# 7. Review of Clinical Studies

## *7.1 Overview of Clinical Development*

The zolmitriptan development program was conducted according to ethical principles derived from the Declaration of Helsinki. All protocols were reviewed and approved by independent IRB's. Written informed consent was obtained from all subjects.

All data from case report forms received by the sponsor on or before 8/22/96 are included in this original NDA. The abbreviated 4 month safety update has a cutoff date of 12/15/96. The safety update and study 030, the hepatic failure PK tolerability study, are reviewed in section 9, (Four Month Safety Update), page 66, and section 7.5.2, (Study 030 (N=30)), page 35.

### *7.1.1 Patient Selection*

The inclusion/exclusion criteria were similar across the nine clinical efficacy and safety trials included in this NDA. Across all studies, patients had to have an established diagnosis of migraine with our without aura as defined by the International Headache Society (IHS). Enrollment was open to males and females. Women of child-bearing potential needed to be non-pregnant or have no reasonable chance of becoming pregnant during the study.

Most studies required a history of migraines ≥ 1 year, with age of onset < 40-50 years. In addition, patients were required to have an average of 1-6 headaches per month over the previous 3-6 months.

In general, patients with significant medical or psychiatric conditions were excluded. In addition, patients receiving chronic concomitant medications which could potentially affect safety and/or efficacy were also excluded. This requirement was relaxed in later trials.

### *7.1.2 Efficacy Evaluation*

For all outpatient studies (008, 015, 017, 018, 026, 042), patients recorded their assessments of symptoms on a diary card which was later reviewed with the investigator at a clinic visit. Data were then transferred to the CRF. For inpatient studies (002, 006, 007), data on migraine symptoms were collected from patients and entered directly onto the CRF.

In the majority of studies, the primary efficacy variable was headache relief at 2 hours post-dose. Headache relief was defined prospectively as an improvement from moderate or severe headache pain pre-treatment to mild or no pain post-treatment. In study 018, the sumatriptan comparison trial, "complete response" as defined below, was used as the primary efficacy variable.

Efficacy was calculated by quantifying pre-treatment to post-treatment changes in headache severity using a four point scale (none, mild, moderate, severe). In addition, a number of other parameters were used to assess efficacy: presence/absence of associated symptoms such as nausea, photophobia, or phonophobia; time to meaningful migraine relief (as defined by the patient), use of rescue/escape medications, headache recurrence, degree of activities impairment during migraine headache, and time missed from paid employment. Headache recurrence was defined as a migraine which responded to treatment, but returned (moderate or severe pain) within 24 hours. An additional derived measure, "complete response" was also used to assess efficacy. Complete response was defined as headache response at 2 hours without recurrence within 24 hours of treatment.

### *7.1.3 Safety Evaluation*

Each of the studies contributed safety data. Adverse experience (AE) reports, physical and neurological examinations including vital signs, clinical laboratory tests, and ECG's were collected in most studies. Particular attention was paid to the collection of safety data relating to the cardiovascular system because of the known AE profile of sumatriptan.

### *7.1.4 Studies for Treatment of Single Attacks*

The first phase I study (001, Table 2, page 8) established that single doses up to 25 mg were safe and well tolerated. Study 002, an open-label uncontrolled study involving 18 patients began in September, 1992. This study suggested that zolmitriptan was effective as 82% reported headache relief 2 hours after a single 25 mg dose.

The first dose-range finding study (006) began in March, 1993. Eighty-four (84) patients participated in this randomized, double-blind, placebo controlled, inpatient study. Patients treated a single migraine attack with either zolmitriptan or placebo, doses of 1, 5, 25 mg were tested. In this study, an optional second dose of study medication was allowed after 2 hours.

Response rates at 2 hours after the initial dose were 15%, 27%, 62%, and 81% for the placebo, 1, 5 and 25 mg groups. Response rates for the 5 mg and 25 mg doses were significantly different from placebo at the $p<0.05$ level, whereas the response rate for the 1 mg tablet was not. The frequency of adverse experiences increased with increasing dose and was relatively high in the 25 mg dose group.

While 006 was ongoing, a second, open-label, uncontrolled inpatient study (007) was initiated in May 1993. Twenty (20) patients were enrolled in this study, which gained additional pilot efficacy data, and gathered PK data during a migraine attack versus a headache free period. Patients treated a single migraine headache with zolmitriptan 10 mg and received a second dose during a migraine free period. Fifty five percent (55%) reported headache relief at 2 hours post-dose.

The next study (008) was the first outpatient study in migraine patients. This large, randomized, double-blind, parallel design, placebo controlled study enrolled 1,181 patients throughout Europe and Australia, and was initiated in September 1993. Based on 002, 007, and interim results of 006, which suggested that the recommended dose of zolmitriptan would probably be between 5 and 20 mg, doses of 5, 10, 15, and 20 mg were examined in study 008.

Two hour response rates in this study were 19%, 66%, 71%, 69% and 77% for the placebo, 5, 10, 15, and 20 mg groups, respectively. As with study 006, adverse events increased with increasing dose. Thus the results of 008 suggested that a 5 mg dose provided near-maximal efficacy, but was clearly associated with fewer adverse experiences than higher doses.

To further explore the low end of the dose-response curve, a multicenter trial (017) was initiated in November, 1994. This large, randomized, double-blind, parallel-design, placebo controlled study enrolled 1258 patients at 46 US centers and examined the effects of 1, 2.5, 5, and 10 mg doses. This study allowed for an optional second dose to treat a persistent or recurrent headache.

The two hour response rates in 017 were 34%, 53%, 65%, 67%, and 67% for the placebo, 1, 2.5, 5, and 10 mg groups, respectively. This study demonstrated a relatively flat dose-response curve above 1 mg. The data indicated a substantial, and clinically meaningful difference between 1 mg and 2.5 mg doses, with less marked trends for increased efficacy with increasing doses above 2.5 mg. Thus, the 2.5 mg dose appeared to represent a point at the beginning of the plateau of the dose-response curve for efficacy.

The adverse event profile in 017 indicated very little difference between 1 and 2.5 mg, however adverse experiences increased sharply with doses above 2.5 mg. Thus, in this study, 2.5 mg represented a dose at which efficacy was nearly maximized while adverse experiences were minimized.

While 017 was ongoing, a randomized, double-blind, placebo controlled comparison trial of zolmitriptan and sumatriptan (018) was initiated in December, 1994. The purpose of this study was to compare the safety and efficacy of zolmitriptan 5 mg and sumatriptan 100 mg, and placebo for the treatment of acute migraine headache. The primary efficacy variable used was "complete headache response," which was different from that used in all other clinical studies (the 2 hour headache response). A total of 1311 patients were enrolled in this study. On complete response, zolmitriptan and sumatriptan rates did not differ from each other or from placebo (39%, 38%, and 32% respectively). Both were superior to placebo on a number of secondary efficacy variables. Both were well tolerated and the safety profiles were comparable.

Study 042 confirmed the efficacy of zolmitriptan 2.5 mg in that 62% of the zolmitriptan treated patients versus 36% of the placebo treated patients showed a response at 2 hours post-dose.

### *7.1.5 Studies for Treatment of Multiple Attacks*

A large, uncontrolled, long-term treatment study (015) was initiated at clinical centers throughout the world in December, 1994. Zolmitriptan 5 mg was used in this study. Patients in this study treated multiple migraine attacks for up to 1 year with 5 mg doses. In addition, a second, optional, 5 mg dose was available if needed.

A total of 2266 patients were enrolled, of which 2058 treated at least one migraine headache. A total of 31,579 migraines were treated, ranging from 1 to 125 attacks per patient, with an average of 15 attacks per patient. The overall 2 hour response rate of 81% was slightly higher than seen in previous studies. More importantly, this response rate, as well as other efficacy measures, was maintained over repeated exposures. The long-term safety profile was also favorable (Section 8.6.3.3 Long-Term Study (015), page 50).

### *7.1.6 Studies for Migraine Prevention*

A small, randomized, double-blind, study (026) was initiated in September 1994 to determine whether zolmitriptan would be effective in aborting a migraine attack if taken during the aura phase. Successful prevention of a migraine headache was attributed to study medication if no headache developed within 24 hours of study drug administration. Patients in this study treated two migraine auras, one with zolmitriptan and one with placebo.

A total of 40 patients were enrolled and 30 were included in the efficacy analyses. All patients who treated an attack with placebo in this study (n=21) went on to develop a migraine headache, whereas 4 of 23 patients who used zolmitriptan did not develop a migraine

headache. This was not statistically significant, but is encouraging and a larger study in the future seems worthwhile.

### *7.2 Clinical Pharmacology Studies*

This section contains a brief summary of the clinical pharmacology studies (Table 2, page 8). All safety results are reviewed separately in Section 8, Integrated Review of Safety, page 36.

#### *7.2.1 Clinical Pharmacology Study 011 (N=6), Excretion*

This was an open label study to determine the metabolic profile and rates and routes of excretion of zolmitriptan and its metabolites. Six healthy volunteers received a single oral dose of zolmitriptan 25 mg containing 100 μCi of $^{14}$C-labelled zolmitriptan. Blood, urine, and fecal samples were collected. Total radioactivity in all samples was determined. Key conclusion: 64% of zolmitriptan is excreted in the urine and 27% in the feces.

#### *7.2.2 Clinical Pharmacology Study 012 (N=27), PK Men vs. Women, Young vs. Elderly*

This was a double-blind, placebo controlled, randomized, balanced, four way crossover safety, tolerability, PK, PD study in healthy young and elderly subjects. All 27 volunteers received four treatments (placebo, 5, 10, 15 mg), which were administered at least one week apart. Conclusion:

- In young adults, plasma concentrations of zolmitriptan were higher in women than men. In the elderly, plasma concentrations of zolmitriptan and N-desmethyl zolmitriptan were similar to those in young adults with no difference between genders.

#### *7.2.3 Clinical Pharmacology Study 013 (N=33), Hypertension*

This was a double-blind, randomized, four treatment, four period, cross over study designed to evaluate safety, PK and PD of zolmitriptan and placebo in normotensive and hypertensive volunteers. Each volunteer received a single dose of placebo, 5, 10, or 20 mg of zolmitriptan at weekly intervals in random order. Conclusions:

- There were no clinically significant differences in the pressor response to zolmitriptan between volunteers with mild to moderate hypertension and normotensive volunteers or between males and females.
- Female volunteers had zolmitriptan plasma concentrations which were about twice those of males.
- zolmitriptan PK were dose proportional over the range of 5 to 20 mg.

#### *7.2.4 Clinical Pharmacology Study 024 (N=31), Renal Failure*

This investigation was an open, single occasion, parallel group, PK and tolerability study in renal failure patients and normal volunteers. Subjects were administered a single oral dose of zolmitriptan 10 mg. Conclusion:

- Zolmitriptan 10 mg was well tolerated by patients in renal failure and PK of both parent compound and its active n-desmethyl metabolite were little different from those in matched controls.

