 (19)	69 (40)	80 (53)	48 (19)	81 (55)
Body as a Whole	**23 (13)**	**13 (8)**	**24 (14)**	**28 (20)**	**13 (7)**	**30 (22)**
Asthenia/fatigue	9 (7)	4 (3)	10 (8)	13 (11)	5 (4)	13 (12)
Pain, chest	4 (3)	3 (3)	5 (4)	7 (6)	1 (1)	7 (7)
Pain, abdominal	3 (1)	2 (<1)	3 (1)	3 (1)	2 (<1)	3 (1)
Flu-like illness	<1 (0)	0	<1 (0)	2 (<1)	<1(0)	2 (<1)
Fever	1 (0)	<1 (0)	2 (0)	2 (0)	1 (<1)	2 (<1)
Chills	<1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Edema/swelling	<1 (<1)	<1 (0)	<1 (<1)	1 (<1)	0	1 (<1)
Pain§	<1 (<1)	0	<1 (<1)	1 (<1)	0	1 (<1)
Heat sensitivity	<1 (<1)	1 (1)	<1 (<1)	<1 (<1)	<1 (<1)	1 (<1)
Malaise	1 (<1)	<1 (<1)	1 (<1)	<1 (<1)	0	<1 (<1)
Trauma	1 (0)	<1 (0)	<1 (0)	<1 (0)	<1 (0)	<1 (0)
Warm sensation	1 (<1)	0	1 (<1)	<1 (<1)	<1 (<1)	<1 (<1)
Cardiovascular System	**4 (3)**	**3 (<1)**	**4 (3)**	**6 (3)**	**2 (<1)**	**7 (4)**
Palpitation	2 (1)	<1 (<1)	2 (2)	2 (1)	<1 (<1)	2 (1)
Tachycardia	1 (1)	<1 (<1)	1 (1)	1 (1)	<1 (<1)	1 (1)
Hypertension¶	<1 (0)	<1 (0)	<1 (0)	1 (<1)	0	1 (<1)
Digestive System	**30 (17)**	**12 (6)**	**31 (18)**	**35 (22)**	**15 (7)**	**38 (23)**
Nausea	15 (10)	8 (6)	17 (11)	20 (14)	7 (5)	21 (15)
Vomiting	7 (4)	2 (<1)	7 (4)	8 (4)	3 (<1)	9 (4)
Dry mouth	4 (4)	<1 (<1)	4 (4)	4 (3)	2 (1)	4 (4)
Diarrhea	3 (1)	<1 (0)	3 (1)	4 (2)	<1 (<1)	4 (2)
Dyspepsia	2 (1)	0	2 (1)	3 (2)	2 (<1)	4 (2)
Acid regurgitation	2 (<1)	<1 (0)	2 (<1)	2 (<1)	1 (<1)	2 (<1)
Pain, dental	<1 (0)	0	<1 (0)	2 (0)	<1 (0)	2 (0)
Constipation	<1 (0)	<1 (0)	<1 (0)	1 (<1)	<1 (0)	1 (<1)
Gastroenteritis, infectious	1 (0)	<1 (0)	1 (0)	1 (0)	0	1 (0)
Infection, dental process	<1 (0)	0 (0)	<1 (0)	1 (0)	0	1 (0)
Thirst	1 (1)	0	1 (1)	<1 (<1)	0	<1 (<1)
Hemic and Lymphatic	**<1 (0)**	**0**	**<1 (0)**	**<1 (<1)**	**2 (<1)**	**1 (<1)**

