

Body System COSTART Term	Eletriptan (N= 6419)		Placebo (N=1054)		Sumatriptan (N=892)		Cafergot (N=203)		POT (N=278)	
	A/C	T/R	A/C	T/R	A/C	T/R	A/C	T/R	A/C	T/R
<i>Nervous</i>										
Dizziness	8.3	6.3	3.9	2.8	7.4	5.3	7.4	5.4	4.3	3.6
Hypertonia	3.4	2.6	0.7	0.3	1.3	0.4	0.5	0.5	4.7	1.8
Paresthesia	4.6	4.1	1.7	1.3	2.7	2.4	2.0	2.0	6.8	5.4
Somnolence	8.4	7.3	3.6	3.1	4.0	3.1	0.5	0.5	5.8	4.0
Tremor	1.0	0.8	0.8	0.5	0.3	0.2	3.0	2.0	1.1	0.4
<i>Respiratory</i>										
Pharyngitis	2.6	1.5	0.8	0.1	1.8	0.4	1.5	1.0	5.8	2.9
Respiratory Tract	2.8	0.1	1.5	0.0	1.7	0.1	1.0	0.5	4.7	0.0
Infection Sinusitis	1.0	0.0	0.3	0.0	0.7	0.0	0.0	0.0	4.0	0.7

A/C = all causality; T/R = treatment related, POT = physician optimized treatment

8.5.3 Adverse Events in Single Attack and First of Multiple Attack Studies

Table 50 (ISS page 22) summarizes the incidence of adverse events from the single attack phase 2/3 studies and the first attack data from short term multiple attack phase 2/3 studies for eletriptan and placebo. The mean eletriptan dose per attack was 64.9mg. The overall incidence was higher for eletriptan treated patients than placebo patients (44.6% vs. 32.5%). As in the "all phase 2/3" protocol set, the COSTART body systems with the most frequent reports of AE's for both eletriptan and placebo were "body as a whole," "digestive," and "nervous" systems.

Table 50: Adverse Events ($\geq 3\%$) in Single Attack and First of Multiple Attack Studies

	Eletriptan (N= 4597)		Placebo (N= 988)	
	All Causality	Treatment Related	All Causality	Treatment Related
At least 1 AE	2050 (44.6%)	1494 (32.5%)	304 (30.8%)	182 (18.4%)
<i>Body as a Whole</i>				
Asthenia	334 (7.3%)	243 (5.3%)	26 (2.6%)	15 (1.5%)
Headache	172 (3.7%)	77 (1.7%)	27 (2.7%)	15 (1.5%)
<i>Digestive</i>				
Dry Mouth	145 (3.2%)	139 (3.0%)	22 (2.2%)	21 (2.1%)
Nausea	294 (6.4%)	190 (4.1%)	47 (4.8%)	27 (2.7%)
Vomiting	91 (2.0%)	39 (0.8%)	43 (4.4%)	16 (1.6%)
<i>Nervous</i>				
Dizziness	298 (6.5%)	231 (5.0%)	30 (3.0%)	22 (2.2%)
Paresthesia	158 (3.4%)	142 (3.1%)	15 (1.5%)	11 (1.1%)
Somnolence	276 (6.0%)	229 (5.0%)	35 (3.5%)	30 (3.0%)

Studies: 102, 103, 104, 105, 302, 305, 307, 314, 318

The most commonly occurring AE's occurred in a higher percentage with eletriptan use compared to placebo in all cases except vomiting, which was more often reported in placebo patients. This is probably a reflection of the reduction in vomiting seen with eletriptan use (see efficacy review section 7.3.11 on Vomiting, page 31). Chest pain did not make this list as the sponsor use a $\geq 3\%$ cutoff incidence for the table. The incidence of chest pain in this population was 2.9% (135/4957) for eletriptan and 0.8% (8/988) for placebo (taken from sponsor table 2.8.6.3.15, not shown here). There were 21 adverse

events that occurred with incidences greater than 1% in eletriptan treated patients. These were:

- Body as a whole: abdominal pain, asthenia, back pain, chest pain, headache, pain
- Cardiovascular: vasodilatation
- Digestive: diarrhea, dry mouth, dyspepsia, dysphagia, nausea
- Musculoskeletal: myalgia
- Nervous: dizziness, hypertonia, hypesthesia, paresthesia, somnolence
- Respiratory: pharyngitis, rhinitis
- Skin and appendages: sweating

Generally, there was a dose response relationship between the total eletriptan dose taken for the attack and adverse event incidence, as shown in Table 51 (adapted from sponsor table 2.8.6.3.16).

Table 51: AE's by Total Dose in Single Attack and 1st Attack of Multiple Attack Studies

Body System COSTART Preferred Term	5mg		20mg		30mg		40mg		80mg		160mg		PBO	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
N Treated	87		431		91		1774		1932		282		988	
N with AE's	33	37.9	139	32.3	35	38.5	743	41.9	962	49.8	138	48.9	304	30.8
Body as a whole	9	10.3	47	10.9	15	16.5	279	15.7	416	21.5	67	23.8	95	9.6
Cardiovascular	8	9.2	19	4.4	13	14.3	75	4.2	106	5.5	22	7.8	41	4.1
Digestive	11	12.6	42	9.7	8	8.8	263	14.8	353	18.3	45	16	125	12.7
Hemic/lymphatic	2	2.3	0	0	0	0	4	0.2	2	0.1	2	0.7	3	0.3
Metabolic and nutritional	1	1.1	4	0.9	1	1.1	17	1	20	1	5	1.8	4	0.4
Musculoskeletal	2	2.3	8	1.9	4	4.4	54	3	68	3.5	11	3.9	6	0.6
Nervous	12	13.8	53	12.3	17	18.7	326	18.4	452	23.4	74	26.2	104	10.5
Respiratory	1	1.1	13	3	2	2.2	68	3.8	117	6.1	15	5.3	27	2.7
Skin and appendages	2	2.3	6	1.4	2	2.2	36	2	54	2.8	6	2.1	15	1.5
Special senses	3	3.4	6	1.4	3	3.3	58	3.3	60	3.1	10	3.5	18	1.8
Urogenital	3	3.4	9	2.1	2	2.2	20	1.1	44	2.3	5	1.8	12	1.2

Studies: 102, 103, 104, 105, 302, 305, 307, 314, 318

The sponsor then performed an analysis of AE's by initial dose. This does not take into account whether a second dose was taken for recurrence or non-response. This analysis also shows a dose related increase in AE's between 20mg and 80mg. The overall incidence of AE's were 30% for placebo, 33.% for eletriptan 20mg, 42.8% for 40mg and 54.9% for 80mg. The incidence of treatment related AE's showed a similar pattern. Table 52 (ISS page 36) shows the most common AE's (≥3%) according to initial dose of study medication taken. A dose-response for most categories is evident in the table.

Table 52: AE's by Initial Dose in Single Attack and 1st Attack of Multiple Attack Studies (≥3%)

Body System COSTART Term	Eletriptan 20mg (N=531)	Eletriptan 40mg (N=2138)	Eletriptan 80mg (N=1518)	Placebo (N=1235)
At least 1 AE	33.5%	42.8%	54.9%	30.0%
<i>Body as a Whole</i>				
Asthenia	4.0%	5.2%	12.2%	2.8%
Chest Pain	0.9%	2.4%	4.7%	1.2%
Headache	3.2%	3.6%	4.5%	2.5%
<i>Cardiovascular</i>				
Vasodilatation	2.1%	1.9%	3.5%	1.9%
<i>Digestive</i>				
Dry Mouth	1.9%	3.1%	4.0%	2.0%
Dysphagia	0.6%	1.8%	3.0%	0.3%
Nausea	4.7%	5.4%	8.8%	5.0%
Vomiting	0.9%	1.7%	2.8%	3.9%
<i>Nervous</i>				
Dizziness	3.4%	6.3%	8.3%	3.2%
Hypertonia	1.5%	1.6%	3.4%	0.5%
Paresthesia	3.2%	2.9%	4.5%	1.5%
Somnolence	2.8%	6.0%	7.8%	3.4%

Studies: 102, 103, 104, 105, 302, 305, 307, 314, 318

8.5.4 Adverse Events in Placebo-controlled Short-term Multiple Attack Studies

Of 3,466 patients who received eletriptan in short term multiple attack studies, 1957 (56.5%) had at least one adverse event, and 1469 (42.4%) were deemed treatment related. For the 666 placebo treated patients, 268 (40.2%) had at least one adverse event and 154 (23.1%) were felt to be treatment related. Severe adverse events were reported by 11.2% of eletriptan patients and in 8.7% of placebo treated patients. The mean eletriptan dose per attack was 68.8mg. The most commonly reported adverse events were similar to those reported after a single attack (abdominal pain, asthenia, chest pain, headache, vasodilatation, dry mouth, dysphagia, nausea, vomiting, dizziness, hypertonia, paresthesia, somnolence). The absolute incidences were generally higher than the single attack incidences as there was more opportunity to report an AE with treatment of multiple attacks.

8.5.5 Adverse Events in Placebo-controlled Active Comparator Studies

The three placebo-controlled sumatriptan comparator studies (104, 314, and 318) were analyzed separately to compare AE incidences for eletriptan, sumatriptan, and placebo. A total of 1124 patients received eletriptan in these studies. Of these, 570 (50.7%) had at least one adverse event, compared with 378/841 (44.9%) for sumatriptan, and 103/319 (32.3%) for placebo. Treatment related AE incidences were 37.6%, 28.4%, and 17.9% for eletriptan, sumatriptan, and placebo, respectively. Severe AE's were reported by 10.9%, 9.6%, and 7.8%, respectively. In these three analyses, eletriptan treated patients tended to report more AE's than either sumatriptan or placebo treated patients.

Table 53 (ISS page 28) summarizes the most commonly reported AE's in these studies (≥3% incidence in any treatment group). Numerically, incidences of AE's were generally

higher in eletriptan treated patients compared to sumatriptan, with the exceptions of dry mouth (similar for the two) and vomiting (higher for sumatriptan). The incidence of chest pain, in particular, was more than twice as high in eletriptan patients compared to sumatriptan patients (3.7% vs. 1.9%). The mean eletriptan dose per attack was 66mg and for sumatriptan it was 90.3mg.

Table 53: Adverse Events in Placebo-controlled Sumatriptan Comparator Studies

Body System COSTART Term	Eletriptan (N=1124)		Sumatriptan (N=841)		Placebo (N=319)	
	All Causality	Trt Related	All Causality	Trt Related	All Causality	Trt Related
At least 1 AE	570 (50.7%)	423 (37.6%)	378 (44.9%)	239 (28.4%)	103 (32.3%)	57 (17.9%)
<i>Body as a Whole</i>						
Asthenia	8.8%	6.6%	6.3%	5.0%	2.8%	1.9%
Chest Pain	3.7%	3.7%	1.9%	1.7%	1.9%	1.3%
Headache	4.7%	2.1%	3.8%	1.8%	2.8%	1.3%
<i>Cardiovascular</i>						
Vasodilatation	3.5%	2.7%	2.4%	2.4%	1.3%	1.3%
<i>Digestive</i>						
Dry Mouth	3.5%	3.3%	3.8%	3.3%	3.1%	3.1%
Dyspepsia	3.2%	2.1%	2.7%	1.5%	0.9%	0.6%
Nausea	10.1%	7.0%	9.4%	4.9%	6.0%	3.1%
Vomiting	3.5%	1.2%	4.8%	1.5%	5.6%	1.9%
<i>Nervous</i>						
Dizziness	8.6%	6.9%	7.6%	5.5%	3.4%	2.8%
Paresthesia	4.9%	4.3%	2.4%	2.0%	2.5%	1.9%
Somnolence	6.9%	5.6%	4.0%	3.3%	2.8%	2.5%

Studies 104, 314, 318

The following table shows the same results, but AE incidences are reported for each treatment group according to the initial dose of study medication taken. This does not take into account whether a second dose was taken for non-response or recurrence. As seen in Table 52, page 58, there is generally a dose related increasing incidence of AE's with eletriptan use. Chest pain occurred in 4.7% of patients treated with eletriptan 80mg and 1.3% of patients treated with sumatriptan 100mg.

Table 54: AE's in Placebo-controlled Sumatriptan Comparator Studies, By Initial Dose

Body System COSTART Term	Eletriptan			Sumatriptan			Placebo (N=319)
	20mg (N=144)	40mg (N=495)	80mg (N=485)	25mg (N=180)	50mg (N=362)	100mg (N=298)	
At least 1 AE	34.0%	39.2%	51.5%	36.1%	33.1%	38.9%	25.7%
<i>Body as a Whole</i>							
Asthenia	3.5%	4.6%	9.1%	0.6%	3.0%	7.4%	1.6%
Chest Pain	0.7%	1.8%	4.7%	0.6%	1.4%	1.3%	1.6%
Headache	2.1%	3.8%	3.7%	0.6%	3.3%	3.0%	2.2%
<i>Cardiovascular</i>							
Vasodilatation	3.5%	1.8%	3.5%	1.1%	1.9%	2.3%	1.3%
<i>Digestive</i>							
Diarrhea	0.7%	2.4%	1.4%	3.9%	1.9%	0.0%	0.9%
Dry Mouth	2.1%	2.6%	3.3%	3.9%	2.8%	2.7%	2.8%
Dyspepsia	3.5%	2.2%	2.9%	2.2%	0.6%	3.4%	0.6%

Body System COSTART Term	Eletriptan			Sumatriptan			Placebo (N=319)
	20mg (N=144)	40mg (N=495)	80mg (N=485)	25mg (N=180)	50mg (N=362)	100mg (N=298)	
Nausea	4.2%	4.8%	9.5%	3.9%	8.3%	5.7%	3.8%
Vomiting	1.4%	0.8%	3.1%	2.8%	3.6%	2.3%	4.7%
<i>Nervous</i>							
Dizziness	3.5%	6.7%	7.6%	5.0%	6.6%	5.0%	2.5%
Hypertonia	0.7%	0.4%	3.7%	0.0%	1.4%	1.3%	0.3%
Paresthesia	5.6%	3.2%	5.6%	1.7%	1.4%	3.4%	2.2%
Somnolence	2.1%	5.1%	7.0%	3.3%	2.5%	4.4%	2.5%

Studies 104, 314, 318, all causality

In the single Cafergot comparator study (307), the incidences of adverse events were 47%, 61%, 46%, and 56% for eletriptan 40mg, 80mg, Cafergot 2 tablets, and placebo, respectively. The most commonly reported AE's in eletriptan treated patients were similar to those reported in other studies (asthenia, nausea, dizziness, etc.).

8.5.6 Adverse Events in Long-Term Studies

The adverse event data for the long-term studies (108 and 317) are split into three groups to reflect the design of the studies. Each study had a 6-headache run-in period during which the eletriptan dose could be changed, followed by a stabilized dose period where patients took either 40mg or 80mg. The three groups comprise patients who had stabilized on 40mg, stabilized on 80mg, and those who had treated fewer than 7 migraines and had not yet stabilized on a particular dose. The incidence of AE's in the non-stabilized group is much lower than the other two groups since patients had fewer exposures to study medication in this group and had fewer opportunities to develop and report adverse events. Patients who received physician optimized therapy (POT) are not presented according to their stabilization status, and their data represent average incidences across all attacks treated. Each patient on eletriptan treated on average 21.1 attacks and each patient on POT treated an average of 15.9 attacks each. Data from a third long-term safety study (316) are not presented since the data were still blinded at the time of the safety cutoff of 4/30/98.

Of 1309 patients who received eletriptan in long-term phase 3 studies, 756 (57.8%) had at least one adverse event over the course of long-term therapy, compared with 144/278 (51.8%) of those on POT. The incidences for those AE's felt to be treatment related were 40% and 30.9%, respectively. The incidences of severe AE's were 11.2% and 6.1% for eletriptan and POT, respectively.

The most common adverse events reported during long-term therapy are shown in Table 55 (ISS page 32). It includes AE's with incidences $\geq 5\%$ in any treatment group.