#### *7.2.5 Clinical Pharmacology Study 016 (N=12), Bioavailability*

This was an open PK, tolerability study with three treatment periods. During the first period, each subject received zolmitriptan 2.5 mg administered i.v. as a test dose. During the second and third periods, subjects received a 3.5 mg i.v. dose or a single 10 mg tablet in a randomized, balanced manner. Conclusion:

- Mean oral bioavailability of a 10 mg tablet was 49% (geometric mean 44%) in 6 men and 6 women with a ratio estimate of 64%. Relatively more drug is metabolized after

administration and the gender difference, which is particularly apparent after oral dosing, is probably due to greater first-pass metabolism in men.

*7.2.6 Clinical Pharmacology Study 045 (N=20), Bioavailability*

This was an open label, randomized, balanced, single dose, four period crossover PK study with a washout period of at least 5 days between doses. Ten males and 10 females were randomly assigned in a crossover design to receive zolmitriptan on four dosing occasions, tablets (2.5 or 5 mg), on two dosing occasions and i.v. injections on two other occasions. Conclusion:

- The absolute bioavailability of zolmitriptan was for the 2.5 mg tablet and . . . for the 5 mg tablet. No gender difference was observed at the lower dose. A small gender difference was found for the 5 mg tablet (ratio male/female ). The absolute bioavailability for the 5 mg tablet was , in males in in females.

*7.2.7 Clinical Pharmacology Study 025 (N=24), Bioequivalence*

This was an open label, randomized, balanced, single dose, four period crossover PK study with a washout period of at least 5 days between doses. Each subject received a single oral dose of zolmitriptan 2.5 and 5 mg, both as the production process tablet and as the clinical trial material (CTM) tablet. Conclusion: The production batch formulations were bioequivalent to the CTM formulations at both the 2.5 and 5 mg doses.

*7.2.8 Clinical Pharmacology Study 044 (N=12), Food Interaction*

This was an open label, randomized, balanced, single dose, four period crossover PK study with a washout period of at least 5 days between doses. Each subject received a single oral dose of 2.5, 5, and 10 mg in a fasting state and single oral dose of 5 mg after eating. Conclusion: After doses of 2.5, 5, and 10 mg administered in the fasting state, the $C_{max}$ and $AUC_{0-\infty}$ were proportional to dose and clearance was independent of dose.

*7.2.9 Clinical Pharmacology Study 001 (N=12), PK and Tolerability*

This was a double-blind, randomized, placebo controlled, dose escalating PK and tolerability study. The dose was to be escalated as follows: 1, 3, 6, 12, 25, 50, 100, 200, 300 mg orally. When the maximum well tolerated dose was reached, volunteers crossed over to receive the alternative treatment (*i.e.*, active or placebo) under double-blind conditions. Dose escalation was stopped after 50 mg due to somnolence in most subjects. In addition, four volunteers participated in an additional dosing occasion in which two 5 mg tablets (10 mg total) were administered sublingually. Conclusions:

- Zolmitriptan was absorbed after oral administration and plasma concentrations showed considerable inter-subject variability.
- Dose proportionality of AUC was observed for zolmitriptan and its pharmacologically active metabolite, N-desmethyl zolmitriptan, in the range of 6 to 50 mg. The UAC values of N-desmethyl zolmitriptan were approximately half those of zolmitriptan and its plasma elimination half life was similar to that of the parent drug (2.5-3 hours).
- Zolmitriptan may be associated with water diuresis.
- Zolmitriptan in this formulation was not absorbed sublingually.

*7.2.10 Clinical Pharmacology Study 014 (N=12), PK and Tolerability*

This was a randomized, crossover PK and tolerability study of 4 treatment regimens given at 1 week intervals. One regimen was given openly as a single 10 mg dose to determine the single dose PK of zolmitriptan and its metabolites. The other three regimens (PBO, 5 mg, or 10 mg)

were each given in a double-blind fashion as repeat doses at 6 hourly intervals over 24 hours (*i.e.*, five doses over 24 hours). Conclusions:

- Peak concentrations of zolmitriptan and its metabolites were increased following multiple dosing compared with single dosing. The half life of zolmitriptan was significantly longer following multiple dosing compared with single dosing.
- The plasma concentrations of zolmitriptan and its metabolites were generally dose proportional after multiple dosing with5 and 10 mg. Other PK parameters were generally independent of dose.

*7.2.11 Clinical Pharmacology Study 009 (N=13), Sublingual Absorption*

This was a double-blind, placebo controlled, randomized, dose escalation, cross over PK, tolerability study. The dose was to be escalated as follows: 0.5, 1, 2.5, 5, 10, and 20 mg. Tablets were administered sublingually. Conclusion: There was no evidence of sublingual absorption of zolmitriptan with this formulation.

*7.2.12 Clinical Pharmacology Study 311C-1 (NW1) (N=12), PK and Tolerability*

This was a double-blind, placebo controlled, randomized, dose escalation PK, tolerability study. Single oral doses of 1, 2.5, 5, and 10 mg were used. Conclusion: Zolmitriptan was well tolerated across the dose range (1 to 10 mg) studied.

*7.2.13 Clinical Pharmacology Study 311C-2 (NW2) (N=12), PK and Tolerability*

This was a double-blind, placebo controlled, randomized dose escalation PK study. There were three treatment periods at weekly intervals. During each treatment period, subjects received doses of zolmitriptan or placebo three time a day for 2 days. Zolmitriptan doses used were 2.5 mg, 5 mg, and 10 mg. Conclusion: Zolmitriptan was well tolerated.

*7.2.14 Clinical Pharmacology Study 028 (N=8), Absorption*

This was an open, balanced, randomized, two period crossover study of single oral doses of zolmitriptan solution 10 mg and a film coated 10 mg tablet. Conclusion: The rate of absorption of zolmitriptan from the film coated tablet was observed to be slightly slower than from the buffered solution but the bioavailability and $C_{max}$ were similar for the two formulations.

*7.2.15 Clinical Pharmacology Study 023 (N=13), Cognitive Effects*

This was a double-blind, randomized, six way crossover design comparing single oral doses of zolmitriptan 5, 10, 15, or 20 mg to a single dose of lorazepam 2 mg and placebo. Volunteers completed a battery of psychometric tests prior to and at specified intervals after dosing. Conclusions:

- Doses of 5, 10, or 15 mg of zolmitriptan did not cause significant impairment of performance on any of the tasks used in this study. At 20 mg, only one test showed any effect of the study drug.
- Doses of 5, 10, 15, and 20 mg of zolmitriptan produced mild, transient increases in subjective ratings of mental sedation which were dose related in intensity.
- This study suggested that zolmitriptan was unlikely to cause clinically significant sedation at doses lower than 10 mg.

*7.2.16 Clinical Pharmacology Study 010 (N=12), Cafergot*

This was a double-blind, randomized, balanced, 4 way crossover PK, PD study. Volunteers received either a single zolmitriptan 20 mg tablet, 2 mg ergotamine and 200 mg caffeine (2 Cafergot tablets), the two drugs in combination, or placebo. Measures of cardiovascular

parameters were made at baseline, and at intervals for 4 hours post dose with BP and heart rate being measured for 24 hours post dose. Conclusions:

- At a dose 4-8x higher than that anticipated for acute migraine therapy, zolmitriptan was well tolerated when administered alone or in combination with oral Cafergot.
- Both zolmitriptan and Cafergot had vasoconstrictor and pressor actions, but Cafergot had less effect than zolmitriptan. When the two drugs were administered concomitantly, their pressor effects were generally not significantly greater than those of zolmitriptan alone.

*7.2.17 Clinical Pharmacology Study 021 (N=14), Propranolol*

This was a randomized, double-blind blind, crossover drug interaction study of two treatment regimens. Volunteers were randomized to receive either propranolol 160 mg/d for 7 days or matching placebo in a blinded fashion. On the last day of each period, volunteers also received a single zolmitriptan 10 mg tablet (unblinded). BP, heart rate and ECG were monitored for 24 hours post dose. Conclusions:

- Zolmitriptan was well tolerated alone and in the presence of propranolol.
- Propranolol did not affect the small increases in blood pressure associated with zolmitriptan.
- Metabolic clearance of zolmitriptan was reduced in the presence of propranolol, resulting in higher concentrations of zolmitriptan and lower concentrations of n-desmethyl zolmitriptan and the indole acetic acid metabolite.

*7.2.18 Clinical Pharmacology Study 033 (N=15), Acetaminophen, Metoclopramide*

This was an open, randomized, five arm crossover, drug interaction study in which subjects were given five dose regimens:

1. zolmitriptan 10 mg alone
2. paracetamol 1 g alone
3. zolmitriptan + paracetamol (acetaminophen)
4. zolmitriptan + metoclopramide 10 mg
5. zolmitriptan + paracetamol + metoclopramide

Conclusions:

- Zolmitriptan was well tolerated whether given alone or in combination with metoclopramide and / or paracetamol.
- Zolmitriptan 10 mg appeared to both delay and reduce peak concentrations of paracetamol and slightly reduced the extent of absorption.
- In the presence of paracetamol, zolmitriptan exposure increased with an 11% increase in $AUC_{0-\infty}$ associated with a small reduction in $CL_R$ (9%). There was no associated change in heart rate, BP, or AE profile.
- In these healthy volunteers, metoclopramide had no effect on the PK profile of zolmitriptan or n-desmethyl zolmitriptan, or on the effect of zolmitriptan on paracetamol pharmacokinetics.

*7.2.19 Clinical Pharmacology Study 034 (N=13), Pizotifen*

This was a randomized, double-blind, crossover, drug interaction study of two treatment regimens, given at least two weeks apart. Each subject took either 1.5 mg pizotifen or placebo daily for eight days. On the last day of treatment, subjects were given a single dose of zolmitriptan 10 mg. Conclusions:

- Prior administration of pizotifen for one week did not affect tolerability to a single oral dose of zolmitriptan 10 mg or increase its effect on blood pressure.
- In some individuals, pizotifen may delay but not reduce the absorption of zolmitriptan

### *7.2.20 Clinical Pharmacology Study 035 (N=20), Fluoxetine*

This study was a randomized, double-blind, placebo controlled, two period crossover drug interaction study of the effect of multiple doses of fluoxetine on the PD and PK of a single dose of zolmitriptan. During each dosing period, volunteers received a single fluoxetine 20 mg dose or placebo for 28 days. On day 28, they also received zolmitriptan 10 mg in the fasting state. Dosing periods between the treatment arms of the study were separated by a 35 day washout. AE's, vitals signs, ECG's and Holter monitoring were the safety monitors. Conclusion:

- Pretreatment with multiple doses of fluoxetine did not affect the PD or PK of zolmitriptan and its metabolites.