	Percent of Patients Reporting (% Drug-Related)					
	Rizatriptan 5 mg			Rizatriptan 10 mg		
	(N=700)†	(N=244)	(N=711)	(N=825‡)	(N=354)	(N=834)
	APP	SUR	CUM	APP	SUR	CUM
Metabolic/Nutritional/ Immune	**2 (<1)**	**1 (0)**	**3 (<1)**	**2 (<1)**	**1 (0)**	**3 (<1)**
Allergy§	<1 (0)	<1 (0)	<1 (0)	1 (0)	<1 (0)	1 (0)
Musculoskeletal System	**18 (4)**	**10 (3)**	**19 (4)**	**26 (8)**	**12 (3)**	**27 (9)**
Pain, back	4 (0)	1 (0)	4 (0)	5 (<1)	3 (<1)	6 (<1)
Pain, neck	2 (<1)	1 (<1)	3 (<1)	4 (1)	2 (<1)	4 (1)
Stiffness	1 (<1)	1 (<1)	2 (<1)	3 (2)	<1 (0)	3 (1)
Pain, shoulder	2 (0)	<1 (0)	2 (0)	3 (<1)	1 (0)	3 (<1)
Myalgia	2 (<1)	<1 (0)	2 (<1)	3 (<1)	<1 (0)	3 (<1)
Heaviness, regional	<1 (<1)	<1 (<1)	<1 (<1)	2 (2)	<1 (<1)	2 (2)
Pain, musculoskeletal	1 (<1)	0	1 (<1)	2 (<1)	0	2 (<1)
Pain, knee	<1 (<1)	0	<1 (<1)	1 (0)	<1 (0)	2 (0)
Tightness, regional	<1 (<1)	<1 (<1)	<1 (<1)	1 (1)	<1 (<1)	1 (1)
Weakness, muscle	<1 (<1)	<1 (<1)	<1 (<1)	1 (1)	<1 (<1)	1 (1)
Pain, arm	<1 (<1)	<1 (0)	1 (<1)	1 (<1)	<1 (<1)	1 (<1)
Tendonitis	1 (0)	0	1 (0)	<1 (0)	<1 (0)	1 (0)
Cramp, muscle	<1 (<1)	0	<1 (<1)	<1 (<1)	<1 (<1)	1 (<1)
Arthralgia§	<1 (0)	0	<1 (0)	1 (<1)	<1 (0)	1 (<1)
Pain, leg	<1 (<1)	<1 (<1)	<1 (<1)	<1 (<1)	<1 (0)	<1 (<1)
Sprain, neck	1 (<1)	0	1 (<1)	<1 (0)	0	<1 (0)
Nervous system	**33 (22)**	**12 (7)**	**34 (23)**	**48 (34)**	**23 (14)**	**50 (36)**
Dizziness	9 (7)	3 (3)	10 (7)	15 (14)	5 (4)	16 (14)
Somnolence	7 (7)	1 (<1)	7 (7)	15 (14)	5 (5)	15 (14)
Headache	8 (2)	2 (<1)	9 (2)	11 (2)	3 (1)	12 (3)
Paresthesia	4 (3)	3 (2)	5 (4)	7 (6)	2 (2)	8 (7)
Mental acuity decreased	1 (1)	<1 (<1)	1 (1)	4 (3)	<1 (<1)	4 (3)
Insomnia	3 (1)	1 (0)	3 (1)	4 (1)	1 (0)	4 (1)
Depression	2 (<1)	2 (0)	2 (<1)	4 (<1)	2 (0)	4 (<1)
Hypesthesia	2 (2)	2 (<1)	3 (2)	4 (3)	1 (<1)	4 (3)
Tremor	<1 (<1)	<1 (<1)	<1 (<1)	2 (2)	<1 (<1)	2 (2)
Anxiety	2 (<1)	<1 (0)	2 (<1)	2 (<1)	<1 (<1)	2 (<1)
Migraine	<1 (<1)	<1 (0)	<1 (<1)	2 (<1)	<1 (0)	2 (<1)
Nervousness	1 (1)	0	1 (1)	1 (1)	<1 (0)	2 (1)
Vertigo	1 (<1)	<1 (<1)	1 (<1)	1 (1)	2 (2)	2 (2)
Ataxia	1 (<1)	<1 (0)	1 (<1)	1 (1)	<1 (<1)	1 (1)
Spasm	<1 (<1)	<1 (0)	<1 (<1)	<1 (0)	<1 (0)	1 (0)

	Percent of Patients Reporting (% Drug-Related)					
	Rizatriptan 5 mg			Rizatriptan 10 mg		
	(N=700)†	(N=244)	(N=711)	(N=825‡)	(N=354)	(N=834)
	APP	SUR	CUM	APP	SUR	CUM
Respiratory System	**27 (3)**	**11 (1)**	**28 (4)**	**37 (9)**	**16 (2)**	**39 (9)**
URI	10 (<1)	3 (0)	11 (<1)	13 (<1)	5 (0)	14 (<1)
Sinusitis	5 (<1)	3 (0)	5 (<1)	8 (0)	4 (0)	9 (0)
Pharyngitis	3 (0)	<1 (0)	3 (0)	5 (<1)	2 (<1)	6 (<1)
Influenza	6 (0)	2 (0)	7 (0)	5 (0)	3 (0)	6 (0)
Discomfort, pharyngeal	<1 (<1)	<1 (<1)	1 (<1)	4 (4)	<1 (<1)	4 (4)
Cough	2 (<1)	0 (0)	2 (<1)	3 (<1)	1 (0)	4 (<1)
Bronchitis	2 (0)	<1 (0)	2 (0)	3 (0)	1 (0)	4 (0)
Sinus disorder	2 (0)	<1 (0)	2 (0)	3 (<1)	<1 (0)	3 (<1)
Dyspnea	<1 (<1)	<1 (<1)	<1 (<1)	2 (2)	0	2 (2)
Rhinorrhea	<1 (0)	0	<1 (0)	<1 (<1)	<1 (<1)	1 (<1)
Congestion, nasal	1 (<1)	<1 (0)	2 (<1)	1 (<1)	<1 (0)	1 (<1)
Congestion, respiratory	<1 (<1)	0	<1 (<1)	1 (<1)	<1 (0)	1 (<1)
Pneumonia	<1 (0)	0	<1 (0)	1 (0)	0	1 (0)
Asthma	<1 (0)	0	<1 (0)	1 (<1)	<1 (<1)	1 (<1)
Rhinitis, allergic	<1 (0)	0	<1 (0)	<1 (0)	<1 (0)	1 (0)
Tonsillitis	1 (0)	<1 (0)	1 (0)	<1 (0)	<1 (0)	<1 (0)
Skin and Skin Appendage	**8 (2)**	**5 (1)**	**9 (3)**	**11 (4)**	**5 (1)**	**13 (5)**
Flushing	<1 (<1)	0	<1 (<1)	2 (2)	<1 (<1)	2 (2)
Pruritus	1 (<1)	<1 (<1)	2 (<1)	1 (1)	<1 (<1)	1 (1)
Rash	2 (<1)	<1 (<1)	2 (<1)	1 (<1)	0	1 (<1)
Sweating	<1 (<1)	0	<1 (<1)	<1 (<1)	<1 (<1)	1 (1)