Table 55: Adverse Events in Long-Term Studies (≥5%)

Body System COSTART Term	Eletriptan 40mg (N=390)		Eletriptan 80mg (N=486)		Eletriptan NS (N=433)		POT (N=278)	
	A/C	T/R	A/C	T/R	A/C	T/R	A/C	T/R
At least 1 AE	65.6%	43.3%	63.4%	43.4%	44.3%	33.0%	51.8%	30.9%
<i>Body as a Whole</i>								
Abdominal Pain	8.7%	3.6%	5.8%	3.3%	1.4%	0.7%	2.5%	0.7%
Asthenia	19.5%	15.9%	14.4%	11.3%	9.9%	9.2%	10.1%	7.2%
Back Pain	6.7%	2.3%	11.3%	3.1%	2.8%	1.2%	8.3%	2.5%
Chest Pain	6.2%	5.9%	3.9%	3.5%	3.2%	3.0%	5.4%	4.7%
Flu Syndrome	6.7%	0.3%	4.7%	0.2%	0.5%	0.0%	2.9%	0.0%
Headache	8.7%	2.8%	8.4%	3.1%	3.5%	0.7%	5.4%	1.8%
Pain	6.9%	5.1%	7.6%	2.7%	2.3%	1.8%	4.0%	2.5%
<i>Digestive</i>								
Dysphagia	4.4%	4.1%	6.0%	5.6%	3.0%	3.0%	4.7%	4.7%
Nausea	18.7%	10.3%	15.6%	8.6%	10.2%	7.4%	13.3%	7.2%
Vomiting	6.9%	0.5%	9.3%	1.6%	4.6%	2.1%	5.4%	1.1%
<i>Musculoskeletal</i>								
Arthralgia	5.9%	3.1%	7.0%	2.3%	1.2%	0.7%	5.0%	0.7%
<i>Nervous</i>								
Dizziness	9.5%	6.7%	11.9%	8.8%	6.5%	5.5%	4.3%	3.6%
Hypertonia	3.8%	2.8%	9.1%	6.4%	3.5%	2.5%	4.7%	1.8%
Paresthesia	4.6%	3.8%	6.8%	5.3%	3.7%	3.5%	6.8%	5.4%
Somnolence	13.1%	11.5%	13.4%	12.8%	6.7%	6.5%	5.8%	4.0%
<i>Respiratory</i>								
Pharyngitis	6.9%	3.8%	6.2%	2.5%	0.9%	0.5%	5.8%	2.9%
RTI	10.8%	0.3%	9.1%	0.6%	2.3%	0.0%	4.7%	0.0%

Studies 108, 317; A/C = all causality, T/R = treatment related, RTI = respiratory tract infection

The most commonly reported AE's in long-term studies were similar to those reported in shorter term studies. The respiratory AE's (pharyngitis, and respiratory tract infection) were not generally felt to be treatment related by investigators. It is important to remember that these studies were open-label and patients were randomized to eletriptan or POT but there was no randomization between eletriptan doses. Although incidence of AE's between 40mg and 80mg eletriptan groups are generally comparable, it is not possible to conclude that 40mg and 80mg have similar AE profiles over the long-term due to the lack of randomization between these two groups. Incidence of AE's between stabilized eletriptan groups and POT generally showed higher incidence of AE's with eletriptan use. Chest pain was reported in 6.2%, 3.9%, and 5.4% of patients on eletriptan 40mg, 80mg, and POT, respectively.

Because, on average, eletriptan patients treated more attacks than patients on POT, there was more opportunity to develop and report AE's in the former group. The sponsor therefore conducted an analysis of AE's by attack. The 1309 patients on eletriptan treated a total of 27,594 attacks (21.1 attacks/pt) and the 278 POT patients treated 4,408 attacks (15.9 attacks/pt). The incidence of AE's per attack was 20.1% for eletriptan and 21.3% for POT. Treatment related AE's were 12.5% and 13.6%, respectively, and incidences of severe AE's were 1.3% and 0.7% respectively. This suggests that the higher incidence of AE's per patient in long-term eletriptan therapy was in part due to the increased number of attacks treated per patient.

The sponsor also analyzed AE's in patients treating at least 2 attacks per month. Of the 1309 eletriptan patients, 756 (57.8%) treated at least 2 attacks per month, compared with 148/278 (53.2%) of POT patients. Of those 756 eletriptan patients who treated 2 attacks per month, 462 (61.1%) had at least one AE compared with 56.1% for POT patients. The most common AE's reported was similar to those seen in the entire population. In general, incidences of individual AE's were slightly higher, but this could be explained on the basis that patients in this subgroup treated more attacks and therefore had more opportunity to develop and report AE's.

8.5.7 Demographic Characteristics

8.5.7.1 Age

Table 56 (ISS page 41) summarizes, by age grouping, the incidences of AE's from the single attack 1st attack from short-term multiple attack phase 2/3 studies. The number of patients in the 65-74 age group were small and comparison with the other age groups is problematic for that reason. For the 18-40 and 41-64 age groups, there were no substantial differences in the incidences of the most commonly reported adverse events. In particular, chest pain was reported roughly equally (2.9% vs. 3.1%) in the 18-40 vs. 41-64 age groups, respectively. The mean eletriptan dose for the 18-40 age group was 64.9mg, 66.3mg for the 41-64 age group, and 77.4mg for the 65-74 age group.

Table 56: Adverse Events (≥3%) by Age, in Single Attack and 1st Attack of Multiple Attack Studies

Body System COSTART Term	Eletriptan					
	18-40yrs (N= 2191)		41-64yrs (N=2200)		65-74yrs (N=41)	
	A/C	T/R	A/C	T/R	A/C	T/R
At least 1 AE	45.0%	33.1%	44.6%	32.4%	34.1%	19.5%
<i>Body as a Whole</i>						
Asthenia	6.9%	5.1%	8.0%	5.7%	2.4%	0.0%
Chest Pain	2.9%	2.6%	3.1%	2.8%	0.0%	0.0%
Headache	3.7%	1.6%	4.0%	1.8%	2.4%	0.0%
<i>Digestive</i>						
Dry Mouth	3.0%	2.9%	3.5%	3.4%	0.0%	0.0%
Nausea	7.4%	4.8%	5.5%	3.5%	0.0%	0.0%
<i>Nervous</i>						
Dizziness	6.2%	5.0%	6.7%	5.0%	4.9%	2.4%
Paresthesia	3.7%	3.3%	3.4%	3.0%	2.4%	2.4%
Somnolence	6.6%	5.6%	5.2%	4.4%	7.3%	7.3%

A/C = all causality; T/R = treatment related

8.5.7.2 Gender

Table 57 (ISS page 42) summarizes, by gender, the incidences of AE's from the single attack and 1st attack from multiple attack phase 2/3 studies. The proportion of females to males in these studies was approximately 5.3:1, with females outnumbering males by about 5.6:1 in the eletriptan treatment arms. The mean eletriptan dose per attack was 69.9mg for males and 65.6mg for females.

In subjects receiving eletriptan, the incidences of AE's were generally higher in females compared to males; however, this pattern was also seen in placebo, Cafergot, and sumatriptan treatment groups.

Table 57: Adverse Events (≥3%) by Gender, in Single Attack and 1st Attack of Multiple Attack Studies

Body System COSTART Term	Eletriptan			
	Males (N= 696)		Females (N= 3901)	
	A/C	T/R	A/C	T/R
At least 1 AE	277 (39.8%)	193 (27.7%)	1773 (45.4%)	1301 (33.4%)
<i>Body as a Whole</i>				
Asthenia	42 (6.0%)	29 (4.2%)	292 (7.5%)	214 (5.5%)
Chest Pain	16 (2.3%)	15 (2.2%)	119 (3.1%)	106 (2.7%)
Headache	22 (3.2%)	9 (1.3%)	150 (3.8%)	68 (1.7%)
<i>Digestive</i>				
Dry Mouth	24 (3.4%)	22 (3.2%)	121 (3.1%)	117 (3.0%)
Nausea	36 (5.2%)	23 (3.3%)	258 (6.6%)	167 (4.3%)
<i>Nervous</i>				
Dizziness	39 (5.6%)	30 (4.3%)	259 (6.6%)	201 (5.2%)
Paresthesia	19 (2.7%)	19 (2.7%)	139 (3.6%)	123 (3.2%)
Somnolence	31 (4.5%)	21 (3.0%)	245 (6.3%)	208 (5.3%)

A/C = all causality; T/R = treatment related

8.5.7.3 Race

In the single attack and 1st attack of multiple attack phase 2/3 studies, 45% of white experienced at least one AE, compared with 38% blacks, 34.6% Asians, and 38.5% of other races. The mean dose per attack 65.2mg for white, 60.8mg for black, 59.6mg for Asians and 59mg of other races. Since the large majority of patients were white (95%), no definite conclusions can be drawn regarding race differences since the numbers of non-white patients were so small.

8.5.8 Additional Analyses and Explorations

The sponsor's analyses of Adverse Events generally included pooled safety data from 9 single attack and short-term multiple attack studies. These nine studies included the seven pivotal efficacy studies, and study 105, the adolescent study, and study 302, an inpatient efficacy study. I chose to reanalyze the AE data with 105 and 302 excluded. I excluded 105 since the intended treatment population is adults, and I excluded 302 since the conditions of inpatient administration were so different from those expected in clinical practice. The remaining 7 studies, I felt, provided the data which best mimic eletriptan use under expected outpatient conditions. These studies were 102, 103, 104, 305, 307, 314, and 318.

The sponsor provided a single SAS transport file for each study, called "ae.xpt." I pooled the data from all 7 studies to create a single pooled AE dataset. There were a total of 18,445 AE's reported among 3/624 patients. I then selected all AE's that occurred during attack 1 only (since 102, 103, 104, 305, and 318 treated multiple attacks). This resulted in a smaller dataset consisting of 7,863 AE's reported among 2,691 patients. This dataset contained AE reports from patients who took one or two doses for their attack. The

second dose was not necessarily the same as the first dose. This made analyzing the AE data difficult. None of the studies used a single dose, therefore it is impossible to generate a table that clearly demonstrates the effects of a single dose of medication on the incidence of adverse events. Therefore, I chose to analyze the AE data in several ways:

- Incidence of AE's after treating 1 attack, regardless of the number of doses used
- Incidence of AE's after taking 1 dose of study medication
- Incidence of AE's according to the cumulative dose taken for the attack.

As the sponsor did, I chose to analyze all AE's reported for each patient (all causality). I chose not to analyze "treatment-related" AE's since this is ultimately a judgement call as to what is treatment related and is prone to bias.

In analyzing the data, I came across some limitations in the way the data were presented that impacted my review. The sponsor provided the date and time that the adverse event began, but did not provide the date and time that the patient took the first or second dose of study medication. Therefore, I was unable to determine whether the adverse event reported occurred after the first or second dose. The sponsor did, however, provide a variable ("TRTONSET") which coded for the study period at the time of the onset of the adverse event. In six of the seven studies (all except study 314), the variable coded whether the AE was associated with dose 1 or dose 2. In study 314, there was no such distinction made, even though by design patients were allowed to take a second dose within 4-24 hours for treatment of a recurrent headache. In the case of study 314, I arbitrarily chose to attribute all AE's reported in that study to dose 1. In that study, there were 177 AE's reported to have occurred in patients who took two doses, and 322 AE's occurred in patients who took only one dose.

The dataset contained 675 adverse events which occurred prior to treatment with any study medication. Since these could not possibly be treatment related, I discarded them from the analysis. This resulted in a total of 7,188 post-treatment AE's reported among 2,527 patients. In order to calculate incidences, I used the denominators shown in Table 9: Completed Phase 2/3 Oral Eletriptan Studies, Dosing Information, page 17.

8.5.8.1 Incidence of AE's After Treating 1 Attack

Table 58 shows the incidence of patients reporting at least 1 adverse event in the seven placebo controlled adult outpatient efficacy studies. Most studies generally showed a dose-related increase in adverse events. Overall, the eletriptan 40mg dose had a similar AE incidence compared with sumatriptan 100mg. Eletriptan 80mg had the highest incidence of adverse events overall, including all comparator doses.

Table 58: (RA) – Incidence of Adverse Events After Treatment of 1 Attack

Study	Eletriptan			PBO	Sumatriptan			Cafergot
	20mg	40mg	80mg		25mg	50mg	100mg	
102	97/290 33.4%	132/296 44.6%	160/312 51.3%	125/292 42.8%	-	-	-	-
103	-	212/507 41.8%	-	42/124 33.9%	-	-	-	-
104	-	72/184	95/180	32/93	65/180	61/181	-	-

Study	Eletriptan			PBO	Sumatriptan			Cafergot
	20mg	40mg	80mg		25mg	50mg	100mg	
		39.1%	52.8%	34.4%	36.1%	33.7%		
305	-	193/452 42.7%	263/461 57%	81/238 34%	-	-	-	-
307	-	90/210 42.9%	115/214 53.7%	47/105 44.8%	-	-	-	93/203 45.8%
314	49/144 34%	47/135 34.8%	73/141 51.8%	24/142 16.9%	-	-	52/129 40.3%	-
318	-	75/175 43.9%	83/164 50.6%	26/84 31%	-	59/181 32.6%	64/169 37.9%	-
Total	146/434 33.6%	821/1959 41.9%	789/1472 53.6%	377/1078 35%	65/180 36.1%	120/362 33.1%	116/298 38.9%	93/203 45.8%

All Causality

Table 59 shows the most commonly occurring AE's (all causality) in the seven adult outpatient efficacy studies, grouped by initial dose of treatment. Those occurring with an incidence of at least 2% in the high dose group (80mg) are listed. The most commonly occurring AE's are typical for those reported with other triptan medications. All high dose-associated AE's listed occurred at incidences greater than those seen with placebo with the exception of vomiting. This is probably an indication of the medication's therapeutic effect on vomiting, as described in the efficacy portion of this review (section 7.3.11, page 31).

Table 59: (RA) – Most Common Adverse Events, Grouped by Initial Dose (≥2%)

AE	20mg	40mg	80mg	PBO
ASTHENIA	3.9	5.3	12.4	3.1
NAUSEA	4.6	5.4	8.7	6.1
DIZZINESS	3.2	6.0	8.2	3.7
SOMNOLENCE	3.0	5.8	7.6	4.1
PARESTHESIA	3.2	3.1	4.5	1.9
CHEST PAIN	0.5	2.5	4.4	1.9
HEADACHE	3.0	3.6	4.3	3.3
DRY MOUTH	2.1	3.2	4.1	2.3
VASODILATATION	1.6	2.0	3.4	1.9
HYPERTONIA	1.6	1.5	3.3	0.7
DYSPHAGIA	0.7	1.7	2.9	0.7
VOMITING	0.9	1.5	2.7	4.7
ABDOMINAL PAIN	0.9	1.8	2.6	0.9
BACK PAIN	0.5	1.2	2.3	1.4
SWEATING	0.5	1.5	2.1	0.8
PHARYNGITIS	1.2	1.1	2.0	0.9

This analysis is limited because it ignores the fact that an adverse event may have occurred as a result of a second dose of medication, which may have been different than the first dose. The other analyses presented below attempt to address this issue.

8.5.8.2 Incidence of AE's Attributed to 1st Dose

The sponsor identified AE's on the basis of whether they occurred as a result of the first dose of treatment or as a result of the second dose. It is not clear to me what criteria they

used to establish this. Nonetheless, it allowed me to analyze just the AE's that occurred in association with the first dose of treatment. Of the 7,188 AE's reported post-treatment, 5,087 were attributed to the first dose of treatment. I remind the reader that in study 314, the sponsor did not provide this information, therefore I arbitrarily assumed all AE's in study 314 occurred as a result of the first dose. In study 314, the second dose was always the same as the first dose, so a patient who received placebo initially also received placebo as a second dose for recurrent pain.

Table 60 lists the most common AE's which were attributed to the first dose of study medication. It includes safety data from the seven adult outpatient efficacy studies. The table differs little from Table 59.

Table 60: (RA) Most Common AE's Attributed to 1st Dose (≥2%)

AE	20mg	40mg	80mg	PBO
ASTHENIA	3.7	3.9	10.5	1.4
NAUSEA	3.5	3.9	6.9	2.2
SOMNOLENCE	2.3	4.4	6.6	2.1
DIZZINESS	3.0	4.4	6.3	1.7
PARESTHESIA	3.2	2.6	4.1	1.3
CHEST PAIN	0.5	1.9	3.9	0.7
HEADACHE	2.3	2.5	3.7	1.5
DRY MOUTH	1.4	2.7	3.4	1.2
VASODILATATION	1.6	1.8	3.1	1.0
HYPERTONIA	0.9	0.8	2.6	0.3
DYSPHAGIA	0.7	1.6	2.6	0.2
ABDOMINAL PAIN	0.7	1.5	2.2	0.2
SWEATING	0.2	1.0	2.0	0.5
VOMITING	0.9	1.0	2.0	2.0

This, too, has its limitations. It is possible that a patient who took 80mg and then placebo may have experienced an AE after the placebo dose which was actually due to the initial 80mg ingestion. This AE is not captured by this analysis.

8.5.8.3 Incidence of AE's Grouped by Cumulative Dose Taken :

My final adverse event analysis grouped the most commonly occurring AE's according to the cumulative dose taken for the attack. In order to calculate the denominators, I used the pooled efficacy dataset which I had generated for my efficacy review. In this dataset, I calculated cumulative doses for each patient depending on whether a second dose was taken. This gave me the denominators for each cumulative dose group. This is shown in Table 61. Table 62 uses these denominators to summarize the most common AE's grouped by cumulative dose taken for attack 1.