### *7.2.21 Clinical Pharmacology Study 038 (N=12), MAO Inhibitors*

This was an open, randomized, crossover, drug interaction study of three treatment regimens. Subjects received either selegiline, moclobemide, or nothing for 7 days, with a zolmitriptan 10 mg dose administered on the last day. BP and heart rate were monitored daily. Vital signs and ECG were recorded before and for 24 hours after zolmitriptan dosing. Conclusions:

- Zolmitriptan was well tolerated. Adverse experiences were similar after all treatments, and there was no clinically meaningful effect of either selegiline or moclobemide on the small pressor response to zolmitriptan.
- Administration of selegiline was virtually without effect on the PK of zolmitriptan and its metabolites, indicating that MAO-B is probably not involved in their metabolism.
- Administration of moclobemide was associated with a small increase in plasma concentration of zolmitriptan. $C_{max}$ and $AUC_{0-\infty}$ of its active metabolite, n-desmethyl zolmitriptan were increased 2.5 and 3 fold, respectively, while concentrations of the inactive indole acetic acid metabolite were markedly decreased. The results indicate that MAO-A is of little importance for metabolism of the parent compound but is important for the conversion of n-desmethyl zolmitriptan to the indole acetic acid metabolite.
- The results suggest that inhibition of MAO-B has no implications for treatment with zolmitriptan. Inhibition of MAO-A is likely to result in substantial increases in concentration s of the active metabolite, n-desmethyl zolmitriptan. At the dose of 10 mg employed in this study, this was not associated with any increase in AE's or changes in BP. Since the therapeutic dose is likely to be considerably lower than this does, the increased metabolite concentration is probably of no clinical consequence.

### *7.2.22 Clinical Pharmacology Study 039 (N=14), Oral DHE*

This was a double-blind, randomized, balanced, two period crossover, drug interaction study in which 12 healthy volunteers received DHE 5 mg orally or placebo twice daily for 10 days with a single oral dose of zolmitriptan 10 mg taken with the last dose. BP was taken at regular intervals and a 24 hour Holter monitor was collected. Conclusion: There were no clinically significant differences in tolerability, changes in BP, or PK of zolmitriptan and its metabolites after zolmitriptan administration in the presence or absence of pretreatment with DHE 5 mg bid for 10 days.

### *7.2.23 Clinical Pharmacology Study 032 (N=12), Intranasal Spray*

This was initially a double-blind, dose escalating study using doses of zolmitriptan 2.5, 5, and 10 mg administered as an intranasal spray. All subjects then participated in an open, randomized, three arm crossover design, receiving 10 mg as an intranasal spray, a tablet, and an oral solution. Conclusions:

- All formulations were well tolerated. AE's were typical of this class of drug, but there were fewer following intranasal administration than following oral administration. Bad taste, however, was commonly reported with intranasal zolmitriptan.
- $C_{max}$ values for zolmitriptan and n-desmethyl zolmitriptan were lower following intranasal administration with a broader, flatter profile than with oral formulations.
- $AUC_{0-t}$ for zolmitriptan was similar for all formulations.

*7.2.24 Clinical Pharmacology Study 041 (N=12), Intranasal Spray*

This was a randomized, balanced, open, three period crossover study in 12 healthy volunteers. Zolmitriptan 2.5 mg were administered on three occasions with at least 5 days between doses. The treatments were 2.5 mg as an intranasal solution pH=5.0, 2.5 mg as an intranasal solution pH=7.4, and 2.5 mg tablet. Conclusions: The two intranasal solutions and the oral tablet were well tolerated. PK data could not be analyzed in time for submission; full report will follow.

### *7.3 Controlled Clinical Studies*

There were a total of 5 controlled trials (017, 042, 006, 008, and 018, Table 2, page 8). **Studies 017 and 042 were the only 2 that tested the 2.5 mg recommended dose.** Higher doses were used in the remaining 3 studies. Study 018 compared zolmitriptan to sumatriptan and placebo.

*7.3.1 Clinical Study 017*

*7.3.1.1 Title*

A multicenter, double-blind, randomized, placebo-controlled, parallel group study to confirm the efficacy and safety of 311C90 (zolmitriptan) in the treatment of acute migraine headache.

*7.3.1.2 Objectives*

7.3.1.2.1 PRIMARY:

- To determine the optimal dose or doses of oral zolmitriptan effective for the treatment of migraine headache.

7.3.1.2.2 SECONDARY:

- To determine the safety of oral zolmitriptan by evaluating the incidence and nature of AE's and changes in ECG or clinical laboratory assessments.
- To determine the headache response over time, and time at which patients experience meaningful migraine headache relief.
- To determine percentages of patients who were headache free, who had a "complete response", who had a recurrent headache, and who used escape medication.
- To determine improvement in non-headache symptoms of migraine attack.
- To determine the headache response in relationship to factors such as age, gender, weight, presence of aura, duration of headache at treatment, usual duration of untreated headache, initial headache severity, and menstruation.
- To determine the headache response to an optional second tablet of zolmitriptan for the treatment of migraine headache recurring or persisting 4 to 24 hours after initial treatment.
- To determine the effect of zolmitriptan on activities impairment during migraine headache, on the time to resumption of normal activities, and on the time missed from paid employment.

### *7.3.1.3 Design*

This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study designed to assess the efficacy of placebo vs. 1, 2.5, 5, and 10 mg zolmitriptan (using a 1:1:2:2:2 allocation ratio) for the treatment of migraine headache. The treatment phase consisted of outpatient treatment of a single, moderate or severe migraine headache with an initial dose of zolmitriptan or placebo within 12 hours of headache onset or of waking with a headache. Patients were allowed to use approved escape medication after completing the 4 hour headache assessment. Patients with a persistent or recurrent headache were eligible to take an optional second dose of study medication from 4 to 24 hours after the initial dose. The 2nd dose was randomized to placebo or a repeat of the initial dose. The severity of the headache and presence of photophobia, phonophobia, nausea, and/or vomiting were assessed at pre-dose and at 0.5, 1, 2, and 4 hours after the first dose and at 2 hours after the second dose. In addition, the patient evaluated the effect of the migraine on his or her normal activities.

### *7.3.1.4 Number of Subjects*

| | |
|---|---|
| Total no. of patients (All-Treated Population) | 1144 |
| Total no. of patients receiving zolmitriptan | 1004 |
| Total no. of patients receiving placebo | 140 |
| Total no. of patients whose data were excluded from efficacy analysis | 145 |
| Total no. of patients whose data were excluded from safety analysis | 0 |

### *7.3.1.5 Key Inclusion Criteria*

- male or female 12-65 yrs with migraine diagnosis (with or without aura)
- migraine history > 1 yr, age of onset <50 yrs, 1-6 migraines/mo. for the preceding 6 months
- normal laboratory values at screening, no evidence of heart disease

### *7.3.1.6 Duration of Treatment*

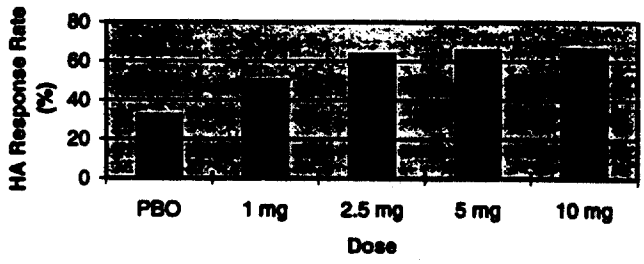
Patients took one tablet for the treatment of a single migraine headache. Patients were eligible to take an optional second tablet if the headache recurred or persisted 4 to 24 hours after the initial dose.

### *7.3.1.7 Summary of Results*

#### 7.3.1.7.1 EFFICACY

Headache response rate at 2 hours, the primary efficacy measure, was 50, 63, 65, and 66% for 1, 2.5, 5, and 10 mg zolmitriptan respectively, compared to 32% for the placebo group in the All-Treated population (Figure 2). The odds ratios (odds of response relative to placebo) for patients in the 1, 2.5, 5, and 10 mg groups were 2.3, 4.1, 4.4, and 4.4 respectively ($p<0.001$).

***Figure 2: Headache Response Rates, Study 017***



All additional efficacy measures were evaluated in the Protocol-Preferred population. Headache response to zolmitriptan was evident as early as 1 hour post-treatment. By four hours, 57% of patients in the 1 mg group and 75% to 78% of patients in the 2.5, 5, and 10 mg groups had a headache response. Complete response was more common in the zolmitriptan groups than in the placebo groups (zolmitriptan doses: 30 to 50%, placebo: 17%). The percentage of patients with recurrence after a headache response at 2 hours was lower in the zolmitriptan groups (26% to 37%) than in the placebo group (46%) and appeared to be dose-related. Zolmitriptan was also effective in providing relief from photophobia and phonophobia. Doses of 2.5, 5, and 10 mg appeared to be more effective in relief of these symptoms than 1 mg. There were no clear difference in headache response at 2 hours in patients categorized by age, weight, migraine history, or baseline characteristics other than severity. Males appeared more likely to respond to higher doses of zolmitriptan compared to 1 mg or placebo.

The efficacy of a second dose of zolmitriptan for the treatment of moderate or severe, recurrent or persistent headache was evaluated. Headache response rates 2 hours after the second dose were 45 to 70% in the zolmitriptan groups compared to 35% in the placebo group. A dose of 10 mg produced the highest response rates in the treatment of persistent or recurrent headaches.

7.3.1.7.2 SAFETY

Zolmitriptan was well tolerated at all dose levels. There were no serious AE's. AE's were more frequent in the zolmitriptan dose groups (39, 44, 58, and 67%) than in the placebo group (30%), and less frequent in the 1 and 2.5 mg groups than in the 5 or 10 mg groups.

The most common AE's were dizziness, asthenia, nausea, somnolence, paresthesia, warm sensation, tightness reported in the throat or chest. The incidence of these AE's appeared to be dose-related but was similar for patients in the 1 and 2.5 mg groups. Zolmitriptan was not associated with treatment emergent changes in clinical laboratory examinations or in ECG's.