	Percent of Patients Reporting (% Drug-Related)					
	Rizatriptan 5 mg			Rizatriptan 10 mg		
	(N=700)†	(N=244)	(N=711)	(N=825‡)	(N=354)	(N=834)
	APP	SUR	CUM	APP	SUR	CUM
Special Senses	**8 (3)**	**3 (1)**	**8 (4)**	**9 (4)**	**2 (<1)**	**10 (5)**
Blurred vision	2 (1)	<1 (<1)	2 (1)	1 (<1)	0	1 (<1)
Otitis	<1 (0)	0	<1 (0)	1 (0)	0	1 (0)
Tinnitus	<1 (<1)	0	<1 (<1)	<1 (<1)	<1 (<1)	1 (<1)
Urogenital System	**9 (1)**	**6 (<1)**	**10 (1)**	**12 (2)**	**7 (1)**	**13 (3)**
Infection, urinary tract	2 (0)	2 (0)	2 (0)	3 (0)	<1 (0)	3 (0)
Hot flashes	<1 (<1)	<1 (<1)	<1 (<1)	2 (2)	2 (<1)	2 (2)
Menstruation disorder	2 (<1)	2 (0)	2 (<1)	2 (<1)	1 (<1)	2 (<1)
Cystitis	<1 (0)	<1 (0)	<1 (0)	1 (0)	<1 (0)	1 (0)
Vaginitis	<1 (0)	0	<1 (0)	<1 (0)	<1 (0)	1 (0)

Adverse experiences are in order of decreasing incidence by rizatriptan 10 mg CUM within each body system.

† Includes 5 patients who had been continuing in extension, but had yet to treat an attack.

‡ Includes 8 patients who had been continuing in extension, but had yet to treat an attack.

§ These adverse experiences were erroneously reported as <1% in the original application data, but actually occurred at 1% in patients on rizatriptan 10 mg.

Patients with more than one clinical adverse experience within any given column (APP, SUR, CUM), are counted only once in that column under "Patients with any clinical adverse experience".

Although a patient may have two or more adverse experiences in a body system category, the patient is counted only once in the body system total.

Within a given body system, individual adverse experiences are listed in descending order according to the Rizatriptan 10 mg cumulative data.

Patients with adverse experiences (by body system or individual adverse experiences) reported in both the original APP and SUR reporting periods are counted only once in the CUM column.

APP=original application data SUR=safety update report period CUM=cumulative

9.5 Laboratory Data

The laboratory experience in the original application demonstrated that lab abnormalities were similar to that of placebo or standard care. The data in the SUR continue to support these findings. No serious laboratory adverse experiences occurred in the SUR and no patient discontinued due to a laboratory abnormality. No new laboratory abnormalities not previously reported in the NDA occurred.

9.6 Vital Signs

There were no adverse experiences reported due to vital signs abnormalities in the safety update.

9.7 ECG

Three (3) ECG adverse events in 2 patients were reported in the safety update. One took rizatriptan 5mg, and the other took 10mg. The ECG AE's reported were similar to that seen in the NDA. Therefore, the percentages and types of ECG abnormalities were almost identical to those seen in the original application.

None of the three ECG adverse events was serious, nor did they result in a discontinuation. Two ECG's showed premature ventricular contractions (PVC's) and another one showed 1st degree AV block.

9.8 Pregnancies

Four new pregnancies were reported in the safety update. One patient on standard care experienced a spontaneous abortion. One patient still on blinded

treatment also experienced a spontaneous abortion. A third patient on blinded treatment was continuing her normal pregnancy as of 7/30/97. No information was provided on the fourth pregnancy.

Follow-up information was reported on four pregnancies already documented in the original application. Normal deliveries are now reported in these patients randomized to 5mg and 10mg in protocols 022 and 030.

As of 7/31/97, a cumulative total of 11 normal deliveries had occurred--10 in women on rizatriptan and 1 on standard care.

9.9 Safety Update Conclusion

The safety update data is remarkably benign and does not give rise to new safety questions or concerns about the drug. It supports the evidence presented from the original application that rizatriptan 5mg and 10mg are generally safe. The safety profile resembles other 5-HT_1 agonists.

10. Labeling Review

22 Page(s) Redacted

DRAFT LABELING