Table 61: (RA) Cumulative Dose Groups for 1st Attack, by Study

Study	Total	0 mg	Eletriptan				Sumatriptan				Cafergot	
			20 mg	40 mg	80 mg	160 mg	25 mg	50 mg	100 mg	200 mg	C	Cx2
102	1190	182	225	291	442	50	0	0	0	0	0	0
103	631	30	0	363	238	0	0	0	0	0	0	0
104	818	93	0	157	183	24	99	194	68	0	0	0

Study	Total	0 mg	Eletriptan				Sumatriptan				Cafergot	
			20 mg	40 mg	80 mg	160 mg	25 mg	50 mg	100 mg	200 mg	C	Cx2
305	1151	238	0	339	475	99	0	0	0	0	0	0
307	732	15	0	200	274	40	0	0	0	0	68	135
314	691	142	109	134	138	39	0	0	93	36	0	0
318	773	84	0	139	170	30	0	80	181	89	0	0
All Studies	5986	784	334	1623	1920	282	99	274	342	125	68	135

Table 62: (RA) Most Common AE's, Grouped by Cumulative Dose ($\geq 2\%$ at 80mg)

	0mg n=784	20mg n=334	40mg n=1623	80mg n=1920	160mg n=282
ASTHENIA	2.6	4.5	5.2	9.6	11.0
NAUSEA	5.4	3.9	5.5	8.0	7.4
DIZZINESS	2.9	3.0	5.6	7.2	10.6
SOMNOLENCE	3.6	3.3	5.4	7.1	6.7
CHEST PAIN	0.9	0.3	2.3	4.3	2.8
HEADACHE	3.1	3.3	3.5	4.2	3.9
PARESTHESIA	1.8	3.0	3.1	4.0	3.9
DRY MOUTH	2.2	2.4	3.5	3.5	2.8
HYPERTONIA	0.8	1.5	1.2	2.8	3.5
DYSPHAGIA	0.3	0.9	1.8	2.6	1.4
VASODILATATION	1.5	1.2	2.5	2.6	3.9
VOMITING	5.1	1.2	1.8	2.3	2.5
DYSPEPSIA	0.5	1.5	1.8	2.0	1.1

The most common adverse events, grouped by cumulative dose taken, are remarkably similar to those seen in the previous analyses. There were additional AE's occurring at $\geq 2\%$ incidence in the 160mg cumulative dose group that are not shown here because they occurred at less than 2% in the 80mg group. These were abdominal pain (2.5%), back pain (2.5%), hypesthesia (2.5%), vertigo (2.5%), and palpitation (2.3%). Incidences for placebo for all of these were less than 1.1%.

8.5.9 Common and Drug-Related Adverse Events

Typically, one is interested in the most common and drug-related side effects seen after administration of single dose of a triptan. Unfortunately, none of the large, adult outpatient efficacy trials employed a single dose design. All permitted the use of a second dose for treatment of either persistent pain or recurrent pain. Often, the second dose was not the same as the first, making analysis of the AE data difficult. The sponsor and I have presented several approaches at analyzing these data. The results of these analyses are generally similar and one can draw certain conclusions about which AE's are common and most likely to be drug related. Table 63 summarizes the most common and drug related side effects. I included all AE's that were common to Table 59, Table 60, and Table 62 and which occurred at an incidence with the 80mg dose greater than placebo in all three tables. One can see that many of the side effects are typical of those seen with other triptans.

Table 63 (RA) Most Common and Drug-Related Side Effects

Asthenia
Nausea
Dizziness
Somnolence
Paresthesia
Chest pain (pressure, tightness)
Headache
Dry mouth
Vasodilatation (warmth, flushing)
Hypertonia (tightness, stiffness)
Dysphagia

8.6 Laboratory Findings

Laboratory results in the safety database were analyzed in two ways: median changes in vital signs from baseline to the last observation following treatment (analysis of central tendencies) and the incidence of clinically significant changes in vital signs (using pre-defined abnormality criteria, Table 65 (sponsor table 2.8.6.4.1)).

8.6.1 Extent of Laboratory Testing During Development

In the phase 2/3 studies, 6254 patients had at least one post-treatment laboratory sample analyzed. Since most of these studies were outpatient, the elapsed time between study administration and sample collection, which was often several days (most protocols drew lab samples within 7 days following outpatient treatment). The sponsor's abnormality algorithm did not take into account baseline abnormality status. Thus, reported incidences include those with baseline abnormalities.

8.6.2 Analysis of Central Tendencies

The percent median change in laboratory test variables measured from baseline for the single attack and 1st attack from multiple attack studies are shown in Table 64 (adapted from sponsor table 2.8.6.4.18). There were no clinically significant changes from baseline in any laboratory parameter measured. I assume that "median change from baseline" represents percent change, but that's not clear from the sponsor's table.

Table 64: Laboratory Test Data – Median Change from Baseline (Phase 2/3 Studies)

Lab Test	Units	Eletriptan			Placebo		
		N	Baseline Median	Median Δ Baseline	N	Baseline Median	Median Δ Baseline
Hemoglobin(F)	G/ DL	3,689	13.30	0.00	744	13.30	0.1
Hemoglobin(M)	G/ DL	648	15.00	0.1	168	14.70	0.00
Hematocrit(F)	%	3,661	40.00	0.2	739	39.70	0.2
Hematocrit(M)	%	644	44.75	0.4	168	44.00	0.2
Red Blood Cells	10 ⁶ /MM ³	4,336	4.40	0.00	912	4.47	0.02
MCV	Microns	4,288	91.00	0.00	901	90.93	0.00
MCH	pg	4,319	31.00	0.00	906	30.70	0.00
MCHC	G/ DL	4,291	33.50	0.00	904	33.49	0.00
Platelets	10 ³ /MM ³	4,316	247.00	0.00	902	248.00	1
White Blood Cells	10 ³ /MM ³	4,336	6.40	0.1	912	6.50	0.1
Lymphocytes (Abs)	10 ³ /MM ³	3,161	2.00	0.02	635	2.02	0.02

Lab Test	Units	Eletriptan			Placebo		
		N	Baseline Median	Median Δ Baseline	N	Baseline Median	Median Δ Baseline
Lymphocytes (%)	%	3,300	31.00	0.40	695	31.10	1.00
Neutrophils (Abs)	10 ³ /MM ³	3,147	3.79	0.1	632	3.90	0.1
Neutrophils (%)	%	3,289	58.80	0.3	692	59.00	1
Basophils (Abs)	10 ³ /MM ³	3,106	0.04	0.00	629	0.04	0.00
Basophils (%)	%	3,117	0.60	0.00	647	0.60	0.00
Eosinophils (Abs)	10 ³ /MM ³	3,141	0.15	0.00	632	0.16	0.00
Eosinophils (%)	%	3,225	2.20	0.00	675	2.20	0.00
Monocytes (Abs)	10 ³ /MM ³	3,146	0.42	0.00	632	0.42	0.00
Monocytes (%)	%	3,287	6.30	0.00	692	6.50	0.00
Total Bilirubin	MG/ DL	4,393	0.44	0.00	925	0.44	0.00
ALT (SGPT)	IU/ L	4,390	19.00	0.00	924	20.00	0.00
AST (SGOT)	IU/ L	4,226	18.00	0.00	815	18.00	0.00
Alkaline Phosphatase	IU/ L	4,235	73.00	0.00	815	72.00	0.00
Protein (total)	G/ DL	4,389	7.20	0.00	925	7.20	0.1
Albumin	G/ DL	361	4.50	0.00	107	4.50	0.00
Blood Urea Nitrogen	MG/ DL	2,094	12.00	0.00	411	12.00	0.00
Urea	MG/ DL	2,300	26.36	0.00	513	26.50	0.20
Creatinine	MG/ DL	4,393	0.80	0.00	925	0.80	0.00
Sodium	MEQ/ L	4,392	139.00	0.00	925	140.00	0.00
Potassium	MEQ/ L	4,319	4.20	0.00	905	4.20	0.00
Calcium	MG/ DL	4,390	9.30	0.04	925	9.30	0.08
Glucose (fasting)	MG/ DL	2,387	90.10	1.08	478	91.00	1.00
Glucose (random)	MG/ DL	1,932	88.30	0.00	425	89.00	0.00
Creatine Kinase	IU/ L	4,183	75.00	0.00	803	72.00	1.00
CK M'B (European)	IU/ L	146	5.00	0.00	52	4.50	0.5
CK M'B (US)	NG/ mL	55	2.40	0.10	4	2.45	0.15

8.6.3 Analysis of Outliers

Of the 6254 patients, 35.1% (2197) had clinically significant laboratory abnormalities, as defined by Table 65 (sponsor table 2.8.6.4.1).

Table 65: Criteria for Clinically Significant Laboratory Abnormalities (Outliers)

	Lab Test	Units	Criteria
HEMATOLOGY	Hemoglobin(F)	G/ DL	> 20% decrease
	Hemoglobin(M)	G/ DL	> 20% decrease
	Hematocrit(F)	%	> 20% decrease
	Hematocrit(M)	%	> 20% decrease
	Red Blood Cells	106/ MM3	> 25% decrease
	MCV		< LLN 1std > ULN 1std
	MCH		< LLN 1std > ULN 1std
	MCHC		< LLN 1std > ULN 1std
	Platelets	103/ MM3	< 75
	Platelets	103/ MM3	> 700
	White Blood Cells	103/ MM3	< 2.5

	Lab Test	Units	Criteria
			> 17.5
	Lymphocytes (Abs)	103/ MM3	< 0.5 x LLN > ULN 1std
	Lymphocytes (%)	%	< 0.5 x LLN > ULN 1std
	Neutrophils (Abs)	103/ MM3	< 1 > ULN 1std
	Neutrophils (%)	%	< 0.5 x LLN > ULN 1std
	Basophils (Abs)	103/ MM3	> ULN 1std
	Basophils (%)	%	> ULN 1std
	Eosinophils (Abs)	103/ MM3	> ULN 1std
	Eosinophils (%)	%	>= 10
	Monocytes (Abs)	103/ MM3	> ULN 1std
	Monocytes (%)	%	> ULN 1std
LIVER FUNCTION	Total Bilirubin	MG/ DL	> 1.5 x ULN
	AST/SGOT	IU/ L	> 3 x ULN
	ALT/SGPT	IU/ L	> 3 x ULN
	Alk Phos	IU/ L	> 3 x ULN
	Protein (total)	G/ DL	< 0.9 x LLN
	Protein (total)	G/ DL	> 1.1 x ULN
	Albumin	G/ DL	< 0.9 x LLN > 1.1 x ULN
RENAL FUNCTION	BUN	MG/ DL	> 1.3 x ULN
	Urea	MG/ DL	> 1.3 x ULN
	Creatinine	MG/ DL	> 1.3 x ULN
ELECTROLYTES	Sodium	MEQ/ L	< 0.95 x LLN > 1.05 x ULN
	Potassium	MEQ/ L	< 0.9 x LLN > 1.1 x ULN
	Calcium	MG/ DL	< 0.9 x LLN > 1.1 x ULN
	Glucose (fasting)	MG/ DL	< 0.8 x LLN > 1.2 x ULN
	Glucose (random)	MG/ DL	< 0.8 x LLN > 1.5 x ULN
URINE	Urine Glucose	No unit	>= 2
	Urine Protein	No unit	>= 2
	Urine Hemoglobin	No unit	>= 1
OTHER	Creatine Kinase	IU/ L	> 2 x ULN
	CK MB (European)	IU/ L	> 2 x ULN
	CK MB (US)	NG/ ML	> 2 x ULN

The next table (Table 66, ISS page 51) summarizes the most common lab abnormalities found in phase 2/3 testing. All incidences for eletriptan were comparable to incidences seen for placebo or other treatments. The incidence of ALT elevation was small (0.4%) but higher than placebo (0.2%), but lower than POT (1.2%). The high level of urinary hemoglobin was present in all treatment groups and most likely reflects the high proportion of menstruating females in the study population.

Table 66: Incidence of Common Clinically Significant Laboratory Abnormalities in Phase 2/3 Studies ($\geq 1\%$ in any group with $n > 50$)

Laboratory Test (direction of abnormality)	Eletriptan	Sumatriptan	Cafergot	POT	PBO
MCV (decrease)	1.4%	1.2%	0.0%	1.6%	2.4%
MCV (increase)	2.8%	2.0%	3.0%	2.3%	1.8%
MCH (decrease)	1.2%	2.1%	2.5%	1.2%	2.0%
MCH (increase)	1.3%	0.9%	4.0%	1.2%	0.4%
MCHC (decrease)	1.3%	1.3%	4.0%	2.3%	1.0%
Lymphocytes (increase)	1.0%	1.8%	0.0%	0.5%	1.2%
Neutrophils (increase)	1.2%	2.9%	0.8%	0.5%	0.6%
Basophils (increase)	1.5%	0.9%	0.0%	1.5%	0.6%
Eosinophils (increase)	1.8%	3.4%	0.0%	2.1%	3.0%
Monocytes (increase)	0.7%	0.9%	0.8%	1.5%	0.0%
Total Bilirubin (increase)	0.7%	0.4%	2.0%	0.0%	1.4%
ALT [SGPT] (increase)	0.4%	0.1%	0.0%	1.2%	0.2%
Potassium (increase)	0.6%	0.6%	1.0%	0.8%	1.0%
Fasting Glucose (increase)	4.2%	3.1%	0.0%	9.1%	5.3%
Random Glucose (decrease)	1.4%	1.2%	1.2%	2.2%	1.6%
Urine Hemoglobin ($\geq 1+$)	18.0%	15.8%	7.0%	16.3%	15.0%
Creatine Kinase (increase)	2.2%	3.4%	1.0%	3.1%	1.2%

Although the incidence of clinically significant liver function abnormalities were low (all less than 1%), there were 11 subjects who were discontinued due to clinically significant liver function abnormalities and they deserve special mention. Eight of the eleven were on eletriptan and four of the eight were considered treatment-related according to the investigator. I describe these cases in detail in section 8.7 below.

8.6.4 Clinical Pharmacology Studies

The clinical pharmacology studies offered a chance to collect laboratory samples soon after (hours) drug administration. The sponsor analyzed the median change from baseline in laboratory data from oral and i.v. studies separately (tables 2.8.6.4.31 and 2.8.6.4.32, not shown here). There were no clinically important differences in the median change from baseline for any measure when comparing eletriptan and placebo.

8.7 Elevated Liver Function Tests

As I reviewed the various sections of the NDA (serious adverse events, adverse dropouts, other adverse events, and laboratory data), I came across several cases of elevated liver enzymes, usually transaminases, associated with eletriptan use. Rather than discuss these cases in various separate sections of my review, I decided to discuss these cases in one location in this section.

The sponsor reports that throughout the phase 2/3 studies, there was a low incidence of clinically significant abnormalities of liver function (ALT, AST, bilirubin), all less than 1%, and within the range of spontaneous reporting in clinical studies. In the analysis of central tendencies of laboratory data presented earlier in the review (section 8.6.2, page 68), there appears to be no differences in median ALT, AST, and bilirubin levels between pre- and post-treatment measurements. The incidences of clinically significant ALT, AST, and bilirubin elevations for eletriptan treated subjects were 0.5%, 0.1% and 0.2%

respectively and for placebo were 0.8% and 0%, and 0%. These low numbers suggest that there is little reason to suspect that eletriptan causes elevations in liver enzymes.

What struck me initially as unusual were the number of discontinuations due to elevated liver enzymes reported by the sponsor. Overall, the sponsor reported 11 adverse dropouts due to clinically significant liver function abnormalities. Eight of the 11 were on eletriptan, and 4 of the 8 were considered treatment related. Unfortunately, the sponsor does not provide incidences or rates for these abnormalities, nor have I been able to easily and accurately determine the denominators to calculate them myself. The sponsor did not identify these 11 cases in their submission so I found it impossible to review all of these cases and form my own opinion as to whether the abnormality may or may not be treatment related. They did, however, identify the 4 adverse dropouts which were considered treatment related and I was able to review these.

As rough estimates, the sponsor reports 8 eletriptan-associated ADO's due to liver function abnormalities. There were a total of 5,562 patients exposed to eletriptan during drug development, for a crude incidence of 1.4 per thousand. For comparison, the rizatriptan NDA reported 4 rizatriptan-associated ADO's due to elevated LFT's out of 3,949 patients exposed, for an incidence of 1 per thousand. These are certainly comparable numbers and I found this somewhat reassuring. A more useful number, however, would take into account observation times.

I searched the pooled adverse events dataset which the sponsor used for its overall clinical safety (OCS) analyses. I found only one occurrence of hepatitis. This was subject 108-60030873. She was a 54 y/o white female from Canada who entered the study in 8/97 and treated 19 attacks with 32 doses of eletriptan 80mg. She was hospitalized in 11/97 with severe hepatitis A and was discontinued from the study. (ALT 194 (ULN 37), AST 104 (ULN 37), T.bili 209 μ mol/L (ULN 21) and AlkPhos 239 (ULN 121)). The investigator indicated that the incident was not treatment related. I reviewed the case report form, and it does document the diagnosis of hepatitis A; however, the laboratory serology results are not present (possibly because they were obtained during the inpatient stay and not included in the CRF).