*7.3.1.8 Conclusions*

- Zolmitriptan at doses of 1, 2.5, 5, and 10 mg was significantly more effective than placebo in producing headache response at 2 hours.
- The dose relationship for efficacy, based on headache response at 2 hours, appeared relatively flat for doses in the range of 2.5 to 10 mg. There was a trend for higher doses to provide increased efficacy relative to the 1 mg dose.
- Zolmitriptan was also effective for the treatment of migraine symptoms such as photophobia and phonophobia, and the 2.5, 5, and 10 mg doses were more effective in relieving these symptoms than the 1 mg dose.
- The additional efficacy of higher doses was seen especially in the number of patients who have a complete headache response or who were pain-free.
- Headache response 2 hours after a second dose were 45 to 70% in the zolmitriptan compared to 35% in the placebo group. Doses of 10 mg produced the highest response rates in the treatment of persistent or recurrent headache.
- Zolmitriptan was well tolerated. There were no serious AE's. The overall incidence of AE's was lower in patients in the 1 and 2.5 mg dose groups than in patients in the 5 and 10 mg groups. The most common AE's included dizziness, asthenia, nausea, somnolence, paresthesia, warm sensations, and tightness reported in the throat or chest.
- Zolmitriptan does not alter hematology or clinical chemistry laboratory parameters. There were few patients with treatment-emergent laboratory values beyond the expanded

- Zolmitriptan was not associated with treatment-emergent ECG abnormalities.
- A dose of 2.5 mg is the appropriate initial dose for the treatment of migraine headache and its associated symptoms. Higher doses of 5 or 10 mg provided some additional efficacy benefit but had a higher likelihood of adverse experiences, while the lower dose of 1 mg of zolmitriptan provided unacceptable efficacy for many aspects of migraine headache and provided no clear safety advantage.

## *7.3.2 Clinical Study 042*

### *7.3.2.1 Title*

A multicenter, double-blind, randomized, placebo-controlled study to confirm the efficacy and safety of a 2.5 mg dose of zolmitriptan in the acute treatment of migraine headache.

### *7.3.2.2 Objectives*

#### 7.3.2.2.1 PRIMARY

- To confirm the efficacy of a 2.5 mg oral dose of zolmitriptan for treatment of migraine headache, as measured by headache response at 2 hours.

#### 7.3.2.2.2 SECONDARY

- To determine the safety or oral zolmitriptan by evaluating the incidence and nature of AE's, changes in ECG's, and changes in laboratory assessment.
- To determine (1) the headache response at 1 and 4 hours post-dose and the time at which patients experienced meaningful migraine relief; (2) the percentages of patients who were headache free, had recurrent headaches, and had complete responses; (3) the improvement in non-headache symptoms of migraine, including photophobia, phonophobia, and nausea; (4) the percentage of patients who required other medications as an escape therapy; (5) the headache response in relationship to factors such as age, gender, weight, presence of aura, duration of headache at treatment, usual duration of untreated headache, initial headache severity, and menstruation; and (6) the effect of zolmitriptan on activities impairment during migraine headache and the time missed from paid employment.

### *7.3.2.3 Design*

This was a multicenter, double-blind, placebo-controlled outpatient study in which patients were randomized to receive either 2.5 mg zolmitriptan or placebo (in a 2:1 ratio) to treat a single moderate or severe migraine headache, with or without aura. Treatment was administered within 12 hours of headache onset or waking with a headache. Patients were allowed to take escape medication after completing the 4 hours assessment. Patients evaluated the severity of the headache, the presence of photophobia, phonophobia, and nausea at pre-dose and at 1, 2, and 4 hours, and the effect of the migraine headache on normal activities.

### *7.3.2.4 Number of Subjects*

| | |
|---|---|
| Total no. of patients | 301 |
| Total no. of patients receiving zolmitriptan | 200 |
| Total no. of patients receiving placebo | 101 |
| Total no. of patients whose data were excluded from efficacy analysis | 31 |
| Total no. of patients whose data were excluded from safety analysis | 0 |

*7.3.2.5 Key Inclusion Criteria*

- male or female 12-65 yrs with migraine diagnosis (with or without aura)
- migraine history > 1 year, age of onset < 50 yrs, 1-6 migraines/mo. for 6 months
- normal laboratory values at screening, no evidence of heart disease

*7.3.2.6 Duration of Treatment*

A single dose was administered.

*7.3.2.7 Summary of Results*

7.3.2.7.1 EFFICACY

The response rate at 2 hours was 62% for zolmitriptan vs. 36% for placebo ($p<0.05$). Zolmitriptan also appeared to be more effective than placebo based on most of the secondary efficacy measures.

7.3.2.7.2 SAFETY

No deaths or serious AE's were reported. The overall incidence of AE's was higher in the zolmitriptan treatment group (48%) than in the placebo group (29%). The AE's most frequently observed by zolmitriptan treated patients were nausea, dizziness, paresthesia, tightness in chest, and somnolence. No significant treatment emergent ECG or clinical laboratory abnormalities were identified.

*7.3.2.8 Conclusions*

- There was a statistically significant difference in the 2 hour headache response rate between the zolmitriptan treated group (62%) and the placebo group (36%). In addition, zolmitriptan appeared to be more effective than placebo based on the 2 hour headache response rate in most patient subpopulations.
- Zolmitriptan appeared to be more effective than placebo in treating migraine headaches, based on most of the secondary efficacy measures.
- Zolmitriptan was well tolerated. The majority of AE's reported were mild or moderate in intensity. There were no deaths or serious AE's. The most common AE's experience by zolmitriptan treated patients were nausea, dizziness, paresthesia, tightness in chest, and somnolence.

*7.3.3 Clinical Study 006*

*7.3.3.1 Title*

A single center, double-blind, placebo controlled dose finding study to investigate the efficacy, safety and pharmacokinetics of oral doses of zolmitriptan in the acute treatment of migraine with or without aura.

*7.3.3.2 Objectives*

7.3.3.2.1 PRIMARY

- To determine the efficacy of zolmitriptan within 2 hours of treatment.
- To approximate the optimal therapeutic dose.
- To obtain the side effect profile of various doses of zolmitriptan during a migraine attack.

7.3.3.2.2 SECONDARY

- To examine the PK of zolmitriptan up to 4 hours after the last dose during a migraine attack.

- To determine whether zolmitriptan may be effective in treating the non-pain accompaniments of a migraine attack.
- To determine the headache recurrence rate after an initial response to zolmitriptan.

*7.3.3.3 Design*

This was a double-blind, placebo controlled, randomized study in which migraine patients (with or without aura) were asked to attend the clinic during a moderate or severe headache. Patients received the first dose of study drug (1, 5, 25 mg or placebo) at 0 hours and could take an optional second dose (15, 20, 0 or 10 mg zolmitriptan, respectively) at 2 hours. Escape medication was allowed at 3 hours for patients taking a single dose, and at 4 hours post-first dose for those patients taking a second optional dose.

*7.3.3.4 Number of Subjects*

| | |
|---|---|
| Total no. of patients | 84 |
| Total no. of patients receiving zolmitriptan | 79 |
| Total no. of patients receiving placebo | 20 |
| Total no. of patients whose data were excluded from efficacy analysis | 4 |
| Total no. of patients whose data were excluded from safety analysis | 0 |
| Total no. of patients whose data were excluded from PK analysis | 0 |

*7.3.3.5 Key Inclusion Criteria*

- 18-55 yrs, with >1 year history of migraine, ≤ 6 migraines per month
- no cardiac, renal, hepatic disease, hypertension
- no prophylactic migraine medications, or other chronic daily medications

*7.3.3.6 Duration of Treatment*

Study medication was given for a single attack. The first dose was given within 12 hours of headache onset or on waking with a headache. The optional second dose could be taken only at 2 hours after the first dose.

*7.3.3.7 Summary of Results*

7.3.3.7.1 EFFICACY

Headache response rates at 2 hours were 15% for the placebo treatment group and 27, 62, and 81% for the 1, 5, and 25 mg treatment groups, respectively. Logistic regression modeling showed that 5 and 25 mg treatment groups had a statistically significantly improved chance of producing a headache response compared to placebo. The dose of zolmitriptan, the intensity of the headache pre-dose, and the age of the patient had an effect on the headache response at 2 hours. Headache recurrence of moderate or severe intensity was experienced by approximately one-third of the patients in each study group, with the exception of the 25 mg treatment group where only 7% of patients had a recurrence. Both the 5 and 25 mg doses appeared to be more effective in relieving photophobia and nausea than placebo.

7.3.3.7.2 PHARMACOKINETICS

The percentage of patients with detectable plasma concentrations of zolmitriptan at 2 hours increased with increasing dose. Within each treatment group, the median plasma concentrations of zolmitriptan and N-desmethyl zolmitriptan were higher in patients responding at 2 hours than non-responders, but the range was wide.

7.3.3.7.3 SAFETY

No serious AE's were reported. Most AE's were mild in intensity and transient in duration. The most common AE's with zolmitriptan were asthenia, somnolence, dry mouth, dizziness, heaviness in arms and legs, and cold sensation.

*7.3.3.8 Conclusions*

- Zolmitriptan is efficacious in the acute treatment of migraine at doses of 5 and 25 mg and has beneficial effects on the accompanying symptoms of photophobia and nausea.
- Plasma concentration is not clearly predictive of efficacy.
- The side effect profile of zolmitriptan during a migraine attack showed that doses up to 25 mg are well tolerated and that the 5 mg dose is clearly associated with fewer AE's than the 25 mg dose.
- There were no measurable effects on cardiovascular parameters at doses up to 25 mg.
- Further dose-range finding studies involving larger numbers of patients are required to determine the optimal dose or dose-range of zolmitriptan in the acute treatment of migraine.

*7.3.4 Clinical Study 008*

*7.3.4.1 Title*

A multicenter, randomized, double-blind, placebo controlled, parallel group, dose-range finding study to investigate the efficacy and safety of oral doses of zolmitriptan (5 to 20 mg) in the treatment of acute migraine with or without aura.

*7.3.4.2 Objectives*

7.3.4.2.1 PRIMARY

To determine the optimal therapeutic dose for zolmitriptan by examining the efficacy (treatment of headache pain at 2 hours post-dose) and side effect profile of four doses of zolmitriptan and placebo during a single migraine attack.

7.3.4.2.2 SECONDARY

- To compare the efficacy of the four dose strengths of zolmitriptan and placebo by examining: (1) headache pain at 1 hour post dose, (2) proportion of patients pain free at 1 and 2 hours post-dose, (3) use of escape medication at 2 hours post dose, (4) effect on non-pain components of migraine, (5) headache recurrence rate up to 24 hours post dose recurrence, (6) complete response rate, and (7) efficacy in different subgroups of patients, such as in presence or absence of aura, by gender, by time from onset of headache to administration of study drug.

*7.3.4.3 Design*

This was a double-blind, placebo controlled, randomized, parallel group study. Patients were randomized in a ratio of 1:2:2:2:2 to receive placebo, 5, 10, 15, or 20 mg zolmitriptan and were to treat a moderate or severe migraine headache with study drug. Baseline information on the treated migraine was recorded in a standard diary by the patient. Information on the migraine symptoms, AE's and medication use were collected at 1, 2 and 24 hours post-treatment. Conventional escape medication, except for sumatriptan and ergotamine, were allowed 2 hours post-treatment. Sumatriptan and ergotamine could be taken as escape medication 12 hours post-treatment.

*7.3.4.4 Number of Subjects*

Total no. of patients (All Treated Population)

| | |
|---|---|
| Total no. of patients receiving zolmitriptan | 852 |
| Total no. of patients receiving placebo | 99 |
| Total no. of patients whose data were excluded from efficacy analysis | 111 |
| Total no. of patients whose data were excluded from safety analysis | 0 |

*7.3.4.5 Key Inclusion Criteria*

- 18-65 yrs, > 1 year history of migraines, age of onset ≤ 40 yrs, 1-6 migraines/month
- no HTN, cardiac, renal, hepatic, vascular, psychiatric, other neurological disease
- no chronic treatment with psychoactive drugs or drugs active at 5HT receptors

*7.3.4.6 Duration of Treatment*

Patients took one study tablet for treatment of a single migraine attack within 6 hours of headache onset or on waking with the headache.

*7.3.4.7 Summary of Results*

7.3.4.7.1 EFFICACY

The odds ratios representing the odds of having a headache response at 2 hours with a particular zolmitriptan dose relative to placebo (after adjusting for gender, age, presence of aura, baseline headache severity) was statistically significantly improved ($p<0.001$) at 2 hours post-treatment with zolmitriptan in both the All-Treated (odd ratio: 6.0, 7.7, 7.2, and 10.2 for 5, 10, 15, and 20 mg, respectively) and Protocol-Preferred populations. For the All-Treated population, the headache response rate was 21% in the placebo group and ranged from 61% to 74% across the zolmitriptan dose groups. Secondary measures of efficacy also showed improvement.

7.3.4.7.2 SAFETY

Zolmitriptan was well tolerated at all levels. The frequency of AE's appeared to be dose dependent. The most commonly reported AE's were asthenia, dizziness, paresthesia, heaviness in various parts of the body (excluding chest, neck, throat and jaw), somnolence, warm sensation, dry mouth, and vertigo. The majority of AE's were rated as mild or moderate in intensity, not serious, and were transient, and resolved without intervention. One serious AE (tachycardia) that resolved spontaneously without sequelae was reported in a patient with pre-existing Wolff-Parkinson-White Syndrome. No clinically significant changes in the post-treatment 12 lead ECG's or clinical laboratory examinations were observed.

*7.3.4.8 Conclusions*

- Zolmitriptan was significantly superior to placebo in the acute treatment of migraine headache at doses of 5, 10, 15, and 20 mg.
- In the dose range 5-20 mg, there was no linear dose-response relationship for efficacy and the efficacy of 5 mg was comparable to that of the higher doses. There was a trend for increased efficacy at 20 mg.
- Zolmitriptan was also effective in treating non-pain symptoms of migraine.
- Zolmitriptan was well tolerated at all doses with clear evidence that fewer AE's occurred at lower doses, which was notable clinically with 5 mg.
- Zolmitriptan did not consistently alter any laboratory parameters or affect ECG's post-treatment.
- Zolmitriptan 5 mg had a particularly favorable efficacy and safety profile with a lower incidence of AE's than with higher doses but with similar efficacy.

## *7.3.5 Clinical Study 018*

### *7.3.5.1 Title*

A multicenter, randomized, double-blind, placebo controlled, parallel group study to compare the efficacy and safety of 5 mg of zolmitriptan and 100 mg sumatriptan in the treatment of migraine headache.

### *7.3.5.2 Objectives*

#### 7.3.5.2.1 PRIMARY

- To compare the "complete response" rates of zolmitriptan, sumatriptan, and placebo in the acute treatment of migraine headache, as defined by the proportion of patients who have a response at 2 hours post-dose and do not experience a recurrent headache within 24 hours of study drug administration.

#### 7.3.5.2.2 SECONDARY

- To compare the efficacy of zolmitriptan, sumatriptan, and placebo as measured by the following additional parameters: the proportion of patients (1) who exhibit a response at 1, 2, and 4 hours post-dose; (2) who are headache pain-free at 1, 2, and 4 hours post-dose; (3) who use escape medication at 2 hours post-dose; (4) who experience a recurrent headache within 24 hours after administration of study drug; (5) who exhibit varying degrees of headache response; and (6) who had other migraine symptoms (*i.e.*, photophobia, phonophobia, nausea, vomiting) treated effectively; the time to meaningful migraine relief as defined by the patient; and measures of activities impairment at 1, 2, 4, and 24 hours post-dose.
- To compare the safety profiles of outpatient administration of zolmitriptan, sumatriptan, and placebo.

### *7.3.5.3 Design*

This was a multicenter, double-blind, placebo controlled, parallel group outpatient study in which patients were randomized in a ratio of 8:8:1 to receive orally zolmitriptan 5 mg, sumatriptan 100 mg, or placebo, respectively. The treatment phase consisted of outpatient treatment of a single, severe or moderate migraine headache with or without aura. Patients were allowed to take approved escape medications after completing the 2 hour assessment. The patient evaluated migraine symptoms and their effects on normal activities at pre-dose and at 1, 2, and 4 hours after treatment. The patient returned to the clinic as soon as possible after treatment for post-treatment evaluations.

### *7.3.5.4 Number of Subjects*

| | |
|---|---|
| Total no. of patients (All-Treated Population) | 1058 |
| Total no. of patients receiving zolmitriptan | 498 |
| Total no. of patients receiving sumatriptan | 504 |
| Total no. of patients receiving placebo | 56 |
| Total no. of patients whose data were excluded from efficacy analysis | 181 |
| Total no. of patients whose data were excluded from safety analysis | 0 |

### *7.3.5.5 Key Inclusion Criteria*

- 18-65 yrs, > 1 year history of migraines, age of onset ≤ 50 yrs, 1-6 migraines/month
- no HTN, cardiac, renal, hepatic, vascular, psychiatric, other neurological disease
- no previous use of sumatriptan, zolmitriptan, or any other 5-HT$_1$-like agonists

*7.3.5.6 Duration*

A single dose was administered.

*7.3.5.7 Summary of Results*

7.3.5.7.1 EFFICACY

The study did not demonstrate statistically significant differences between the treatment groups (39, 38, and 32% for zolmitriptan, sumatriptan, and placebo, respectively). The complete response results demonstrated a statistically significant treatment effect of zolmitriptan (compared to placebo) for patients in the All Treated population who took study drug to treat a migraine headache of moderate intensity. The protocol preferred analysis approached statistical significance (p=0.06).

Statistically significant effects of zolmitriptan (as well as sumatriptan) compared to placebo were demonstrated on a number of secondary efficacy endpoints in the All Treated population. With regard to 2 hour headache response, zolmitriptan and sumatriptan response rates were similar to each other and higher than for placebo. In the All Treated population, the zolmitriptan and sumatriptan vs. placebo difference was statistically significantly at 2 hours post-dose; at 1 and 4 hours post-dose, both compounds were also statistically different from placebo in the All Treated population. No difference were observed between zolmitriptan and sumatriptan for these endpoints. Zolmitriptan and sumatriptan produced similar efficacy responses in the secondary efficacy measures. The placebo response rate in this study was higher than observed in previous studies of zolmitriptan. The small size of the placebo group and its uncharacteristic high response rate hindered the conduct of any subgroup analyses.

7.3.5.7.2 SAFETY

Both zolmitriptan and sumatriptan were well tolerated. AE's were more frequent in the zolmitriptan and sumatriptan groups (58, 57, and 23%, respectively). The most common AE's for zolmitriptan and sumatriptan were asthenia, dizziness, paresthesia, feelings of heaviness, warm sensation, nausea, somnolence, and neck pain. Three serious AE's were reported, one in each treatment group. None were judged by investigators to have a reasonable possibility of being caused by the study drugs.

The incidence of treatment emergent ECG abnormalities was similar in all three groups. Only two patients (one zolmitriptan and one sumatriptan patient) had a significant change in ECG between screen and follow-up. The patient receiving zolmitriptan went from abnormal ECG at screen to normal at follow-up.

*7.3.5.8 Conclusions*

- No statistically significant difference were observed among the three treatment groups for the primary efficacy variable, complete response.
- The placebo response rate was uncharacteristically high.
- Statistically significant effects of zolmitriptan compared to placebo were also demonstrated on a number of other analyses for secondary efficacy endpoints.
- zolmitriptan and sumatriptan were well tolerated and had comparable safety profiles.

***7.4 Uncontrolled Clinical Studies***

There were three uncontrolled trials, 002, 007, and 015 (Table 2, page 8). Studies 002 and 007 were small (n=18, and 20, respectively). Study 015 was the large, multiple attack, long term safety study.

## 7.4.1 Clinical Study 002

### 7.4.1.1 Title

An open study to investigate the pharmacokinetics and tolerability of oral zolmitriptan and to obtain a preliminary indication of efficacy in patients with migraine.

### 7.4.1.2 Objectives

- To investigate the tolerability of zolmitriptan
- To obtain a preliminary indication of efficacy of oral zolmitriptan
- To examine the absorption of oral zolmitriptan

### 7.4.1.3 Design

This was an open label, single treatment study. Headache symptoms were assessed pre- and post-treatment with an oral dose of zolmitriptan 25 mg. Patients could take escape medication at 2 hours if necessary. After blood sample collection at 4 hours, patients could leave the clinic. Patients were contacted approximately 24 hours post-dose for assessment of any other symptoms or headache recurrence.

### 7.4.1.4 Number of Subjects

| | |
|---|---|
| Total no. of patients (All-Treated Population) | 18 |
| Total no. of patients receiving zolmitriptan | 18 |
| Total no. of patients receiving placebo | 0 |
| Total no. of patients whose data were excluded from efficacy analysis | 1 |
| Total no. of patients whose data were excluded from safety analysis | 0 |
| Total no. of patients whose data were excluded from PK analysis | 0 |

### 7.4.1.5 Key Inclusion Criteria

- 18-45 yrs, with migraine headaches with or without aura
- No clinically significant abnormalities at screening
- no suspicion of heart disease, no regular medications

### 7.4.1.6 Duration

A single dose was administered.

### 7.4.1.7 Summary of Results

#### 7.4.1.7.1 EFFICACY

Eighty-two percent (14/17) showed a significant response within 2 hours of dosing. There was no apparent relationship between the pre-treatment duration of headache and the probability of response. Symptoms of nausea, vomiting, and photophobia also declined. Of the14 patients who responded within 2 hours post-dose, one took escape medication, therefore, 13 patients could be assessed for headache recurrence. Twenty-three percent (3/13) had a recurrence within 24 hours post-dose.

#### 7.4.1.7.2 SAFETY

All patients reported AE's; however, these were generally mild to moderate in intensity and none was serious.

#### 7.4.1.7.3 PHARMACOKINETICS

The $AUC_{0-4}$ in the 17 female patients with migraine were similar to that observed in another study with healthy male volunteers.

*7.4.1.8 Conclusions*

- A single oral dose of zolmitriptan 25 mg showed promising efficacy in the treatment of migraine headache
- zolmitriptan was effective irrespective of the duration of the symptoms before treatment.

*7.4.2 Clinical Study 007*

*7.4.2.1 Title*

An open study to investigate the pharmacokinetics and tolerability of oral zolmitriptan and to obtain a preliminary indication of efficacy in patients with migraine.