I searched the laboratory datasets for the long-term studies searching for occurrences of elevated ALT or AST > 3xULN or elevated bilirubin > 1.5xULN. I found 9 such occurrences. In none of the nine cases were the ALT or AST abnormalities accompanied with a bilirubin abnormality. Interestingly, I did not find the patient listed above, which makes me question the completeness of the laboratory datasets provided. The sponsor does document that the laboratory datasets contain 6 month and 12 month laboratory data, whereas the patient listed above discontinued at 3 months and may not have been included in the datasets provided for that reason.

The sponsor provided patient narratives of serious adverse events and adverse dropouts of all patients in phase 2/3 studies. I searched the electronic narratives for all cases that reported ALT, AST, and/or bilirubin values. I discovered 18 cases where elevated ALT/AST and/or bilirubin were reported. Fourteen (14) of these received eletriptan, 1

received placebo, and 3 were on blinded therapy in the ongoing study 316. All 18 are listed below (and it does include the case described above). Unless otherwise noted, the cases represented elevated ALT/AST. Most cases (13/18) arose from the long-term studies 108, 316, and 317.

Table 67: (RA) – Subjects with Elevated Liver Function Tests (Phase 2/3 Studies)

PTID	Dosage	Doses	Attacks	Duration	Causality	Resolved	Note
305-02040283	80mg	4	3	1 day	Possible	Yes	
102-50110329	80mg	?	2	1 day	Possible	Yes	
108-50110087	80mg	?	3	22 days	Possible	Yes	
108-50290458	40mg	5	3	1.5 mos	Possible	No (↓)	
108-50330099	40-80mg	?	6	5 wks	Possible	No (↓)	
108-50370493	40mg	47	33	10 mos	Possible	No (↓)	
108-50890961	40mg	5	3	2 wks	Possible	Yes	
108-50110002	40-80mg	75	38	8 mos	Possible	Yes	
316-00030572	?	10	10	2 mos	Possible	No	
108-60030873	80mg	32	19	3 mos	Unlikely	No	Hep A
317-00480007	40	81	61	9 mos	Unlikely	No (↓)	Viral Hepatitis
305-01081395	40mg	1	1	1 day	Unlikely	Yes	Elev at baseline
305-01080025	80mg	1	1	1 day	Unlikely	No	Elev at baseline
316-01300782	?	5	5	6 wks	Unlikely	No (↓)	Bili elev at baseline
316-013100805	?	2	2	4 mos	Unlikely	No	Bili, Gilbert's Dz
108-50530494	40-80mg	9	6	3 mos	Unlikely	Yes	Negative rechallenge
317-01080204	40mg	1	1	1 day	Unlikely	?	Elev at baseline
102-50340493	PBO	4	2	7 days	Unlikely	No	Elev bilirubin

I reviewed the narratives and, when necessary, the case report forms. I determined that 9 of the 17 cases (8 eletriptan, 1 blinded therapy) were possibly related to treatment. Those that were unlikely related to treatment included cases where other diagnoses were made (viral hepatitis (2), Gilbert's Disease (1)) or where the liver function tests were elevated at baseline, or in one case with a negative rechallenge.

I describe below the 9 that were possibly related to treatment. In none of the cases did I find the AST/ALT $\geq 3xUNL$ and the bilirubin $\geq 1.5xULN$ in the same patient. One case (108-50110087) had a positive hepatitis B surface antigen and can arguably be taken out of this list. I kept it here because the investigator somehow discounted this finding and attributed the elevation to the drug for reasons that are not clear to me.

305-02040283

This 50-year-old White female took one dose of eletriptan (80mg) for her first headache on 23 Jan 97, and two doses of eletriptan (80mg) on 3 Feb 97 for treatment of a second attack, and one dose of eletriptan (80mg) on 15 Feb 97 for her last attack in the study. She was admitted to hospital on 15 Feb 97 for changes in liver function tests when she presented to the emergency department with severe tightness in the throat which started four hours after taking eletriptan (80mg). The tightness lasted for one hour. The laboratory test results were as follows:

Date	AST	ALT	GGT	LDH	Bilirubin	AP	CK
Normal	<19	<23	4- 18	120- 240	<1.1	60- 170	10- 70
	U/ L	U/ L	U/ L	U/ L	mg/ dL	U/ L	U/ L
16 Dec 96	7	7			0.39	80	34
30 Jan 97	11	15			0.27	81	66
15 Feb 97	63	177					
16 Feb 97	103	234	29	198	0.9	58	33
17 Feb 97	129	304	34	215	0.4	90	33
18 Feb 97	91	259	32	170	0.4	81	
19 Feb 97	83	251	38	183	0.4	83	31
24 Feb 97	31	115	56				
3 Mar 97	12	29			0.28	99	34

The present medical history included cholecystolithiasis (time of diagnosis unknown). Physical examination and ECG were unremarkable. Hepatitis serology was negative. There was no history of alcohol intake. Epstein- Barr antigen was positive. The subject was discharged from the hospital on 19 Feb 97. She took paracetamol as rescue medication on 3 Feb 97 and 4 Feb 97. Her concomitant medication included, dimenhydrinate, estradiol + levonorgestrel (Klimonorm) for climacteric complaints, and metoprolol (Beloc Zok Mite) for migraine prophylaxis. In the opinion of the investigator, the elevated liver enzymes and tightness in the throat were related to study drug.

Reviewer note: although the EBV serology was positive, the acute nature of the clinical symptoms shortly after eletriptan intake suggests a treatment-related event; however, it is impossible to be sure because the elevated LFT's could certainly be unrelated to the acute clinical syndrome described.

102-50110329

This 49- year- old White male took eletriptan (80mg) at 15:30 followed by eletriptan (80mg) at 20:30 on 26 Sep 96. He had labs drawn on 08 Oct 96 during visit 3. His liver function tests revealed AST (SGOT) 108 (normal 6- 37 IU/ L) and ALT (SGPT) 262 (normal 6- 46 IU/ L). He did not treat any further headaches and he was discontinued from the study. A redraw on 14 Oct 96 showed AST (SGOT) back to normal at 30 (normal 6- 37 IU/ L) and ALT (SGPT) still elevated at 73 (normal 6- 46 IU/ L). A hepatitis screen done the same day was negative. The liver function tests returned to normal by 23 Oct 96. No other tests were run

The past medical history included colon polyps. The present medical history included carpal tunnel syndrome and benign prostatic hypertrophy. His screening physical exam was unremarkable. His termination exam was significant for punctate, erythematous eruptions over his trunk in a follicular pattern. His eosinophil and white blood cell count remained normal throughout the study. He had an elevated glucose 135 (normal 680- 118 MG/ DL) on 08 Oct 96 and an elevated potassium 5.7 (normal 3.3- 5.5 MEQ/ DL) on 23 Oct 96. The screening and termination ECGs were both within normal limits. Concomitant medications included Saw- Palmetto clemastine fumarate ciprofloxacin and sumatriptan. The subject reported exposure to paint stripper during the study period. Additional adverse events that occurred were rash, prostatitis, malaise, and dyspepsia. They did not contribute to the subject's discontinuation. In the opinion of the investigator the increased liver function tests were due to the study drug.

108-50110087

This 39-year-old White female had baseline laboratories drawn on 26 Nov 96. They revealed AST (SGOT) 43 IU/L (normal 5-37 IU/L), ALT (SGPT) 22 (normal 6-37 IU/L), and total bilirubin 0.3 MG/DL (normal 0.2-1.2 MG/DL). The subject took eletriptan (40mg) to treat 3 attacks between 29 Nov 96 and 21 Dec 96.

Liver function tests drawn on 30 Dec 96 were normal. The dose was increased to eletriptan (80mg) and the subject treated 13 attacks between 08 Jan 97 and 16 Apr 97. The labs were routinely drawn at the clinic visit 4 on 21 Apr 97. Those results revealed AST (SGOT) 136 IU/ L (normal 5-37 IU/L), ALT (SGPT) 119 IU/L (normal 6-37 IU/L), and normal total bilirubin. The subject did not take any more study medication and was discontinued from the study. A follow up test done on 24 Apr 97 revealed AST 57 IU/L, ALT 61 IU/L, a normal total bilirubin, and a positive hepatitis B surface antigen. A repeat test on 30 Apr 97 revealed normal liver function values. The subject participated in the core study (160-102-5011-0332) and

took 3 doses of eletriptan (40mg) and 2 doses of placebo to treat 3 attacks between 21 Sep 96 and 10 Oct 96.

The past medical history included a fallopian cyst. There was no present medical history. The screening physical examination was unremarkable. The termination physical examination was significant for a few scattered rhonchi. The laboratory findings were remarkable for CK 223 IU/L (normal 24-170) and CKMB-Mass 4.1 NG/ML (normal 0.0- 5.0 NG/ML) on 26 Nov 96, hematocrit 33.4% (normal 35.0-47.0%) on 30 Dec 96, and total protein 5.6 G/DL (normal 6.0-8.4 G/DL) on 30 Dec 96. Concomitant medications included acetaminophen with codeine taken intermittently throughout the study period. Additional adverse events included drowsiness, three upper respiratory infections, tiredness, and a backache. None of them contributed to the subject's discontinuation. In the opinion of the investigator, the event was due to the study drug.

Reviewer's note: This case is questionable, because of the positive hepatitis B surface antigen. I am unable to determine why the investigator discounted this finding and attributed the abnormality to study medication.

108-50290458

This 35-year-old White female took 5 doses of eletriptan (40mg) to treat 3 attacks between 18 Mar 97 and 07 May 97. Rescue medications taken to treat the attack of 05 Apr 97 included meclizemate, naproxen, and metoclopramide hydrochloride. On 09 May 97 she experienced a mild elevation of ALT and was discontinued from the study. The outcome of the adverse event is unknown. The subject had been included in core study 160- 102- 5029- 0916 and took 3 doses of eletriptan (20mg) and 2 doses of placebo to treat 3 attacks from 28 Dec 96 to 10 Feb 97.

Present medical history included degenerative disc and myopia. Concomitant medication taken daily was ethinyl estradiol/ ethynodiol diacetate. The screening and termination physical examinations were unremarkable. The screening laboratory values were not clinically significant with AST 21 (normal 5- 37 IU/L) and ALT 17 (normal 6- 37 IU/L). Laboratory values at visit 2 on 09 May 97 showed AST 39 (normal 5- 37 IU/L) and ALT 63 (normal 6- 37 IU/L). Follow up laboratory values on 15 May 97 showed AST 33 (normal 5- 37 IU/L) and ALT 54 (normal 6- 37 IU/L). Additional concomitant medications taken by this subject included sumatriptan and orphenadrine citrate. The only additional adverse event was sore muscles. In the opinion of the investigator, the event was due to study drug.

108-50330099

This 54-year-old White female had screening liver function tests revealing AST (SGOT) 45 (normal 5-37 IU/L), ALT (SGPT) 50 (normal 6-37 IU/L) and normal total bilirubin on 02 Dec 96. She took eletriptan (40mg) on 10 Dec 96 for a migraine attack. Liver function tests taken on 16 Dec 96 revealed normal values. She treated two more attacks on 12 Dec 96 and 21 Dec 96 with eletriptan (40mg). Labs were drawn on 02 Jan 97. They revealed normal liver function values. The subject's dose was increased to eletriptan (80mg) and doses were taken on 06 Jan 97, 12 Jan 97, and 19 Jan 97. On 29 Jan 97 her liver functions tests showed AST 218, ALT 249, and alkaline phosphatase 214 (normal 31-121 IU/L). The total bilirubin was normal. She treated another migraine attack on 30 Jan 97. Liver function tests were obtained on 7 Feb 97 and they revealed AST 43, ALT 57, and alkaline phosphatase 161. The total bilirubin remained normal. The subject was discontinued from the study. The subject returned for a follow up blood draw on 21 Feb 97. Her results revealed AST 43 (normal 5-37 IU/L), ALT 44 (normal 6-37 IU/L), alkaline phosphatase 130 IU/L (normal 31- 121 IU/L) and a normal total bilirubin. The investigator felt that this set of labs was acceptable and did not need to be repeated. The subject participated in the core study (160-102-5033-0183) and took three doses of eletriptan (80mg) to treat three attacks between 23 Oct 96 and 24 Nov 96.

The past medical history included uterine prolapse and trigeminal neuralgia. The present medical history included allergy to golden rod. The screening and termination physical examinations were unremarkable. Laboratory findings were significant for neutrophils 32.1 (40.9-77%), lymphocytes 47.6 (normal 15.5- 46.6%), and monocytes 13.8 (normal 2.8- 12.9%) on 02 Jan 97. Concomitant medications included nadolol, nortriptyline, propoxyphene napsylate/acetaminophen, sumatriptan, and acetaminophen/codeine.

Additional adverse events that occurred were drowsiness and dizziness which did not contribute to the discontinuation. In the opinion of the investigator, the laboratory abnormalities were due to the study drug.

Reviewer's note: although the LFT's were mildly abnormal at baseline, they did normalize initially and the marked elevation seen subsequently may have been related to treatment.

108-50370493

This 38- year- old White female took six doses of eletriptan (40mg) to treat three attacks between 16 Mar 97 and 30 Mar 97. The dose was increased to eletriptan (80mg). The subject took 41 doses of eletriptan (80mg) to treat 31 attacks between 15 Apr 97 and 29 Jan 98. The clinic visit 6 laboratory draw on 03 Feb 98 revealed the following elevated values: AST (SGOT) of 117 (normal 5- 37 IU/ L) and ALT (SGPT) of 256 (normal 6- 37 IU/ L). The subject was advised to withhold study drug and return to the clinic for follow- up. The retest of 06 Feb 98 indicated AST (SGOT) of 80 (normal 5- 37 IU/ L) and ALT (SGPT) of 192 (normal 6- 37 IU/ L). The investigator discontinued the subject and the termination laboratory enzyme values were AST (SGOT) of 56 (normal 5- 37 IU/ L) and ALT (SGPT) of 110 (normal 6- 37 IU/ L). The investigator noted the AST as not clinically significant and the subject was asked to return for further follow- up. The retest of 19 Feb 98 indicated AST (SGOT) of 54 (normal 5- 37 IU/ L) and ALT (SGPT) of 78 (normal 6- 37 IU/ L). The investigator noted the AST as being not clinically significant. The retest of 27 Feb 98 indicated AST (SGOT) of 50 (normal 5- 37 IU/ L) and ALT (SGPT) of 81 (normal 6- 37 IU/ L). The investigator decided that further follow- up was not necessary. The subject participated in the core study (160- 102- 5037- 1099) and took five doses of eletriptan (20mg) to treat three attacks between 25 Jan 97 and 27 Feb 97.

Propranolol was started as migraine prophylaxis on 25 Jan 98. The screening physical examination was remarkable for the contact dermatitis and the termination examination was notable for the contact dermatitis being resolved. The screening laboratory was within normal limits with AST (SGOT) of 18 (normal 5- 37 IU/ L) and ALT (SGPT) of 14 (normal 6- 37 IU/ L). The liver enzymes remained normal until visit 6. Additional concomitant medications included acetylsalicylic acid, sumatriptan, ibuprofen, naproxen sodium, and acetaminophen/ acetylsalicylic acid/ caffeine. Additional adverse events included tearfulness, and non- migraine headache. In the opinion of the investigator, the elevated liver enzymes were due to study drug.

108-50890961

This 49- year- old White male took five doses of eletriptan (40mg) to treat three attacks between 14 Sep 97 and 26 Sep 97. The clinic visit 2 laboratory values collected on 06 Oct 97 revealed AST (SGOT) of 75 (normal 6- 37 U/ L), ALT (SGPT) of 120 (normal 6- 46 U/ L), and alkaline phosphatase of 126 (normal 31- 121 U/ L). The investigator noted these values to be clinically significant. The subject was asked to withhold study drug and return to clinic for follow- up. A retest on 15 Oct 97 showed AST (SGOT) normal at 31, alkaline phosphatase normal at 108, and ALT (SGPT) slightly elevated at 49. The investigator noted the ALT to be not clinically significant, but discontinued the subject from the study. The termination values were as follows: AST (SGOT) of 27 (normal 6- 37 U/ L), ALT (SGPT) of 40 (normal 6- 46 U/ L), and alkaline phosphatase of 183 (normal 31- 121 U/ L). The investigator determined the elevated alkaline phosphatase to be not clinically significant. The subject participated in the core study (160- 103- 5089- 0442) and took two doses of eletriptan (40mg) to treat one attack on 13 Aug 97 and took one dose of eletriptan (40mg) to treat the second attack on 24 Aug 97. A single dose of eletriptan (20mg) was taken on 15 Aug 97 for pharmacokinetic testing.

No present medical history was noted. Concomitant medications taken daily included nortriptyline and nadolol. The screening physical examination was unremarkable and the termination examination was unchanged. The screening laboratory values were within normal limits. No additional concomitant medications were noted. The only additional adverse event included painful left arm caused by a fall. In the opinion of the investigator, the elevated enzymes were due to study drug.