*7.4.2.2 Objectives*

- To obtain a preliminary indication of the efficacy of an oral dose of zolmitriptan 10 mg
- To investigate the tolerability to an oral dose of zolmitriptan 10 mg
- To compare the absorption of oral zolmitriptan during and between migraine attacks
- To explore the relationship between plasma concentrations, efficacy, and AE's.

*7.4.2.3 Design*

This was an open, nonrandomized, uncontrolled two-period study in hospitalized patients. Each patient received a single 10 mg oral dose of zolmitriptan for treatment of a moderate to severe migraine attack and again on a subsequent occasion after being migraine free for at least 48 hours. Patients were not treated during aura.

*7.4.2.4 Number of Subjects*

| | |
|---|---|
| Total no. of patients (All-Treated Population) | 20 |
| Total no. of patients receiving zolmitriptan | 20 |
| Total no. of patients receiving placebo | 0 |
| Total no. of patients whose data were excluded from efficacy analysis | 0 |
| Total no. of patients whose data were excluded from safety analysis | 0 |
| Total no. of patients whose data were excluded from PK analysis | 0 |

*7.4.2.5 Key Inclusion Criteria*

- 18-55 yrs, with a history of migraine with or without aura
- no HTN, cardiac disease, other significant illness, or taking regular medications.

*7.4.2.6 Summary of Results*

7.4.2.6.1 EFFICACY

Responders were 11/20. Three of the 11 had a recurrence within 24 hours. Eight patients took escape medication after 2 hours.

7.4.2.6.2 SAFETY

AE's were similar during and outside of the attack and were consistent with previous studies. No clinically significant changes in BP or ECG were observed.

7.4.2.6.3 PHARMACOKINETICS

Plasma concentrations showed considerable inter-subject variability. Median $C_{max}$ and AUC values over the first 4 hours were lower during a migraine attack than when studied a second time during the migraine free period (median difference in the $AUC_{0-4}$ 15.7 ng·h/mL (95% CI 6.9, 25.3)). Responders generally had higher plasma concentrations of zolmitriptan than nonresponders during an attack

*7.4.2.7 Conclusions*

- An oral dose of zolmitriptan 10 mg showed efficacy in 11 out of 20 patients with acute migraine in an open study.
- An oral dose of zolmitriptan 10 mg was generally well tolerated and was without clinically important effects on blood pressure and ECG.
- Plasma concentrations of zolmitriptan and its metabolites were lower in the first 4 hours post-dose during a migraine attack compared to a migraine free period.

*7.4.3 Clinical Study 015*

*7.4.3.1 Title*

Multicenter, open study to investigate the long term effects of oral zolmitriptan in the treatment of migraine headache.

*7.4.3.2 Objectives*

7.4.3.2.1 PRIMARY

To provide safety data for a clinically useful dose of zolmitriptan 5 mg in treating migraine headaches on multiple occasions up to one year.

7.4.3.2.2 SECONDARY

To provide data on the response to zolmitriptan in the treatment of multiple migraine headaches over an extended period of time; to provide insight into the pattern of use of zolmitriptan; to obtain preliminary data on the treatment of recurrent migraine headache with zolmitriptan; to pilot a migraine specific quality of life questionnaire; and to obtain data on activity impairment during a migraine attack and recovery thereafter.

*7.4.3.3 Design*

This was an international, multicenter open study with patients treating multiple migraine headaches. A single 5 mg dose could be followed with a second 5 mg dose within 2-24 hours for headache recurrence. Approved escape medication was also allowed. After initial treatment of a single headache, patients were given medication to treat the next 4 headaches. Subsequently, sufficient medication to treat 12 headaches were given.

*7.4.3.4 Number of Subjects*

| | |
|---|---|
| Total no. of patients (All-Treated Population) | 2058 |
| Total no. of patients receiving zolmitriptan | 2058 |
| Total no. of patients receiving placebo | 0 |
| Total no. of patients whose data were excluded from efficacy analysis | 30 |
| Total no. of patients whose data were excluded from safety analysis | 30 |

*7.4.3.5 Key Inclusion Criteria*

- migraineur who met admission criteria for a previous zolmitriptan study
- no HTN, heart disease or other medical condition, not pregnant
- no methysergide or other treatments that may affect safety and efficacy

*7.4.3.6 Duration of Treatment*

Patients had the opportunity to treat multiple migraines, of any intensity, for up to one year from signing informed consent or until the end of January 1996, whichever was sooner. Following treatment of a single migraine with one 5 mg tablet, a second 5 mg tablet (could be

*7.4.3.7 Summary of Results*

7.4.3.7.1 EFFICACY

The two hour response rate was 81%. Meaningful migraine relief, as judged by the patient, was 73%. Resolution of headache to pain free at 2 hours across all migraine attacks with a baseline headache intensity of mild, moderate, or severe was 80, 57, and 35%, respectively.

Efficacy was not modified by gender, age, race, or weight, where sample size was large enough to allow comparison. The two hour efficacy outcomes were maintained over repeated (45) exposures. Menstrually related migraine attacks were as similarly responsive to zolmitriptan as migraine attacks that were not menstrually related. The use of migraine prophylactic medications had no effect on any of the efficacy measurements. The 2 hour response rate was 90% to a second tablet for migraine headaches that initially responded to zolmitriptan and had later recurred.

7.4.3.7.2 SAFETY

Sixty-three percent (63%) of patients completed the study. The primary reasons for premature withdrawal were inadequate response to study drug (11%), consent withdrawn (11%), and adverse experiences (8%). The AE's that led to withdrawal were similar to the most frequently occurring AE's that were reported in the study population. The type of AE's (asthenia, nausea, somnolence, dizziness, and paresthesia.) were similar to those reported in previous studies. The majority of AE's (59%) were mild. The AE's were of short duration, had an onset within 4 hours of administration, were judged to be attributable to study drug, and did not require additional. The types and incidence of AE's were not modified by gender, age, race, or weight where sample size was large enough to allow comparison, although there was some indication of a higher incidence of AE's in females. The use of migraine prophylactic medications or sex hormones did not alter the type or incidence of AE's.

There were 43 serious adverse experiences reported by 39 patients. Two (throat constriction and increase in frequency of migraine attacks) were considered to be possibly attributable to zolmitriptan. No patients died during the course of the study. There were no specific safety concerns regarding the use of a second 5 mg tablet. The frequency of reported AE's decreased with repeated usage. Long-term use had no significant effect on ECG's, laboratory assessments, or vital signs.

*7.4.3.8 Conclusions*

7.4.3.8.1 EFFICACY

- The two hour response rate was 81%. This is higher than in controlled trials and may be due to the open design.
- Meaningful migraine relief was reported in 83% of all treated migraine attacks.
- The use of migraine prophylactic medications had no effect on efficacy.

7.4.3.8.2 SAFETY

- Zolmitriptan was well tolerated following repeated exposures. Eight percent discontinued because of an AE. There were 43 SAE's reported by 39 patients, of which 2 were considered to be possibly attributable to zolmitriptan. No patients died.
- The AE's were similar to those reported in previous studies. Twenty-five percent of treated migraine attacks were associated with an AE. The majority of reported AE's were of mild intensity, of short duration, had an onset within 2 hours of administration, were attributable

- Demographic variables, other than gender, did not appear to modify the incidence or types of AE's. There was some indication that females have a higher incidence of AE's compared to males.
- There were no specific safety concerns regarding the use of a second 5 mg tablet.
- The incidence of reported AE's appeared to decrease with repeated use, although this may have been influenced by the changing population over time. The types of AE's remained relatively constant. There was no indication that long term treatment resulted in the emergence of previously unreported AE's.
- Long term zolmitriptan does not have a clinically significant effect on standard measures of clinical chemistry, hematology, urinalysis, or on the ECG.

### *7.5 Other Studies*

Two additional studies (026, and 030) were performed. Study 026 looked at migraine headache prevention in patients with migraine with aura who take zolmitriptan during an aura, before the headache actually begins and is therefore called a prevention study. Study 030 provides PK/PD data in hepatic disease.

#### *7.5.1 Clinical Study 026*

This was a multicenter, double-blind, placebo controlled, two period crossover study to investigate the efficacy of a 20 mg dose of zolmitriptan in the prevention of migraine headache when taken during an aura. The main objective was to determine whether zolmitriptan 20 mg is able to prevent the development of headache when given during the migraine aura, as defined by the proportion of patients who did not develop a headache within 24 hours after administration of study drug.

Thirty (30) Patients with migraine with aura whose auras were typically followed by a migraine headache were enrolled to treat two migraine attacks during the aura phase. They were randomized in a 1:1 ratio to receive zolmitriptan 20 mg or placebo. A second dose could also be taken at 2 hours during the headache phase, should it occur, and was always zolmitriptan. If the first dose was zolmitriptan 20 mg, the second dose was 5 mg. If the first dose was placebo, the second dose was 20 mg. Following treatment of one migraine, they were then given the other treatment in a cross-over fashion to treat a second migraine attack. Escape medication (except sumatriptan or ergotamines) could be used instead of the second dose of study medication if a migraine headache was present. Escape medication could be taken any time after 2 hours post-dosing with study medication. Study medication was provided to treat two migraine attacks, with the optional second dose at 2 hours.

Sixteen (16) patients completed both treatment periods. Zolmitriptan 20 mg was not statistically significantly better than placebo in preventing migraine headache when taken during an aura. Four of 16 patients responded (*i.e.*, did not develop a headache within 24 hours) to the 20 mg dose of zolmitriptan in the first or second treatment period. None of the patients responded to placebo taken during aura. No serious AE's were reported. Most AE's were mild to moderate in intensity and were transient. One patient withdrew from the study because of an AE (severe chest tightness). No evidence of zolmitriptan related adverse effects on aura were seen.

#### *7.5.2 Study 030 (N=30)*

This study report was not included in the original NDA submission, but was submitted in the abbreviated 4 month safety update submission on 3/24/97. The study compared the pharmacokinetics of and tolerability of a single oral 10 mg dose of zolmitriptan in healthy

all 30 subjects receive a single oral dose of zolmitriptan 10 mg. There were 3 parallel subject groups. Group 1: patients with moderate liver disease (n=10); Group 2: patients with severe liver failure (n=10), and Group 3: normal healthy volunteers matched in age, sex, and smoking status (n=10).

Metabolism of zolmitriptan was reduced in patients with liver disease, resulting in higher $C_{max}$ (approximately 50%, 31 ng/mL vs. 21 ng/mL), increased AUC (226%) and prolonged $T_{max}$ (12 hours vs. 4.7 hours) in severe liver disease (less so with moderate disease). Therefore, the dose may need to be reduced in this population. Zolmitriptan 10 mg was generally well tolerated in volunteers and patients.