108-50110002

This 44- year- old White female had baseline laboratories drawn on 14 Nov 96 that were normal. She took 6 doses of eletriptan (40mg) to treat 3 attacks between 18 Nov 96 and 01 Dec 96. The dose was increased to eletriptan (80mg) and she took 69 doses of eletriptan (80mg) to treat 35 attacks between 10 Dec 96 and 16 Jul 97. Laboratory samples drawn on 07 Jan 97 revealed AST (SGOT) 30 IU/ L (normal 5- 37), ALT (SGPT) 39 IU/ L (normal 6- 37 IU/ L), and a normal creatine kinase. The investigator did not feel that the laboratories were clinically significant. The ALT returned to normal by 07 Apr 97. Laboratory samples drawn on 15 Jul 97 revealed AST (SGOT) 157 (normal 5- 37 IU/ L), ALT (SGPT) 64 (normal 6- 37 IU/ L), and creatinine kinase 4050 IU/ L (normal 24- 170 IU/ L) with CKMB- MASS 12.1 NG/ ML (normal 0.0- 5.0 NG/ ML). She did not demonstrate any clinical correlates to the abnormal laboratories. The study investigator reported that the subject routinely performed strenuous exercise (weightlifting). She did not take any additional study medication and was withdrawn from the study. Subsequent laboratory samples revealed the following:

Date	CK- MB (0.0- 5.0 NG/ ML)	AST (5- 37 IU/ L)	ALT (6- 37 IU/ L)	CK (24- 170 IU/ L)
18Jul97	2. 5	83	68	998
24Jul97		30	54	68
07Aug97		22	29	56

Her laboratory values returned to normal by 07 Aug 97. The subject participated in the core study (160- 102- 5011- 0331) and took three doses of placebo and two doses of eletriptan (80mg) to treat three attacks between 24 Sep 96 and 15 Oct 96. Past medical history included a benign ovarian cyst removed in 1972, heel spur removed in 1991, tubal ligation in 1987, and two cesarean births. Present medical history included colitis since 1992 and non- migraine headaches. Concomitant medication taken daily included multivitamins, L- lysine, and calcium. The baseline physical examination was significant for a systolic murmur grade II/ VI. The electrocardiogram revealed a sinus arrhythmia which was read as not clinically significant by the investigator. The termination examination was significant for resolution of the systolic murmur. The remainder of the laboratories were unremarkable. Additional concomitant medications included acetaminophen/ diphenhydramine, acetylsalicylic acid/ sodium bicarbonate/ citric acid, acetaminophen/ oxycodone hydrochloride, and metoclopramide hydrochloride. Additional adverse events included muscle soreness. The investigator felt that the elevated laboratories were due to physical exertion and not study drug.

Reviewer's note: the livery enzyme abnormalities were accompanied with significant CK elevation; therefore, the origin of the transaminase elevation is most likely muscle and not liver. The sponsor attributed the elevation to strenuous physical exercise, which she routinely performed. I'm not so sure, therefore, this could be treatment related, although not due to liver damage.

316-00030572 (Blinded Treatment)

Core Study: 160- 314 (160- 314- 0003- 0376 - took one dose of double- blind placebo to treat one attack on 21 Sep 95). This 56- year- old White female was included in study 316- 0003- 0572 and took ten doses of double- blind treatment to treat ten attacks between 4 Oct 96 and 11 Dec 96. She was withdrawn from the study and the study drug permanently discontinued on 19 Dec 96 when she was found to have elevated alanine aminotransferase (ALT) from 7 Nov 96. The details of the liver function tests are as follows:

Test Normal Range	Bilirubin 5- 17 mmol/ l	AST 10- 35 U/ l	ALT 10- 35 U/ l	AP 80- 275 U/ l
17 Sep 96 (screen)	7	21	29	184
10 Oct 96	10	35	39	180
7 Nov 96	8	34	64	200
26 Nov 96	7	29	37	200
19 Dec 96	9	37	62	198

There was no significant past or present medical history. The screening and termination physical exams were unremarkable. Her concomitant medications were as follows: paracetamol on 7 Oct 96, 23 Oct 96, 30 Oct 96, 22 Nov 96, and 18 Dec 96; diazepam on 7 Oct 96; and sumatriptan on 23 Oct 96 and 18 Dec 96. In addition the following rescue medications were used:

Medication	Time of dose	Date
Paracetamol	07: 10	20 Oct 96
Paracetamol	06: 00	29 Oct 96
Acetylsalicylate	15: 00	19 Nov 96
Sumatriptan	20: 00	19 Nov 96
Paracetamol	09: 15	20 Nov 96
Metoclopramide	09: 05	7 Dec 96
Paracetamol	09: 05	7 Dec 96
Diazepam	09: 05	7 Dec 96
Paracetamol	08: 30	12 Dec 96
Metoclopramide	22: 00	12 Dec 96
Diazepam	22: 00	12 Dec 96

Additional adverse events that occurred were a whirring feeling in the fingers, edema in the fingers, dryness in the mouth and nausea that did not contribute to the discontinuation. In the opinion of the investigator the event was due to the study drug.

As one can see, none of the cases provides conclusive proof of eletriptan-induced elevated liver function tests, although some of the cases are suggestive. I don't think there is a significant safety signal here, but I would like to review additional data from the long-term safety studies that were ongoing at the time of the submission.

8.8 Vital Signs

Vital signs in the safety database were analyzed in two ways: median changes in vital signs from baseline to the last observation following treatment (analysis of central tendencies) and the incidence of clinically significant changes in vital signs (using pre-defined abnormality criteria). As with the case with laboratory data, most phase 2/3 studies were outpatient studies; therefore, post-treatment vital sign measurements often occurred days after the last dose of study medication was taken and these data do not provide information regarding acute drug-related vital sign changes.

With this limitation in mind, the vital signs data in the phase 2/3 studies failed to reveal any clinically significant changes in vital signs during treatment. In addition, there was no evidence of persistent or progressive changes from the long-term studies. There was no evidence of a dose-response in vital signs changes, and there were no effects of age, gender or race seen on vital signs. I present the median changes from baseline tables and tables of clinically significant vital sign abnormalities in Appendix C - page 118.

I chose to do a limited analysis of vital signs data from the phase 3 adult outpatient efficacy trials. Unlike the sponsor, which chose the last post-treatment vital sign measurement, I chose to analyze all post-treatment measurements. I pooled vital signs data from studies 102, 103, 104, 305, 307, 314, and 318. I discarded data from patients who failed to take study medication. I analyzed all attacks treated and used cumulative dose taken per attack as the grouping variable. There were 5,986 patients who contributed vital signs data for this analysis.

Figure 5 is a scatter plot showing the changes from baseline in post-treatment diastolic blood pressure measurements, grouped by total eletriptan dose. There was no evidence of a dose response increase or decrease in diastolic blood pressure from the graph. Table 68 shows the mean changes from baseline. They were all close to zero. The nominal p value for this analysis (ANOVA) was nominally positive at 0.0435 and a pairwise comparison indicated that the slight drop in diastolic BP for the 160mg group was nominally significant compared with placebo.

Figure 5: (RA) Diastolic Blood Pressure – Changes from Baseline

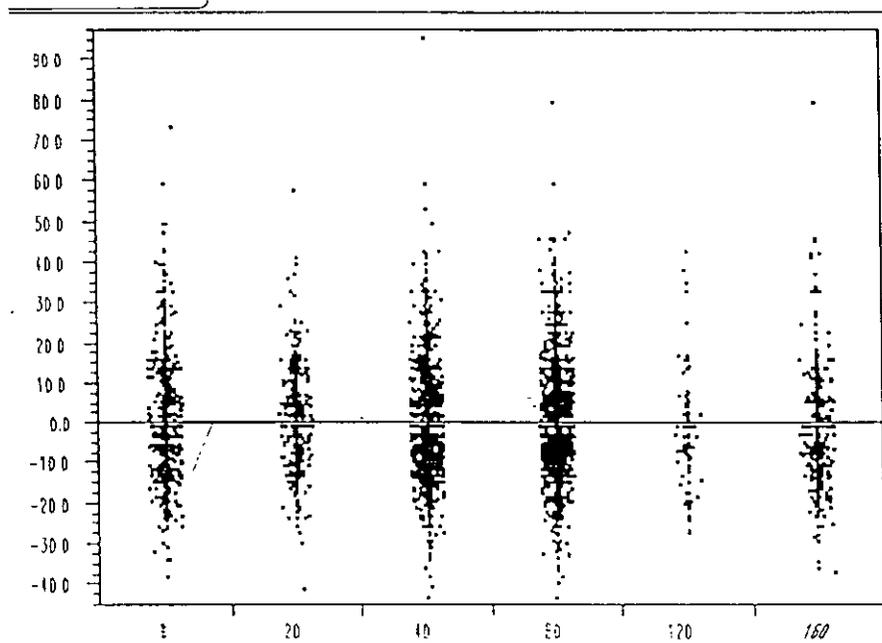


Table 68: (RA) Diastolic Blood Pressure – Mean Changes from Baseline

Total Dose (mg)	N	Mean % Change	Std Error
0	1076	0.75302	0.3569
20	516	0.44326	0.5154
40	2554	0.48570	0.2316
80	3253	0.47180	0.2053
120	92	-1.08098	1.2205
160	682	-0.92576	0.4483

All attacks, studies 102, 103, 104, 305, 307, 314, 318
 Std Error uses a pooled estimate of error variance

Figure 6 shows the same scatter plot, but for systolic blood pressure. Again, no obvious between group difference are seen. Table 69 shows the mean changes in systolic blood pressures by total dose taken. They were all close to zero. The p value for this analysis was not significant (p=0.2366, ANOVA).

Figure 6: (RA) Systolic Blood Pressures – Changes from Baseline

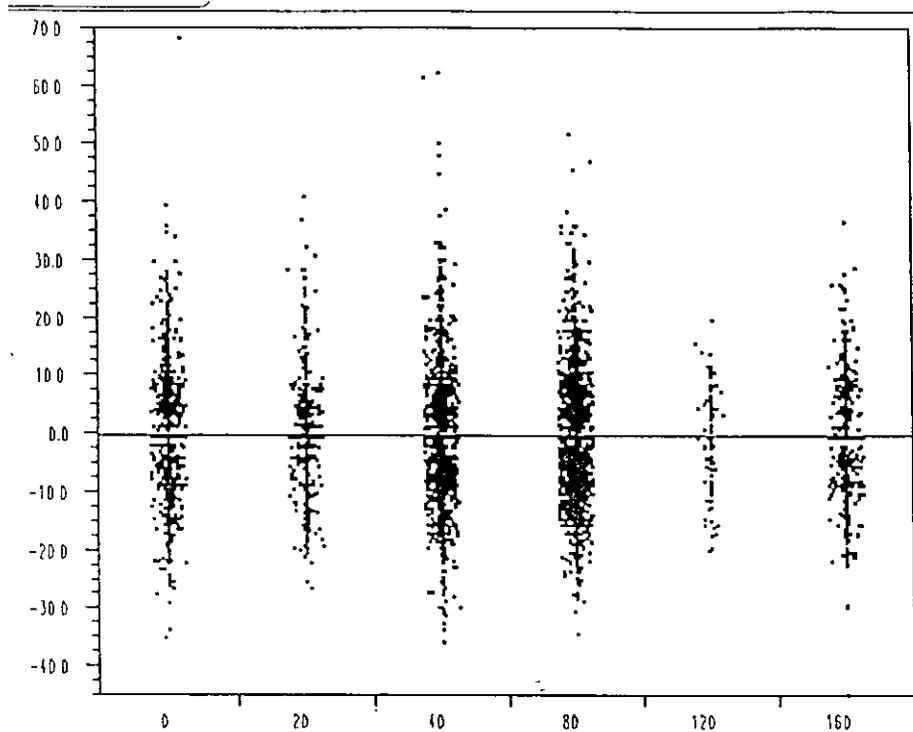


Table 69: (RA) Systolic Blood Pressures – Mean Changes from Baseline

Total Dose (mg)	N	Mean % Change	Std Error
0	1076	0.20009	0.2989
20	516	0.67118	0.4316
40	2553	-0.02909	0.1940
80	3253	-0.04764	0.1719
120	92	-1.04745	1.0221
160	682	-0.63099	0.3754

All attacks, studies 102, 103, 104, 305, 307, 314, 318
Std Error uses a pooled estimate of error variance

Figure 7 shows the same scatter plot, but for pulse. Again, no obvious between group difference are seen. Table 70 shows the mean changes in pulse by total dose taken. The p value for this analysis was not significant (p=0.6384, ANOVA).

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Figure 7: (RA) Pulse – Changes from Baseline

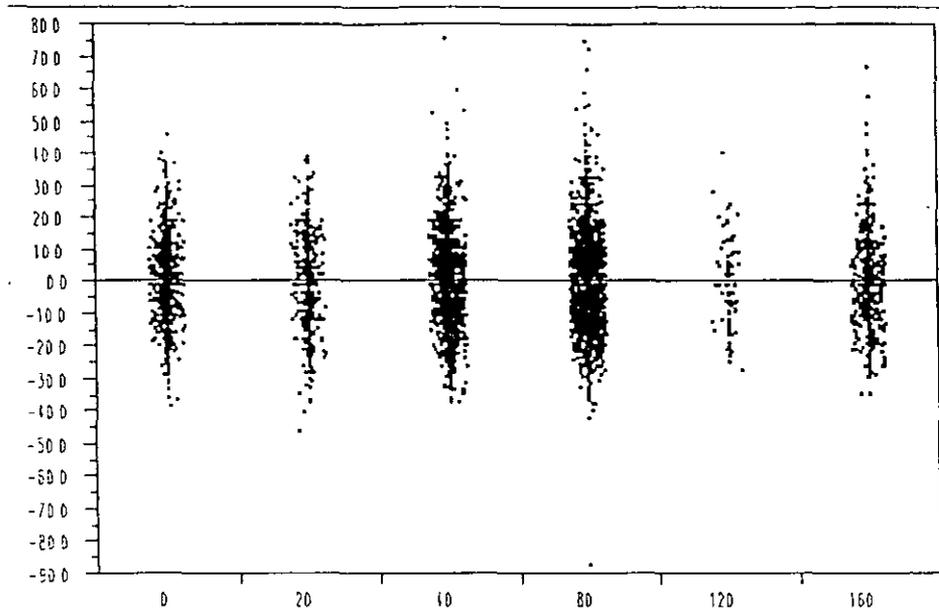


Table 70: Pulse – Mean Changes from Baseline

Total Dose (mg)	N	Mean % Change	Std Error
0	1075	0.741798	0.3917
20	515	0.793419	0.5660
40	2545	0.210392	0.2546
80	3249	0.431362	0.2253
120	93	-0.90459	1.3318
160	682	0.815927	0.4918

All attacks, studies 102, 103, 104, 305, 307, 314, 318
 Std Error uses a pooled estimate of error variance

The sponsor also analyzed the clinical pharmacology studies for changes in vital signs. These afford better data since many studies were inpatient and vital signs were monitored during treatment. The incidence of clinically significant changes in supine blood pressure and pulse rate was very low, with similar percentages reported for eletriptan and placebo, except for decreased pulse, which was higher in placebo-treated subjects.

Several clinical pharmacology studies examined the pharmacodynamic effect of oral and intravenous eletriptan on blood pressure and pulse rate, with measurements taken at specified times post-dose. Eletriptan was associated with small, transient increases in blood pressure consistent with its mechanism of action. Statistically significant changes in diastolic blood pressure were seen at oral doses of 60mg or greater. Statistically significant increases in systolic blood pressure were less frequent and were seen at oral doses of 80mg or greater.

Study 230 was a single dose hemodynamic study in healthy volunteers, including oral doses of eletriptan 40mg, sumatriptan 50mg, and placebo. Blood pressure readings were taken at specified intervals up to five hours post-dose. Arithmetic mean maximum

increases from baseline in supine systolic blood pressure were 12.5mm for eletriptan 40mg, 15.1mm following sumatriptan 50mg, and 10.7mm following placebo. The values for diastolic blood pressure were 15.8mm, 13.6mm, and 10.1mm, respectively.

I refer the reader to the biopharmaceutical review for more details on the clinical pharmacology studies.

8.9 ECG

In the phase 2/3 studies, ECG's were collected at various time intervals ranging from a few hours to a few weeks after dosing with study drug. Therefore, ECG data from this population are limited in their ability to identify acute treatment related cardiac conduction changes. Given this limitation, the median changes in ECG variables (PR, QRS, QT, QTc, heart rate) indicated no clinically significant changes following eletriptan treatment. In addition, there was no evidence of persistent or progressive changes from the long term studies.

The incidence of clinically significant ECG changes was very low. Increases from baseline in QTc interval for all phase 2/3 studies showed a similar distribution for eletriptan, placebo, and sumatriptan, with 1% (52/5208) eletriptan-treated subjects, 1.6% (8/514) placebo-treated subjects, and 1.1% (9/797) sumatriptan-treated subjects having increases from baseline of 60 msec or greater.