# 8. Integrated Review of Safety

## *8.1 Background and Methodology*

The evaluation of safety of zolmitriptan in the exposed population is centered on the information provided in the integrated summary of safety, both paper and electronic versions. In addition, individual narrative summaries for serious adverse events and discontinuations were reviewed. Finally, adverse events SAS transport file datasets, converted to JMP format were used for review and analyses.

Four-thousand-three (4,003) unique subjects participated in the zolmitriptan clinical development program.. Of these 3,096 actually were exposed to zolmitriptan. FDA Table 10 summarizes total participation by study. Many patients participated in more than one study, which explains the total of 6,011 patients.

The zolmitriptan clinical development program includes 36 studies, of which 31 are included in the integrated safety database. The other five studies, and reasons for exclusion from the safety database, are:

1. Study 091 (bioequivalence), data analysis ongoing
2. Study 311C–1 (dose response, pharmacokinetics of a single dose), Japanese study, electronic database not available
3. Study 311C–2 (dose response, pharmacokinetics of multiple doses), Japanese study, electronic database not available
4. Study 030 (liver failure patients), ongoing study
5. Study 043 (migraine patients). ongoing study

The 3,096 subjects exposed to zolmitriptan received almost 50,000 oral doses of the drug, in doses ranging from 0.5-50 mg. A total of 2780 unique patients received zolmitriptan for the treatment of migraine. Another 316 unique non-patient volunteers in the clinical pharmacology studies received the drug. Most patients treated a single migraine with one or two doses of zolmitriptan, but in the long-term safety study (015), over 2,000 patients treated multiple migraine attacks for up to one year. FDA Table 11 summarizes the number unique subjects exposed to zolmitriptan. Again, these differ from the totals in Table 10 since some subjects participated in more than one study and are counted more than once in Table 10.

*Table 10: No. of Subjects Treated in the Zolmitriptan Clinical Development Program*

| Study Type | # | Study Number | Total N | Zolmitriptan N | Placebo N | Other N |
|---|---|---|---|---|---|---|
| Clinical Pharmacology | 1 | 011 | 6 | 6 | 0 | 0 |
| | 2 | 012 | 27 | 27 | 27 | 0 |
| | 3 | 013 | 33 | 33 | 33 | 0 |
| | 4 | 024 | 31 | 31 | 0 | 0 |
| | 5 | 016 | 12 | 12 | 0 | 0 |
| | 6 | 045 | 20 | 20 | 0 | 0 |
| | 7 | 025 | 24 | 24 | 0 | 0 |
| | 8 | 044 | 12 | 12 | 0 | 0 |
| | 9 | 001 | 12 | 12 | 12 | 0 |
| | 10 | 014 | 12 | 12 | 12 | 0 |
| | 11 | 009 | 13 | 13 | 13 | 0 |
| | 12 | 028 | 8 | 8 | 0 | 0 |
| | 13 | 023 | 13 | 13 | 0 | 13 |
| | 14 | 010 | 12 | 12 | 12 | 12 |
| | 15 | 021 | 14 | 14 | 14 | 0 |
| | 16 | 033 | 15 | 15 | 0 | 15 |
| | 17 | 034 | 13 | 13 | 13 | 13 |
| | 18 | 035 | 20 | 20 | 20 | 20 |
| | 19 | 038 | 12 | 12 | 12 | 12 |
| | 20 | 039 | 14 | 14 | 0 | 14 |
| | 21 | 032 | 12 | 12 | 12 | 0 |
| | 22 | 041 | 12 | 12 | 0 | 0 |
| *Sub-total* | | | *347* | *347* | *180* | *99* |
| Controlled Treatment Trials | 23 | 017 | 1144 | 1004 | 140 | 0 |
| | 24 | 042 | 301 | 200 | 101 | 0 |
| | 25 | 006 | 84 | 79 | 20 | 0 |
| | 26 | 008 | 951 | 852 | 99 | 0 |
| | 27 | 018 | 1058 | 498 | 56 | 504 |
| *Sub-total* | | | *3538* | *2633* | *416* | *504* |
| Uncontrolled Treatment Trials | 28 | 002 | 18 | 18 | 0 | 0 |
| | 29 | 007 | 20 | 20 | 0 | 0 |
| | 30 | 015 | 2058 | 2058* | 0 | 0 |
| *Sub-total* | | | *2096* | *2096** | *0* | *0* |
| Prevention | 31 | 026 | 30 | 30 | 24 | 0 |
| *Sub-total* | | | *30* | *30* | *24* | *0* |
| **TOTAL** | | | **6011** | **5106*** | **620** | **603** |

* 30 patients excluded from long term safety analysis (Study 015)

*Table 11: Number of Unique Subjects Exposed to Zolmitriptan, by Study Type*

| Study Type | Zolmitriptan N |
|---|---|
| Clinical Pharmacology Studies | 316 |
| Controlled Treatment Trials | 2,633 |
| Uncontrolled Treatment Trials | 117 |
| Controlled Prevention Trial (026) | 30 |
| **Total** | **3,096** |

In order to limit the array of dose groups to a manageable number and associate events with the lowest dose of zolmitriptan, the sponsor and the FDA agreed to summarize safety data for

For example, AE's occurring after a second dose of zolmitriptan or placebo in patients whose first study drug was zolmitriptan are linked to the initial dose of zolmitriptan. AE's occurring after an optional second dose of zolmitriptan in patients whose first study drug was placebo are also ascribed to the initial dose of zolmitriptan (*i.e.*, the first dose of zolmitriptan taken by the patient). This scheme is applied to other safety data as well (*e.g.*, ECG, laboratory abnormalities, etc.) unless otherwise specified.

### *8.2 Deaths*

There were no deaths reported in the zolmitriptan clinical development program.

### *8.3 Serious Adverse Events*

The integrated safety database of all zolmitriptan studies includes 43 patients who reported a total of 48 SAE's. Forty (40) of these 43 patients received zolmitriptan, one received sumatriptan, one received placebo, and one did not take any study medication after developing breast cancer. Most of the subjects with SAE's (n=38, 37 who took zolmitriptan) were enrolled in Study 015, the long term safety study. The SAE's were not exclusively related to high doses of zolmitriptan. One occurred after zolmitriptan 15 mg exposure, but the remainder occurred at doses of 5 mg or 5+5 mg. None occurred after a 2.5 mg dose, the recommended initial dose. Table 12 lists all the serious adverse events, by COSTART preferred term.

*Table 12: Serious Adverse Events in the Zolmitriptan Development Program (N=3,096)*

| SAE | n | SAE | n |
|---|---|---|---|
| OVERDOSE | 4 | INFECT | 1 |
| INJURY ACCID | 3 | INFECT URIN TRACT | 1 |
| OVAR DISORDER | 3 | ISCHEMIA CEREBR | 1 |
| REACT UNEVAL | 3 | MALABSOPR SYND | 1 |
| NEOPL | 2 | MENINGITIS | 1 |
| PAIN ABDO | 2 | MENS DISORDER | 1 |
| PAIN BACK | 2 | NEOPL BREAST | 1 |
| PYELONEPHRITIS | 2 | NEOPL CERVIX | 1 |
| SYNCOPE | 2 | PAIN BONE | 1 |
| CARCINOMA | 1 | PAIN CHEST | 1 |
| CARCINOMA BREAST | 1 | PAIN LOC SPEC | 1 |
| CYST | 1 | PNEUMOTHORAX | 1 |
| DEPRESSION | 1 | REACT AGGRAV | 1 |
| EDEMA PERIPH | 1 | TACHYCARDIA | 1 |
| HEADACHE | 1 | TIGHTNESS THROAT | 1 |
| HEALING ABNORM | 1 | TORTICOLLIS | 1 |
| HEMORR VAGINAL | 1 | VASC DISORDER | 1 |

Four of the 48 events were judged by investigators and this reviewer to be possibly related to zolmitriptan exposure. These are highlighted in gray (only one of the two syncope events is included in the four). A brief summary of these events follow:

1. ***008-021-021115, Tachycardia (Cardiovascular).*** *35 year old female migraine patient with a history of Wolff-Parkinson-White Syndrome (WPW) experienced tachycardia (estimated at 200 bpm) 30 minutes after exposure to zolmitriptan 5 mg. She spontaneously converted to normal sinus rhythm, rate 110 bpm, approximately 90 minutes after onset. No sequelae were reported. The patient described the episode as a "typical" tachycardic episode.*
2. ***012-001-001112, Syncope (Cardiovascular).*** *A 72 year old female volunteer received one dose of zolmitriptan 15 mg, which was followed by complaints of intermittent light-headedness between 2 and 6 hours post dose,*

*normal. The next day, 26 hours post dose, while standing at a bus stop, she became dizzy, fell and hit her head. Witnesses report < 1 min. loss of consciousness without evidence of seizure activity. Emergency medical evaluation including vitals, ECG, laboratory, were normal.*

3. ***015-220-220505, Increased Migraine Headache Frequency, Reaction Aggravated (Body / General).*** *49 year old female migraine patient received oral zolmitriptan in the open label long term safety study. During her 5 months in the study, she had treated 17 migraine headaches with zolmitriptan. Four days after her last dose of study drug, the patient reported the frequency of her headaches increased from approximately 1 headache to 5 headaches per week for a period of 13 days. She was discontinued from the study.*
4. ***015-320-320020, Throat Constriction, Tightness Throat (Body / General).*** *46 year old female migraine patient was enrolled in the open label long term zolmitriptan study. Two weeks after enrollment, she took zolmitriptan 5 mg. The headache improved within 20 minutes but recurred after one hour. She took a second dose of 5 mg approximately one hour after the first dose (in violation of the protocol). One-half hour later, she experienced throat tightness and difficulty swallowing. She self treated with diphenhydramine 50 mg. She denied rash, pruritus, warmth, palpitations, shortness of breath, cough. The symptoms gradually resolved without sequelae after 4 hours. She was discontinued from the study. She had previously taken 10+10 mg in a previous study without any adverse events.*

## *8.4 Dropouts and "Other Significant Adverse Events"*

Most subjects in the Clinical Pharmacology and placebo controlled patient treatment studies took zolmitriptan for a short period of time, ranging from 1-4 exposures and thus had little opportunity to drop out and the withdrawal rates are very low. In contrast, withdrawal rates were much higher in the long-term safety study (015). There are theoretically five reasons why a volunteer or a patient may have withdrawn from a study. These are: 1) death, 2) adverse experience, 3) administrative (including withdrawal of consent), 4) inadequate response, and 5) protocol violators (including failure to return).

### *8.4.1 Drop-Outs in Clinical Pharmacology Studies*

In the clinical pharmacology studies, 22 of the 347 non-unique individuals were withdrawn. Of these subjects, 14 received zolmitriptan, 4 received placebo, and 4 received other drugs (in drug-drug interaction studies). Across treatment groups, the reasons for withdrawal were adverse experiences (n=13), administrative reasons (n=5), and protocol violations (n=4). AE's leading to withdrawal are discussed in section 8.4.4.