There were no dose related trends in median changes from baseline or incidence of clinically significant ECG abnormalities. There were no evidence of age, gender, or race effects in ECG abnormalities (although certain age and race subgroups were small). I present the median changes from baseline tables and tables of clinically significant ECG abnormalities in Appendix D - page 120.

Across all phase 2/3 studies, there were 5 eletriptan treated subjects (0.1%) who had ECG recorded with QTc \geq 500 msec or greater. The details of these 5 cases are described below.

103-50740097

This patient had baseline ECG data on 4/28/97 of HR 70, QT 460 msec and QTc 497. The subject took eletriptan 40mg on 5/27/97 (one week after dosing) and had their next ECG recorded on 6/3/97 which showed a HR 74, QT 460 and QTc 511 msec. The same subject took eletriptan 80mg on 10/26/97 and had a final ECG 8 days later (11/3/97) showing HR 53, QT 480msec and QTc 451. The subject took loratidine (Claritin), acetaminophen, cisapride, vitamin E and a calcium, zinc, and magnesium preparations.

302-00340230

This patient had screening ECG on 8/26/97 of HR 65, QT 440 msec and QTc 485 msec. A baseline ECG on 9/22/94 showed HR 71, QT 440 msec and QTc 479 msec. The subject took eletriptan 30mg later on 9/22/94 and given lysine aspirin 1 g i.v. as rescue. An ECG on hour after the rescue medication and approximately 5 hours after eletriptan) showed HR 72, QT 460 and QTc 504. The abnormal reading represented a change from baseline of less than 30 msec. The final ECG on 9/29 94 showed a HR 58, QT 420 msec and QTc 413 msec. The abnormal QTc is confounded by the recent use of rescue medication.

302-00400713

This patient had screening ECG on 11/9/94 of HR 75, QT 408 msec and QTc 456 msec. A baseline ECG on 11/26/94 showed HR of 82, QT 460 msec and QTc 538 msec. The subject took eletriptan 30mg that day and ECG 4 hours later showed HR 84, QT 460 and QTc 544. The subject had an abnormal QTc at baseline which changed little post-treatment. A final ECG on 11/30/94 showed HR 70, QT 448, and QTc 484. The subject was also taking ubiquinone at the time of dosing.

307-02190230 and 307-00950276

Both these patients had abnormal QTc values recorded in error. The first subject had their QTc value of 433 msec recorded incorrectly as the QT value. When the QTc was calculated from this value, an erroneous value of 536 msec was obtained. The second subject had an incorrect heart rate of 160 recorded instead of the correct value of 65. The correct QTc using HR 65 was 375 msec (not the erroneous value of 588 msec using the incorrect heart rate).

ECG data from the clinical pharmacology studies were analyzed by calculating median changes from baseline and the incidence of clinically significant changes. Median changes in ECG variables indicated no clinically significant changes following eletriptan treatment. The incidence of clinically significant ECG changes was very low. Increases from baseline in QTc interval showed a similar distribution for eletriptan and placebo in both oral and i.v. studies and there was a single incidence of an eletriptan treated subject having an increase from baseline of 60 msec or greater (following i.v. administration). There were no record of ACE with QTc interval of ≥ 500 msec in the clinical pharmacology program.

ECG data, including evaluation of QTc interval, were obtained at times near C_{max} in six other studies: 001, 002 (pediatric), 003 (lactating women), 004 (menstruation), 101 (migraine patients), and 208. ECG data were also collected on subjects receiving multiple dose eletriptan over a period of 5 or 7 days in study 205. For all of these studies, baseline ECG's were obtained just prior to dosing. Clinically significant QTc changes were defined as a QTc ≥ 500 msec or a ≥ 60 msec change from baseline.

Study 001 evaluated the QTc at 1, 2, 4, 8, 12, 24, and 48 hours after a single dose of 10, 30, 60 90 or 120mg or placebo in a total of 77 healthy males. No subject had a QTc ≥ 500 msec in the study. Two subjects had QTc increased ≥ 60 msec from baseline: one took 30mg had a 76 msec rise from baseline (376 to 452) 8 hours after dosing, and another took 60mg and had a 66 msec rise (367 to 433) 4 hours after dosing. These changes had resolved by the time of the next ECG recording.

Study 002 evaluated the QTc at baseline, 1, 12, and 24 hours after dosing in 24 pediatric subjects using oral doses of 20, 40 or 80mg. Study 003 in 8 healthy lactating women and study 004 in 16 healthy women at different phases of the menstrual cycle evaluated the QTc at baseline, 1 and 24 hours after a single 80mg dose. No clinically significant ECG changes were seen in any of these three studies.

Study 101, which studied migraine patients with eletriptan in the presence and absence of a migraine attack. In this study, ECG's were obtained at baseline (immediately before study drug administration) and at one and two hours after dosing. Clinically significant QTc changes were defined as a QTc interval ≥ 500 msec, or any QTc interval with a ≥ 60

msec increase from baseline. Data were available from 35 subjects treated with migraine absent and 34 with migraine present. No subject had a QTc ≥ 500 msec, or any QTc interval with a ≥ 60 msec increase from baseline.

Study 208 evaluated the QTc interval at baseline, 1, 2, 4, 8, 12, and 24 hours in 16 healthy males taking a single dose of 30, 60, 90, or 120mg. No subjects had a QTc ≥ 500 msec. One subject had a 62 msec increase (392 to 454) approximately 1 hour after oral administration of eletriptan 120mg which resolved at 2 hours.

Study 205 evaluated the QTc in three cohorts receiving multiple dose eletriptan. Seven males in each 2 cohorts received either 20mg, 30mg or placebo over 5 days given bid on days 1-4 and tid on day 5. Eight males in a third cohort received 20mg or placebo bid for 6 days and a single dose on day 7. ECG data for cohorts 1 and 2 were obtained at screening, baseline, and daily during the dosing period. Cohort three had ECG data at screening, baseline, and days 1, 2 and 5, and on the morning after the last study day, and at a follow-up visit. While on study drug, there were no clinically significant QTc changes seen.

In summary, in the clinical pharmacology studies that collected ECG data during study administration, there were random and transient changes in the QTc interval. Only three subjects demonstrated an increase from baseline of ≥ 60 msec; the range was 62 to 76 msec. The results from these studies do not provide evidence of a relationship between oral administration eletriptan and QTc prolongation.

8.10 Safety in Adolescents

The draft eletriptan labeling contains a statement that the safety profile of eletriptan was similar to that observed in adults. This conclusion comes from the safety data from study 105, the adolescent efficacy study. This was a single attack outpatient study in 274 adolescent migraineurs (12-17 years). The 40mg dose was compared to placebo. A second dose of 40mg for both groups was permitted after 2 hours for headache recurrence. Rescue was permitted after 2 hours. As I described in the efficacy section of this review, the study was negative on its primary outcome measure—the 2 hour headache response rates were similar between drug and placebo (57% for both groups).

Overall, 42% of the eletriptan group and 30% of the placebo group reported at least one adverse event. The most commonly occurring AE's were similar to those reported in adults: somnolence, dizziness, asthenia, nausea, abdominal pain, dry mouth, hypertonia (including jaw tightness, neck tightness and stiff neck), chest pain.

There were no deaths and no adverse dropouts. There was one serious adverse event in the placebo/electriptan 40mg group. This patient had status migrainosus which resolved following hospitalization. This was probably due to the underlying illness and not treatment.

The incidence of laboratory test abnormalities were 11.7% in placebo and 25% in eletriptan patients. About half of these were urine hemoglobin. Other than this, there was

no relationship seen between any laboratory test variable and study treatment. Analyses of vital signs and ECG data failed to reveal a clinically significant safety concern.

8.11 Long-Term Safety

Long-term safety data were available from studies 108 and 317. A third long-term safety study (316) was still blinded at the time of the safety cutoff date of 4/30/99. Both 108 and 317 were similar in design. They were open-label, physician optimized controlled studies. Patients on eletriptan had a 6-headache run in period where the eletriptan dose could be adjusted as necessary between 40mg and 80mg. After this period, patients entered a "dose-stabilization" period of either 40mg or 80mg. Patients on physician-optimized therapy generally took sumatriptan.

I previously discussed long-term exposure to eletriptan in section 5.3, page 12, but I repeat that section here for completeness. In the long-term phase 3 studies, a total of 1309 patients had received eletriptan where treatment allocation was known at database cutoff (4/30/98). The long-term exposures are shown in Table 71 (adapted from sponsor table 2.8.2.13 in the NDA summary). One can see that exposures at the high dose comply with ICH and Division guidelines for 1 year exposures (≥ 100 patients exposed for one year, each treating ≥ 2 attacks/month) however the database falls short for 6 months exposures at the high dose (272 actual vs. the ≥ 300 patients requested). I point out that an additional 98 were receiving blinded therapy at 6 months and it is likely that they will achieve adequate exposures to the 80mg dose at 6 months once the blind is broken. I include the safety of chronic intermittent eletriptan therapy in each sub-section of my safety review, and I refer the reader to the appropriate sub-section.

Table 71: Long Term Exposure (sponsor table 2.8.2.13)

	Freq	Treated	Visit at 6 mo.	Visit at 12 mo.
Eletriptan 40 mg	All attacks	390	309	133
	≥ 2 /month	262	212	96
Eletriptan 80 mg	All attacks	486	352	122
	≥ 2 /month	357	272	108
POT	All attacks	278	141	61
	≥ 2 /month	148	87	43
Blinded Therapy	All attacks	411	184	67
	≥ 2 /month	249	98	40

POT = physician optimized therapy

8.12 Four-Month Safety Update

The four-month safety update was very small and provided little new insight into the safety of the medication. The original NDA submission had a safety cutoff date of 4/30/99; however, the sponsor also submitted any SAE's known to have occurred by 7/17/98. The four-month safety update was submitted on 2/22/99. The report includes SAE's reported through 10/31/98. At this time, the sponsor reports these new totals from the three ongoing long-term safety studies:

- 2,533 had enrolled in long-term safety studies (108, 316, 317) of which 749 had completed the study, 1042 had been discontinued, and 742 were ongoing.
- No deaths have been recorded

- In ongoing long-term safety trials, SAE reports during the reporting period (7/17/98 – 10/31/98) number 10 for eletriptan, 4 for comparator, and 1 for blinded therapy. None of the SAE's was attributed to study drug by investigators.

The 10 new SAE's reported for eletriptan were the following: application/injection/insertion site pain (1), pain body as a whole (1), migraine (1), neuralgia (1), goiter (1), malignant breast neoplasm female (1), medical/surgical procedure (1), pulmonary embolism (1), endometriosis (1), renal calculus (1).

The 4 new SAE's reported for sumatriptan were the following: back pain (1), meningitis (1), non-therapeutic abortion (1) and accidental injury (1). The single blinded SAE was medical/surgical procedure.

Patients were randomized 4:1 to eletriptan vs. comparator in two of the three ongoing studies, and 2:1 in the third.

As of the original NDA cutoff date of 4/30/98, there were 91 SAE cases reported for eletriptan treated subjects, one for subjects given eletriptan/propranolol, 20 for subjects given active comparator, 26 for those on blinded therapy, and 6 for subjects given placebo. After the listings had been run for the NDA, one blinded patient had been unblinded and was found to be taking eletriptan. This drug information was included in the death narrative for this patient (see section 8.2, page 47). The sponsor downgraded some cases because there was no study-emergent precipitating event and therefore the cases did not meet the criteria for inclusion in the SAE database. Additionally, 2 cases had been merged with other cases because they were follow-ups to the original cases rather than new cases

The revised numbers, as of 4/30/99, were 99 SAE's for subjects receiving eletriptan, 1 for subjects receiving eletriptan/propranolol, 20 for active comparator, 27 for blinded therapy, and 6 for placebo. The new totals as of 10/31/98 is now 109 for eletriptan, 1 for eletriptan/propranolol, 23 for active comparator, 28 for blinded therapy, and 6 for placebo.

There were 5 new adverse dropouts reported through 10/31/99. These were:

1. 108-50401211 – 17 y/o F on eletriptan 80mg. Last dose was 3/3/98. She was involved in a motor vehicle accident on 4/28/98 and suffered a punctured lung, broken ankle and femur and was discontinued for this reason.
2. 108-50580639 – 38 y/o F on eletriptan 40mg (5 total doses). She developed retinal degeneration right eye and was determined to be legally blind and was discontinued for this reason. The investigator indicated that the cause of the degeneration was unknown but not due to study drug.
3. 108-50770793 – 46 y/o F on eletriptan 40mg (6 doses) and then 80mg (28 doses) through 7/28/98. On 7/14/98 a lump was discovered on her breast and she was eventually diagnosed with malignant breast carcinoma and she underwent lumpectomy.

4. 299-0010002 – 26 y/o M received a single i.v. dose of eletriptan 50 µg/kg on 9/15/98. On 10/9/98 (11 days later) he suffered a fracture of the left tibia while playing rugby.
5. 305-02040283 – 50 y/o F took 4 doses of eletriptan 80mg to treat 3 attacks (1/23/97, 2/3/97, 2/15/97). She was admitted 2/15/97 due to elevated LFT's and severe tightness around the throat starting 4 hours after last dose, lasting 1 hour. Maximum AST was 129 and ALT was 304 on 2/17/97. LDH, bilirubin, AP, and CK were normal. She had a history of cholecystolithiasis. Hepatitis serology was negative. There was no history of alcohol intake. Epstein-Barr antigen was positive. In the opinion of the investigator, the elevated liver enzymes and tightness in the throat were related to study medication. (This case was previously reported as a serious adverse event in the original NDA, which I described on page 50 of my review and it does not represent a new case).

8.13 Cardiovascular and Cerebrovascular Safety

Because of its mechanism of action as a 5HT_{1B/1D} agonist and vasoconstrictors, the sponsor gave special consideration of cardiovascular and cerebrovascular events. These are summarized below.

8.13.1 Vital Signs and ECG Data

In clinical pharmacology studies, oral eletriptan at doses ≥60mg was shown to cause small, transient dose-related increases in blood pressure, predominantly diastolic, consistent with its mechanism of action. In general, the mean maximum changes in both systolic and diastolic blood pressures were between 10-15mm Hg. These changes were not associated with any ECG changes or specific adverse events. In phase 2/3 studies, vital signs were not taken around the time of C_{max} and, not surprisingly, no persistent changes in blood pressure were seen.

In study 001, 48 volunteers (on single dose eletriptan 10mg-120mg) underwent continuous holter monitoring beginning 24 hours before dosing and ending 48 hours after dosing. In study 208, 12 volunteers (on single doses 30mg-120mg) were monitored with telemetry 8 hours post-dose and with holter monitors 24 hours post dose. In both studies, no abnormalities were detected that were suggestive of ischemia. Baseline and post-treatment ECG's were also negative for ischemia.

Throughout the phase 2/3 program, ECG data failed to disclose evidence of coronary ischemia, although ECG's generally were done after drug exposure.

8.13.2 Angiography

Study 211 was a single dose study investigating the effect of i.v. eletriptan (50 µg/kg) on the systemic, pulmonary, and coronary circulation in subjects undergoing diagnostic coronary angiography. Ten subjects with less than 50% stenosis underwent 10 minute infusion of placebo followed five minutes later by a 15 minute infusion of i.v. eletriptan. The mean C_{max} was 92 ng/mL, which is similar to the C_{max} achieved after a single oral dose of 40mg. A light decrease in coronary artery diameter (mean decrease -6%) was seen after eletriptan infusion consistent with a vasoconstrictor effect. There were no clinically significant changes in pulse, blood pressure or ECG during this study.

A single subject did experience a 60-70% reduction in coronary artery diameter in conjunction with symptomatic chest pain. This case is discussed in more detail in section 8.3 Serious Adverse Events, page 50.

8.13.3 Cardiovascular Adverse Events

The phase 2/3 studies excluded patients with known ischemic heart disease or uncontrolled hypertension, and did not set an upper age limit for inclusion in the majority of the studies.

Cardiovascular AE's were more common in eletriptan treated patients. In phase 2/3 studies, 7.1% of eletriptan treated patients and 4.7% of placebo patients experienced at least one cardiovascular AE. This needs special interpretation because there were no placebo patients in the long-term safety studies. Those determined by investigators to be "treatment related" were 5.2% for eletriptan and 3% for placebo. The majority of cardiovascular AE's were "vasodilatation" which was the code term for a warm sensation or flushing.

The incidence of chest pain during long term use was about 4%. The cause of the chest pain remains in most patients generally unknown but in at least one case (mentioned in the previous section on angiography findings), the chest pain was accompanied by documented coronary vasospasm on cardiac angiography.

The sponsor notes that of 6419 eletriptan treated subjects in phase 2/3 studies, only four (<0.1%) had reports classified as angina pectoris, none of which resulted in specific treatment or drug discontinuation. Although I agree that a diagnosis of angina pectoris is possible using established clinical and ECG criteria, I wonder about under-reporting of this condition since I find it difficult to exclude angina pectoris in many other individuals with symptomatic "chest pressure."

There was one case of myocardial infarction (in the long-term study 108), but this occurred seven weeks after the last dose of study medication and was mostly likely related to underlying coronary artery disease, which was subsequently documented as moderate stenosis of the circumflex artery on cardiac catheterization.²

8.13.4 Laboratory Abnormalities

Creatine kinase (CK) abnormalities were found in 2.2% of patients on eletriptan, 3.4% on sumatriptan, and 1.2% on placebo. In eletriptan subjects, 14 CK-MB were found to be abnormal. Three of these were discontinued. None of the abnormal CK were considered to be due to study drug or related to myocardial infarction. The majority of abnormal CK values were related to exercise.

² Since the incidence of triptan-related myocardial infarction is so low, we rarely see treatment-related myocardial infarction during clinical development, but then see cases after approval. This was the case with zolmitriptan development, and, I believe, with sumatriptan (although I was not involved in the review of the latter application).

8.13.5 Cerebrovascular Adverse Events

In the entire development program, there were 3 cerebrovascular events of note. One 45 y/o female in study 104 suffered an acute cerebral infarction and died. It is unclear whether the subject actually took eletriptan, although it cannot be excluded (I discussed this case in section 8.2 - Deaths, page 47). A patient in study 306 took eletriptan 80mg during an aura and experienced an AE summarized by the investigator as either a complicated migraine or a transient ischemic attack. Although the subject experienced similar episodes before in association with migraine attacks, this was more severe and a relationship to study drug could not be excluded. (This study failed to show that eletriptan was effective in preventing headache when taken during an aura, so such use post-approval would not be recommended). In study 317, a 56 y/o female (01690025) suffered transient global amnesia for one day, seven months after starting treatment with POT (which was sumatriptan, subcutaneous or oral). CT and LP were unremarkable. The event resolved and the patient was discharged. There were no other reports of stroke or TIA during the development program.

In the phase 2/3 studies, there were some treatment related events that coded to terms hemiplegia, paralysis, and aphasia. All but one occurred with eletriptan and one occurred with Cafegot. The term hemiplegia was used on only one subject (102-50131084) who had headache and transient left hemiplegia on day 1 (she felt numb and almost paralyzed). This AE resolved spontaneously, was considered treatment related and she was discontinued. The term paralysis was used in four subjects (3 eletriptan and 1 Cafegot). The raw terms were "thick tongue," "tongue thickness," "extremity paralysis," "paralysis sensation," and "paralysed" (sic). The latter term "paralysed" resulted from an English translation of a German word meaning "tiredness." It was reported as moderate in severity, not serious, and did not result in discontinuation. The term aphasia was used in two subjects and included the raw terms "dysphasia" and "speech mixed up/illogical speech (dysphasia) and both subjects discontinued. A unilateral distribution of paresthesia (tingling sensation) was reported by few eletriptan or placebo treated subjects in all the phase 2/3 studies and mainly affected the face and upper limbs. In these cases, it is difficult to determine what is due to treatment and what is due to the underlying migraine.

8.14 Hepatic and Renal Impairment

Study 220 was an open, single dose PK study of eletriptan 40mg and 80mg in 12 subjects with chronic stable hepatic cirrhosis and 12 age and weight matched healthy volunteers. Five of the 12 hepatic patients reported AE's compared with 3/12 for control. For both groups, all AE's were mild and consistent with AE's reported in the development program, except for one case of severe hypertension in a subject with hepatic cirrhosis who received eletriptan 80mg. The subject had a blood pressure reading of 220/96 mm five hours after dosing. The treatment related event persisted for seven hours and resolved without treatment. None of the other subjects with hepatic cirrhosis experienced any degree of hypertension.

Study 229 was an open, single dose PK study of eletriptan 80mg in 16 subjects with varying degrees of renal impairment (six mild, five moderate, and five severe) and six

subjects with normal renal function. Adverse events were reported for two each of the normal, mild impairment and moderate impairment subjects and for three of the subjects with severe renal impairment. All events were mild and consistent with reported during development.

8.15 Withdrawal Phenomenon and Abuse Potential

No specific information regarding withdrawal phenomenon or abuse potential are described in the application.

8.16 Human Reproduction Data

During development, 21 patients became pregnant while taking active study medication and were subsequently withdrawn from the study.

There were 11 pregnancies in eletriptan treated women. Eight pregnancies have resulted in six normal births, and the remaining two are progressing normally. Three other pregnancies were not carried to term: two were miscarriages (one diagnosed with Turner's syndrome). The third pregnancy was aborted at the request of the patient, who then continued in the long-term study 317. She later became pregnant again, with a normal pregnancy.

Two placebo patients had pregnancies progressing normally up until the last contact with investigators. They were subsequently lost to follow-up.

There were 3 normal pregnancies in sumatriptan treated patients. In the POT groups during long-term therapy, two miscarriages were reported and one pregnant subject was lost to follow-up.

In blinded patients, 2 normal pregnancies and deliveries have been recorded.

The sponsor reports published data that spontaneous abortion (miscarriage) is the outcome of 14-19% of registered pregnancies.

Eletriptan is excreted in human milk, but in extremely low quantities. The mean total amount of eletriptan excreted in breast milk over 24 hours was only 0.02% of an 80mg oral dose.

8.17 Overdose

There were no cases of eletriptan overdose reported from the clinical pharmacology or phase 2/3 development programs. The elimination half-life of eletriptan is about four hours and the sponsor recommends monitoring and general supportive therapy for at least 20 hours or while signs and symptoms persist. There is no specific antidote to eletriptan. The effects of hemodialysis or peritoneal dialysis on serum concentrations of eletriptan is unknown.

8.18 Sponsor's Safety Conclusions

1. The sponsor makes the following conclusions regarding the safety of eletriptan:
Eletriptan is well tolerated when administered within the 20 to 80mg dose range

- (including total doses per migraine attack up to 160mg when repeat doses taken for non- response or recurrence). No significant safety concerns were identified.
2. The overall incidence of discontinuation due to adverse events was low and slightly higher for eletriptan than placebo. In sumatriptan controlled studies, the overall incidence of discontinuation due to adverse events was similar for eletriptan, sumatriptan and placebo.
 3. Although adverse events were reported by just over half the eletriptan treated subjects, few were classified as severe. The most common adverse events were those expected for a 5HT_{1B/1D} agonist and also included many recognized symptoms of migraine.
 4. The most common adverse events following eletriptan treatment were asthenia, chest pain (usually sensations of tightness or pressure), headache, vasodilatation (sensation of warmth or flushing), dry mouth, dysphagia (mainly throat tightness or constriction), nausea, vomiting, dizziness, hypertonia (sensation of tightness or stiffness, mostly in the neck/ whole body), paresthesia (tingling or abnormal sensation, mainly affecting the head and face) and somnolence. Commonly reported adverse events were generally mild to moderate, resolved with continued treatment and only resulted in study discontinuation infrequently.
 5. The overall incidence of adverse events increased with increasing eletriptan dose from 20mg to 80mg, but subjects taking a second dose of 80mg 2-24 hours after an initial dose of 80mg did not experience either increased incidence of adverse events or different adverse events.
 6. The pattern of adverse event reporting did not alter with long term use of eletriptan. In addition, data from subjects stabilized on eletriptan 40mg and 80mg in long term studies showed no evidence of increasing incidence of adverse events with dose.
 7. The majority of treatment related cardiovascular adverse events were reports of vasodilatation (flushing). The incidence of cardiovascular adverse events classified as severe by investigators was very low and similar for eletriptan and placebo.
 8. The incidence of clinically significant laboratory test abnormalities was similar for eletriptan, sumatriptan and placebo and there was no evidence of acute or persistent changes or trends in laboratory test variables following eletriptan treatment.
 9. Clinical pharmacology studies showed that eletriptan produced small, transient rises in blood pressure consistent with its mechanism of action. There was no evidence of persistent changes in vital signs from Phase 2/3 studies.
 10. Across the whole development program, there was no evidence of acute or persistent changes in EKG readings and no evidence of a relationship between oral administration of eletriptan and QTc interval prolongation.
 11. The incidences of mortality and serious adverse events were very low: mortality was never considered related to study drug treatment by investigators and serious adverse events were rarely considered related to study treatment.

8.19 Reviewer's Safety Conclusions

I generally agree with the sponsor's conclusions with the following comments.

1. Doses of eletriptan 80mg were associated with substantially increased incidence of adverse events compared to sumatriptan 100mg, with the incidence of chest pain

being more than twice as high in eletriptan patients compared to sumatriptan patients (3.7% vs. 1.9%, Table 53, page 59).

2. There was one eletriptan-associated serious adverse event and several adverse dropouts due to elevated ALT/AST, mostly occurring in the ongoing long-term studies (108, 316, 317). Although I believe the safety signal at this point is weak for reasons described in my review, I believe it is important to obtain and review prior to approval additional data from the long term safety studies (see section 11 - Recommendations, page 110).
3. The sponsor has failed to provide an adequate number of exposures of patients taking eletriptan 80mg on a chronic, intermittent basis over a six month period. Current ICH and Division guidelines request data from at least 300 patients treating an average of 2 headaches per month for six months. Currently, they have provided only 272 patients which fulfill those guidelines (Table 71, page 85). It is likely that, with the unblinding of study 316, they will achieve this number. In contrast, the extent of high dose exposures at one year is adequate.

9. Labeling Review

In this section, I review the draft labeling, as proposed by the sponsor, starting with the Clinical Studies section. Throughout, I used the last approved triptan labeling (Maxalt or rizatriptan) as a template. My labeling comments are based on the assumption that all three doses will be approved.

Draft Labeling

17 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

10. Discussion and Conclusions

In summary, I believe the application supports the efficacy and safety of eletriptan 20mg and 40mg for the treatment of acute migraine. From the information provided, it is quite possible that doses lower than 20mg (*i.e.*, 10mg) may also be effective and may carry a more favorable safety profile.

Although there is some evidence to suggest that the 80mg dose provides greater relief than the 40mg dose, it also carries a greater risk. I am not convinced that the hard-to-quantify risk/benefit ratio of the 80mg dose is sufficiently low to allow approval of this dose. My greatest concern is that the incidence of chest pain at this dose is more than twice that seen with the highest approved dose of sumatriptan (100mg) in those studies where the two were compared head to head. There is controversy regarding the answer to the question "is the chest pain/pressure seen with triptan use cardiac in origin?" Experts have argued that many cases are not. I don't believe we have a definitive answer to this question, and in at least some cases (including one documented case in this application in study 211, described on page 50 of my review) chest pain/pressure and coronary vasospasm coexist. I believe it is best to assume, from a public health perspective, that increased incidence of chest pain/pressure will likely be associated with an increased incidence of coronary vasospasm, and ultimately with adverse cardiac events such as cardiac ischemia, myocardial infarction, and cardiac death. As a result, it is my opinion that the possible increased benefits of the 80mg dose may not justify this potential increase in cardiac risk. This is certainly a judgement call, and some may argue best left to the discretion of the prescribing physician. However, it is my opinion that in the absence of overwhelming evidence of benefit of the 80mg dose, it is best not approved at this time. (As a less compelling point, the sponsor has failed to provide adequate number of patients exposed to the 80mg dose for at least 6 months). The sponsor is collecting additional long-term safety data using eletriptan, sumatriptan, and physician optimized therapy and the safety of the 80mg dose can be revisited with the final safety update.

I also have some residual concerns regarding isolated cases of elevated liver function tests. Although they were, in fact, isolated cases and my very crude estimate of the incidence using the rizatriptan NDA as a historical control suggest that the incidence of these events is similar to that seen with rizatriptan, some were severe enough to be labeled a serious adverse event (1 case), and/or to result in discontinuation from the study in others (at least 4).

11. Recommendations

I recommend an approvable action. Prior to approval, however, I recommend the sponsor submit a final safety update with the final results of the three long-term safety studies

108, 316 and 317 (all of which were ongoing at the time of the original NDA submission. Study 316 was still blinded). The final safety update should contain the following information:

1. Completed study reports for studies 108, 316 and 317.
2. Integrated summary of these studies with special emphasis on:
 - a. extent of exposures, including an update to table 2.8.2.13
 - b. deaths, adverse dropouts, serious adverse events
 - c. occurrence chest pain/pressure; neck/jaw pressure; and cardiac events
 - d. occurrence of elevated liver function tests
3. Patient narratives and case report forms of all deaths, adverse dropouts, serious adverse events, including cases of known or suspected cardiac ischemia, as well as cases with elevated ALT or AST > 3xULN or bilirubin > 1.5xULN.
4. Case Report Tabulations for studies 108, 316 and 317 in electronic format as SAS transport files.

The electronic datasets should include the following information:

Dosing: the dataset should contain one row for each dose of medication taken, important variables are – pt id, treatment assignment, attack number, date of study onset, date/time of dosing, study day of dosing (relative to study onset), amount of dose (in mg).

Adverse events: similar to the datasets provided in the NDA

Laboratory Data: the dataset should contain one row for each laboratory measurement. Important variables are – pt id, treatment assignment, date of study onset, date/time of lab sample, date/time of last dose, amount of last dosage (in mg), study day of lab sample (relative to study onset), lab name (Sodium, ALT, Bilirubin, etc.), lab result, units, baseline lab result, lower limit of normal, upper limit of normal.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. **/S/**

See my memo for comments

ao 7/9/99
cc:
HFD-120
NDA 21-016
electronic copy-Levin

Appendix A - Serious Adverse Events

Table 72: Serious Adverse Events from All Clinical Studies (Sponsor Table 2.8.6.7.1)

Serious Adverse Event	Eletriptan	Eletriptan/ Propranolol	PBO	Sumatriptan	Blinded Therapy
<i>Appl. Inj./ Incision Insertion Site</i>	3	0	0	0	0
Appl./Inj./Incision/ Insertion Site Pain	1	0	0	0	0
Appl./Inj./Incision/ Insertion/ Device Complication	2	0	0	0	0
<i>Body As A Whole</i>	6	0	0	1	1
Asthenia	1	0	0	0	0
Back Pain	1	0	0	1	1
Infection TBC	1	0	0	0	0
Pain	3	0	0	0	0
<i>Cardiovascular, General</i>	2	0	1	0	0
Syncope	2	0	1	0	0
<i>Centr. & Periph. Nerv.</i>	13	0	1	2	10
Convulsions Grand Mal	1	0	0	0	0
Dizziness	1	0	0	0	0
Gait Abnormal	0	0	0	0	1
Headache	2	0	0	0	1
Migraine	6	0	0	1	6
Migraine Aggravated	2	0	1	0	0
Neuropathy	0	0	0	1	2
Tremor	1	0	0	0	0
Vertigo	0	0	0	0	2
<i>Fetal</i>	0	0	0	1	0
Death Fetal	0	0	0	1	0
<i>Gastrointestinal</i>	9	0	0	4	4
Abdominal Pain	1	0	0	2	1
Anus Disorder	0	0	0	0	1
Diarrhea	1	0	0	0	0
Duodenal Ulcer Hemorrhagic	0	0	0	1	0
Enterocolitis	1	0	0	0	0
Fecal Incontinence	1	0	0	0	0
Gastric Ulcer	1	0	0	0	0
Gastritis Hemorrhagic	1	0	0	0	0
Gastrointestinal Disorder	1	0	0	0	0
Hemorrhoids Thrombosed	1	0	0	0	0
Nausea	1	0	0	0	1
Pancreatitis	0	0	0	2	0
Vomiting	1	0	0	0	1
<i>Heart Rate/ Rhythm</i>	3	0	1	1	0
Bradycardia	1	0	0	0	0
Cardiac Arrest	0	0	0	1	0
Fibrillation Atrial	1	0	0	0	0
Tachycardia	1	0	0	0	0

Serious Adverse Event	Eletriptan	Eletriptan/ Propranolol	PBO	Sumatriptan	Blinded Therapy
Tachycardia Ventricular	0	0	1	0	0
<i>Liver/ Biliary</i>	<i>7</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>
Biliary Pain	1	0	0	0	0
Cholecystitis	2	0	0	0	0
Cholelithiasis	1	0	0	1	0
Gall Bladder/ Biliary Tract Disorder	1	0	0	1	0
Hepatic Function Abnormal	1	0	0	0	0
Hepatitis Infectious	1	0	0	0	0
<i>Metabolic/ Nutritional</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
Hypokalemia	1	0	0	0	0
<i>Musculoskeletal</i>	<i>5</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>1</i>
Arthritis Aggravated	1	0	0	0	0
Arthrosis	0	0	0	1	0
Bone Fracture Accidental	2	0	1	0	0
Hernia	1	0	0	0	0
Synovitis	0	0	0	0	1
Tendon Disorder	1	0	0	0	0
<i>Myo, Endo, Pericardial & Valve</i>	<i>3</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>0</i>
Angina Pectoris	1	0	0	1	0
Chest Pain	2	0	0	0	0
Myocardial Infarction	1	0	0	0	0
<i>Neoplasms</i>	<i>7</i>	<i>0</i>	<i>0</i>	<i>3</i>	<i>2</i>
Basal Cell Carcinoma	2	0	0	0	0
Breast Neoplasm Malignant Female	3	0	0	1	0
Carcinoma	1	0	0	0	1
Cervix Carcinoma	0	0	0	1	0
Other and Unspecified Neoplasms	1	0	0	1	0
Pancreas Cyst	0	0	0	1	0
Renal Carcinoma	0	0	0	0	1
<i>Other Adverse Events</i>	<i>27</i>	<i>0</i>	<i>1</i>	<i>3</i>	<i>7</i>
Accidental Injury	2	0	0	1	2
Procedure (Medical/ Surgical/ Health Service)	25	0	1	2	5
<i>Psychiatric</i>	<i>5</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>1</i>
Amnesia	0	0	0	1	0
Anxiety	1	0	0	0	0
Death by Suicide	1	0	0	0	1
Depression	3	0	0	0	0
Drug Dependence	1	0	0	0	0
Suicidal Ideation	1	0	0	0	0
<i>Red Blood Cell</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
Anemia	1	0	0	0	0
Reproductive, Female	8	0	1	2	1
Abortion Non Therapeutic	1	0	0	0	0

Serious Adverse Event	Eletriptan	Eletriptan/ Propranolol	PBO	Sumatriptan	Blinded Therapy
Endometriosis	2	0	0	0	0
Ovarian Cyst	1	0	0	1	0
Pregnancy Ectopic	0	0	1	0	0
Uterine Fibroid	3	0	0	1	1
Uterine Hemorrhage	1	0	0	0	0
<i>Resistance Mechanisms</i>	<i>1</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>2</i>
Abscess	0	0	0	0	1
Infection Bacterial	0	0	0	0	1
Infection Viral	1	0	0	0	0
Sepsis	0	0	0	1	0
<i>Respiratory</i>	<i>6</i>	<i>1</i>	<i>1</i>	<i>2</i>	<i>0</i>
Asthma	0	1	0	0	0
Bronchitis	1	0	0	0	0
Bronchospasm Aggravated	0	0	0	1	0
Pharyngitis	1	0	0	1	0
Pleural Effusion	1	0	0	0	0
Pneumonia	2	0	0	0	0
Pulmonary Collapse	1	0	0	0	0
Rhinitis	0	0	1	0	0
<i>Urinary System</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>1</i>	<i>2</i>
Hematuria	0	0	0	0	1
Renal Calculus	0	0	0	1	0
Renal Pain	0	0	0	0	1
Urinary Tract Infection	0	0	1	0	0
<i>Vascular (Extracardiac)</i>	<i>4</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
Cerebrovascular Disorder	3	0	0	0	0
Gangrene	1	0	0	0	0
TOTAL NUMBER OF EVENTS	115	1	8	28	33

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ADO	N, %											
	Eletriptan		PBO		Sumatriptan		Cafergot		POT		Blinded Therapy	
Increased salivation	1	0	0	0	0	0	0	0	0	0	0	0
LFT abnormal +	3	0	1	0.1	0	0	0	0	0	0	0	0
ENDOCRINE	1	0	0	0	0	0	0	0	0	0	0	0
Goiter	1	0	0	0	0	0	0	0	0	0	0	0
HEMIC & LYMPHATIC	0	0	1	0.1	0	0	0	0	0	0	0	0
Leukopenia +	0	0	1	0.1	0	0	0	0	0	0	0	0
METABOLIC & NUTRITIONAL	12	0.2	1	0.1	0	0	0	0	0	0	1	0.2
Edema	2	0	0	0	0	0	0	0	0	0	1	0.2
SGOT increased +	3	0	0	0	0	0	0	0	0	0	0	0
SGPT increased +	5	0.1	1	0.1	0	0	0	0	0	0	0	0
Dehydration	1	0	0	0	0	0	0	0	0	0	0	0
Peripheral edema	2	0	0	0	0	0	0	0	0	0	0	0
CPK increased +	3	0	0	0	0	0	0	0	0	0	0	0
MUSCULOSKELETAL	10	0.2	0	0	1	0.1	0	0	0	0	0	0
Arthralgia	2	0	0	0	0	0	0	0	0	0	0	0
Arthrosis	1	0	0	0	0	0	0	0	0	0	0	0
Myalgia	4	0.1	0	0	1	0.1	0	0	0	0	0	0
Bone pain	2	0	0	0	0	0	0	0	0	0	0	0
Myasthenia	1	0	0	0	0	0	0	0	0	0	0	0
NERVOUS	67	1	4	0.4	8	0.9	1	0.5	0	0	3	0.7
Aphasia	1	0	0	0	0	0	0	0	0	0	0	0
Ataxia	0	0	0	0	1	0.1	0	0	0	0	0	0
Dementia	1	0	0	0	0	0	0	0	0	0	1	0.2
Dizziness	23	0.4	3	0.3	3	0.3	0	0	0	0	0	0
Hemiplegia	1	0	0	0	0	0	0	0	0	0	0	0
Hypertonia	10	0.2	0	0	0	0	0	0	0	0	0	0
Paresthesia	11	0.2	0	0	1	0.1	0	0	0	0	1	0.2
Paralysis	1	0	0	0	0	0	0	0	0	0	0	0
Tremor	3	0	0	0	1	0.1	1	0.5	0	0	0	0
Vertigo	3	0	0	0	0	0	0	0	0	0	0	0
Anxiety	3	0	0	0	2	0.2	0	0	0	0	0	0
Agitation	5	0.1	1	0.1	0	0	0	0	0	0	0	0
Depression	1	0	0	0	0	0	0	0	0	0	0	0
Euphoria	1	0	0	0	0	0	0	0	0	0	0	0
Insomnia	1	0	0	0	0	0	0	0	0	0	0	0
Nervousness	3	0	1	0.1	1	0.1	0	0	0	0	0	0
Somnolence	14	0.2	0	0	1	0.1	0	0	0	0	0	0
Abnormal dreams	1	0	0	0	0	0	0	0	0	0	0	0
Confusion	5	0.1	0	0	0	0	0	0	0	0	0	0
Speech disorder	2	0	0	0	0	0	0	0	0	0	0	0
Depersonalization	1	0	0	0	0	0	0	0	0	0	0	0
Thinking abnormal	4	0.1	0	0	0	0	0	0	0	0	0	0
Hypesthesia	3	0	0	0	0	0	0	0	0	0	1	0.2
RESPIRATORY	17	0.3	0	0	0	0	0	0	0	0	2	0.5
Hiccup	1	0	0	0	0	0	0	0	0	0	0	0

ADO	N, %											
	Eletriptan		PBO		Sumatriptan		Cafergot		POT		Blinded Therapy	
Asthma	1	0	0	0	0	0	0	0	0	0	0	0
Dyspnea	9	0.1	0	0	0	0	0	0	0	0	0	0
Pharyngitis	4	0.1	0	0	0	0	0	0	0	0	2	0.5
Rhinitis	1	0	0	0	0	0	0	0	0	0	0	0
Bronchitis	1	0	0	0	0	0	0	0	0	0	0	0
Respiratory disorder	1	0	0	0	0	0	0	0	0	0	0	0
Yawn	1	0	0	0	0	0	0	0	0	0	0	0
SKIN AND APPENDAGES	16	0.2	3	0.3	1	0.1	0	0	0	0	0	0
Pruritus	3	0	0	0	0	0	0	0	0	0	0	0
Rash	5	0.1	0	0	0	0	0	0	0	0	0	0
Sweating	7	0.1	2	0.2	1	0.1	0	0	0	0	0	0
Maculopapular rash	1	0	1	0.1	0	0	0	0	0	0	0	0
SPECIAL SENSES	9	0.1	1	0.1	3	0.3	0	0	0	0	1	0.2
Conjunctivitis	1	0	0	0	0	0	0	0	0	0	1	0.2
Tinnitus	3	0	0	0	2	0.2	0	0	0	0	0	0
Eye pain	1	0	0	0	0	0	0	0	0	0	0	0
Abn of accommodation	1	0	0	0	1	0.1	0	0	0	0	0	0
Abnormal vision	4	0.1	1	0.1	0	0	0	0	0	0	0	0
UROGENITAL	7	0.1	0	0	0	0	0	0	0	0	0	0
Hematuria	1	0	0	0	0	0	0	0	0	0	0	0
Menorrhagia	1	0	0	0	0	0	0	0	0	0	0	0
Urinary frequency	1	0	0	0	0	0	0	0	0	0	0	0
Menstrual disorder	1	0	0	0	0	0	0	0	0	0	0	0
Urinary tract disorder	1	0	0	0	0	0	0	0	0	0	0	0
Cervix disorder	1	0	0	0	0	0	0	0	0	0	0	0
Fibrocystic breast	1	0	0	0	0	0	0	0	0	0	0	0
Breast carcinoma	1	0	0	0	0	0	0	0	0	0	0	0

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Appendix C - Vital Signs

Table 74: Median Change from Baseline Vital Signs – All Phase 2/3 Studies (sponsor table 2.8.6.5.1)

	N	P.O.T.		P.O.T.		Blinded Therapy		Blinded Therapy	
		Median Value at Baseline	Median Change from Baseline	Median Value at Baseline	Median Change from Baseline	Median Value at Baseline	Median Change from Baseline	Median Value at Baseline	Median Change from Baseline
Supine									
Systolic BP (mmHg)	103	120.00	0.00	120.00	0.00	120.00	0.00	120.00	0.00
Diastolic BP (mmHg)	103	72.00	0.00	72.00	0.00	72.00	0.00	72.00	0.00

	N	P.O.T.		Blinded Therapy	
		Median Value at Baseline	Median Change from Baseline	Median Value at Baseline	Median Change from Baseline
Supine					
Systolic BP (mmHg)	222	118.00	0.00	118.00	0.00
Diastolic BP (mmHg)	222	75.50	0.00	75.50	0.00
Diastolic BP (mmHg)	222	75.50	0.00	75.50	0.00

Table 75: Clinically Significant Vital Signs Changes – All Phase 2/3 Studies (sponsor table 2.8.6.5.17)

	N	Event	P.O.T.		P.O.T.		Blinded Therapy		Blinded Therapy	
			Count	%	Count	%	Count	%	Count	%
Supine										
Systolic BP (mmHg)	103	1	0.97%	1	0.97%	1	0.97%	1	0.97%	1
Diastolic BP (mmHg)	103	1	0.97%	1	0.97%	1	0.97%	1	0.97%	1

	N	P.O.T.		Blinded Therapy	
		Median Value at Baseline	Median Change from Baseline	Median Value at Baseline	Median Change from Baseline
Supine					
Systolic BP (mmHg)	222	118.00	0.00	118.00	0.00
Diastolic BP (mmHg)	222	75.50	0.00	75.50	0.00
Diastolic BP (mmHg)	222	75.50	0.00	75.50	0.00

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Table 76: Median Change from Baseline Vital Signs – Single Attack and 1st of Multiple Attack Studies (sponsor table 2.8.6.5.2)

	Electrocardiogram			Blood Pressure			Heart Rate			Respiratory Rate		
	N	Median Value at Baseline	Median Change from Baseline	N	Median Value at Baseline	Median Change from Baseline	N	Median Value at Baseline	Median Change from Baseline	N	Median Value at Baseline	Median Change from Baseline
Single Attack	4,186	120.00	0.00	518	120.00	0.00	825	120.00	0.00	213	120.00	0.00
Multiple Attack (1 st)	4,186	76.00	0.00	518	76.00	0.00	825	76.00	0.00	213	76.00	0.00
Multiple Attack (2 nd)	4,175	72.00	0.00	518	72.00	0.00	825	72.00	0.00	213	72.00	0.00

Table 77: Clinically Significant Vital Signs Changes – Single Attack and 1st of Multiple Attack Studies (sponsor table 2.8.6.5.18)

	Electrocardiogram			Blood Pressure			Heart Rate			Respiratory Rate		
	N	Median Value at Baseline	Median Change from Baseline	N	Median Value at Baseline	Median Change from Baseline	N	Median Value at Baseline	Median Change from Baseline	N	Median Value at Baseline	Median Change from Baseline
Single Attack	4,186	120.00	0.00	518	120.00	0.00	825	120.00	0.00	213	120.00	0.00
Multiple Attack (1 st)	4,186	76.00	0.00	518	76.00	0.00	825	76.00	0.00	213	76.00	0.00
Multiple Attack (2 nd)	4,175	72.00	0.00	518	72.00	0.00	825	72.00	0.00	213	72.00	0.00

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Appendix D - ECG

Table 78: Mean and Median Changes from Baseline ECG Parameters – All Phase 2/3 Studies (sponsor table 2.8.6.6.1)

Study	Treatment Group	N	Baseline		Final		Final - Baseline		Median Change	
			Mean	SD	Mean	SD	Mean	SD		
All Phase 2/3 Studies	Electrolyte/ALSAC	2,218	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	ALSAC	2,218	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	Electrolyte/ALSAC	1,779	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	ALSAC	439	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
All Phase 2/3 Studies	Electrolyte/ALSAC	8,737	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
	ALSAC	8,737	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
	Electrolyte/ALSAC	7,197	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
	ALSAC	1,540	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
All Phase 2/3 Studies	Electrolyte/ALSAC	2,218	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	ALSAC	2,218	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	Electrolyte/ALSAC	1,779	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	ALSAC	439	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
All Phase 2/3 Studies	Electrolyte/ALSAC	8,737	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
	ALSAC	8,737	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
	Electrolyte/ALSAC	7,197	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
	ALSAC	1,540	436.22	4.7 73	397.66	4.7 73	436.22	397.73	138.49 - 247.73	0.00
All Phase 2/3 Studies	Electrolyte/ALSAC	2,218	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	ALSAC	2,218	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	Electrolyte/ALSAC	1,779	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00
	ALSAC	439	426.45	4.8 87	389.25	4.3 87	426.45	412.85	147.15 - 217.11	0.00

Table 79: Clinically Significant ECG Abnormalities – All Phase 2/3 Studies (sponsor table 2.8.6.6.17)

Study	Treatment Group	N	Electrolyte		ALSAC		Electrolyte/ALSAC		N
			Total	%	Total	%	Total	%	
All Phase 2/3 Studies	Electrolyte/ALSAC	2,218	3	0.13	2	0.09	5	0.22	3
	ALSAC	2,218	2	0.09	2	0.09	4	0.18	2
	Electrolyte/ALSAC	1,779	3	0.17	2	0.11	5	0.28	3
	ALSAC	439	0	0.00	0	0.00	0	0.00	0

Study	Treatment Group	N	Subject		P.C.T.	
			Total	%	Total	%
All Phase 2/3 Studies	Electrolyte/ALSAC	2,218	0	0.00	0	0.00
	ALSAC	2,218	0	0.00	0	0.00
	Electrolyte/ALSAC	1,779	0	0.00	0	0.00
	ALSAC	439	0	0.00	0	0.00

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Table 80: Mean and Median Changes from Baseline ECG Parameters – Single Attack and 1st of Multiple Attack Studies (sponsor table 2.8.6.6.2)

PARAMETER	TREATMENT GROUP	N	Baseline		Median Change	Single Attack		1 st of Multiple Attacks	
			Mean	SD		Mean	SD	Mean	SD
PR (ms)	Placebo	100	160	15	160	15	160	15	160
	10 mg	100	160	15	160	15	160	15	160
	20 mg	100	160	15	160	15	160	15	160
	40 mg	100	160	15	160	15	160	15	160
PRP (ms)	Placebo	100	160	15	160	15	160	15	160
	10 mg	100	160	15	160	15	160	15	160
	20 mg	100	160	15	160	15	160	15	160
	40 mg	100	160	15	160	15	160	15	160
QRS (ms)	Placebo	100	100	10	100	10	100	10	100
	10 mg	100	100	10	100	10	100	10	100
	20 mg	100	100	10	100	10	100	10	100
	40 mg	100	100	10	100	10	100	10	100
QTc (ms)	Placebo	100	400	10	400	10	400	10	400
	10 mg	100	400	10	400	10	400	10	400
	20 mg	100	400	10	400	10	400	10	400
	40 mg	100	400	10	400	10	400	10	400

Table 81: Clinically Significant QTc Abnormalities – Single Attack and 1st of Multiple Attack Studies (sponsor table 2.8.6.6.18)

PARAMETER	TREATMENT GROUP	Single Attack		1 st of Multiple Attacks	
		n	%	n	%
QTc (ms)	Placebo	0	0	0	0
	10 mg	0	0	0	0
QTc (ms)	Placebo	0	0	0	0
	10 mg	0	0	0	0

PARAMETER	TREATMENT GROUP	Categorized	
		n	%
QTc (ms)	Placebo	0	0
	10 mg	0	0
Increase from Baseline	< 50 msec	0	0
	50 - 60 msec	0	0
	> 60 msec	0	0
	Total	0	0

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