### *8.4.2 Drop-Outs in Controlled Clinical Trials*

In controlled patient treatment studies, 30 out of 2,633 zolmitriptan patients (1%), 1 out of 401 placebo patients (<1%), and 2 out of 504 sumatriptan patients (<1%) withdrew prematurely. The reasons for withdrawal are summarized in FDA Table 13. None of the patients were withdrawn because of death or adverse experiences.

***Table 13: Reasons for Premature Withdrawal from Controlled Treatment Studies***

| Reason | Zolmitriptan (n=2,633) | Placebo (n=401) | Sumatriptan (n=504) |
|---|---|---|---|
| Death | 0 | 0 | 0 |
| Adverse Experience | 0 | 0 | 0 |
| Administrative | 1 | 0 | 0 |
| Inadequate Response | 2 | 0 | 0 |
| Protocol Violation | 27 | 1 | 2 |
| **TOTAL** | **30** | **1** | **2** |

### *8.4.3 Drop-Outs in Uncontrolled Trials*

A total of 757 of the 2,096 patients (36%) treated with zolmitriptan were withdrawn prematurely. The majority were in the long term treatment study (015, n=755). The reasons for withdrawal are summarized in FDA Table 14. There were no withdrawals due to deaths.

***Table 14: Drop-outs from Uncontrolled Patient Treatment Studies***

| Reason | Zolmitriptan (n=2,096) | % |
|---|---|---|
| Death | 0 | 0 |
| Adverse Experience | 167 | 8 |
| Administrative | 225 | 10.7 |
| Inadequate Response | 226 | 10.7 |
| Protocol Violation | 139 | 6.6 |
| **TOTAL** | **757** | **36** |

### *8.4.4 Adverse Events Associated with Dropouts*

One hundred seventy nine (179) patients treated with zolmitriptan were withdrawn because of AE's. Most (n=167) were in study 015, the long-term open label treatment study. This is understandable since the short duration of other trials and the limited exposures to zolmitriptan in those studies do not provide much opportunity for early withdrawals. In study 015, the 167 AE withdrawals represent 8% (167/2058) of the patients treated with zolmitriptan in that study.

***Table 15: AE's leading to withdrawal in Study 015***

| AE | N | % of Total Treated | % of Total AE Withdrawals |
|---|---|---|---|
| Unspecified by Investigator | 17 | <1% | 10% |
| Dizziness | 14 | <1% | 8% |
| Nausea | 14 | <1% | 8% |
| Paresthesia | 14 | <1% | 8% |
| Asthenia | 13 | <1% | 8% |
| Pain - location specified[a] | 11 | <1% | 7% |
| Reaction aggravated[b] | 11 | <1% | 7% |
| Heaviness other than Chest or Neck | 10 | <1% | 6% |
| Somnolence | 10 | <1% | 6% |
| Warm Sensation | 9 | <1% | 5% |

[a]pain in any part of the body other than chest or neck
[b]generally refers to worsening of migraine headache

Most of the AE's leading to withdrawal from all studies were similar to the most frequently reported AE's during the clinical development program (Section 8.5). Two patients withdrew due to treatment emergent diastolic hypertension (105 mm, and 110 mm).

### *8.4.5 Other Significant Adverse Event: Syncope*

There have been a total of 4 reports of syncope in 4 patients following oral zolmitriptan in the clinical pharmacology studies. The syncope did not appear to be dose related (2 after 5 mg, 1 after 10 mg, and 1 after 15 mg). One occurred in an elderly volunteer (72 years) and was considered an SAE. Two of the patients withdrew from the study. The two other reports were not judged attributable to zolmitriptan and did not lead to withdrawal. There was an additional report of syncope following i.v. zolmitriptan. This episode was not serious and not attributable to zolmitriptan. It did not result in withdrawal.

There were no reports of syncope in the controlled clinical trials. In the open label, long-term study (015), there were eight reports of syncope. Six occurred after 5 mg and 2 occurred after 5+5 mg. The overall incidence of syncope was <1%. None of these events were judged attributable to the medication because they were not temporally related to zolmitriptan ingestion (all occurred at least 4 days from dosing). One event was reported as an SAE and occurred 9 days after dosing.

## *8.5 Adverse Events Incidence Tables*

### *8.5.1 Methods*

#### *8.5.1.1 Approach to Eliciting Adverse Events*

AE's were recorded by the investigator in the case report forms (CRF) using standard medical terminology, with notation of onset, duration, severity, seriousness, and attributability to study drug, and any action taken. In the clinical pharmacology studies and inpatient treatment studies, AE's were identified by subject reports and by investigator observation or query. In patient studies involving outpatients, AE's were identified from review of patient diaries and from direct investigator questions with regard to any new medical problems since the last visit. In studies involving migraine headache treatment, headache was not regarded as an AE unless they were unusual, or atypical and present after study drug administration.

#### *8.5.1.2 Adverse Events Categorization and Preferred Terms*

For the purposes of grouping similar AE's and standardizing AE analyses, all AE's recorded in the case report forms (CRF "raw term") were converted to "preferred terms" and assigned to "body systems" using a project-specific, modified COSTART Dictionary (Coding Symbols Thesaurus of Adverse Reaction Terms, 4th Edition).

#### *8.5.1.3 Generation of Adverse Events Incidence Tables*

The sponsor generated summaries of adverse events in the clinical pharmacology studies are presented in section 8.5.2, page 42.

The summaries of adverse events in controlled clinical trials (006, 008, 017, 018, 042) were calculated by this reviewer directly from the SAS datasets provided in the NDA. All analyses were done using JMP Version 3.1.6.2 and are presented in section 8.5.3, page 43. The method used for these calculations are briefly outlined.

The "demographics" datasets contain information regarding total number of exposures to the various study medications used. These data provide the denominator for adverse events incidence calculations. FDA Table 16 summarizes the patient exposure data.

***Table 16: Patient Exposures by Study***

| Study | N enrolled | N exposed | PBO | N exposed to zolmitriptan | 1 mg | 2.5 mg | 5 mg | 10 mg | 15 mg | 20 mg | 25 mg | sums 100 mg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 006 | 84 | 84 | 20 | 79 | 22 | 0 | 21 | 15 | 14 | 10 | 21 | 0 |
| 008 | 1181 | 951 | 99 | 852 | 0 | 0 | 213 | 214 | 215 | 210 | 0 | 0 |
| 017 | 1258 | 1141 | 140 | 1001 | 140 | 297 | 279 | 285 | 0 | 0 | 0 | 0 |
| 018 | 1311 | 1056 | 55 | 498 | 0 | 0 | 498 | 0 | 0 | 0 | 0 | 503 |
| 042 | 327 | 301 | 101 | 200 | 0 | 200 | 0 | 0 | 0 | 0 | 0 | 0 |
| **SUM** | **4161** | **3533** | **415** | **2630** | **162** | **497** | **1011** | **514** | **229** | **220** | **21** | **503** |

The actual adverse events are contained in the "AE" datasets for each study. These were

information regarding one AE report. One patient may have multiple entries, one for each reported event. Furthermore, each event may be listed multiple times per patient if the patient experienced the same event on subsequent exposures. A patients who experienced no AE's were also included as a single empty entry.

The first step was to delete those patients from the dataset who reported no adverse events. The second step was to delete duplicate entries of the same AE for each patient, so that the patient is not counted twice for that adverse event. After sorting the table by unique patient ID (UPID) and by adverse event (AE), the boolean formula:

$$UPID = UPID_{i-1} \; AND \; AE=AE_{i-1}$$

results in a "1" each time an adverse event occurs more than once for that particular patient, and a "0" for each unique AE entry, or each 1st AE entry. Deleting the rows with a "1" resulted in a table in which each AE reported by each patient is present only once.

This new table was summarized along the variable "AE" and summary columns were added for each dose. Incidence columns were constructed by dividing the number of patients experiencing an AE at a particular dose by the total number of patients exposed to that dose, as summarized in Table 16. The table was sorted according to incidence of AE's in the zolmitriptan 2.5 mg group, in descending order.

*8.5.2 Adverse Events in Clinical Pharmacology Studies*

Sponsor Table 17 (ISS, Vol. 211, p 47) summarizes the overall incidence of AE's regarded as at least possibly related to medication in the clinical pharmacology studies. In general, the overall incidence AE's were higher for subjects receiving oral doses of 2.5 mg zolmitriptan than for those receiving orally administered placebo. The overall incidences of subject exposures with AE's were comparable for doses of 2.5 mg and 5 mg zolmitriptan, and these doses had incidence greater than for < 2.5 mg zolmitriptan. Exposures with AE's rated as severe in intensity were absent for doses of < 5 mg zolmitriptan and uncommon at higher doses.

***Table 17: Overall Incidence of AE's in Clinical Pharmacology Studies Combined***

| | Oral | Zolmitriptan - Oral Administration (mg) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PBO | <2.5 | 2.5 | >2.5-<5 | 5 | >5-10 | >10-20 | >20-50 |
| | n=136 | n=22 | n=100 | n=5 | n=183 | n=419 | n=116 | n=24 |
| # (%) Subjects with ≥1 AE | 38 (28%) | 5 (23%) | 52 (52%) | 2 (40%) | 101 (55%) | 252 (60%) | 74 (64%) | 23 (96%) |
| # (%) Subjects with SAE's | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (<1%) | 0 (0%) |
| # (%) Subjects with AE's rated severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (<1%) | 3 (<1%) | 2 (<1%) | 0 (0%) |

Sponsor Table 18 (ISS, Vol. 211, p. 49) lists the most common AE's encountered in the clinical pharmacology studies. The most common reported AE's were asthenia, headache, neck pain, neck tightness, nausea, dizziness, somnolence, and paresthesia. "Most common" in this setting is defined as an AE occurring with an incidence of >5% for at least 3 of the 7 doses, which was regarded at least possibly related to drug.

*Table 18: Most Common AE's After Oral Doses in Clinical Pharmacology Studies*

| # (%) Subject Exposures with: | Oral PBO n=136 | Zolmitriptan - Oral Administration (mg) <2.5 n=22 | 2.5 n=100 | >2.5-<5 n=5 | 5 n=183 | >5-10 n=419 | >10-20 n=116 | >20-50 n=24 |
|---|---|---|---|---|---|---|---|---|
| asthenia | 3 (2%) | 0 0% | 5 (5%) | 1 (20%) | 10 (5%) | 28 (7%) | 10 (9%) | 4 (17%) |
| headache | 19 (14%) | 1 (5%) | 24 (24%) | 0 (0%) | 46 (25%) | 100 (24%) | 20 (17%) | 4 (17%) |
| neck pain | 1 (<1%) | 0 (0%) | 2 (2%) | 0 (0%) | 12 (7%) | 16 (4%) | 12 (10%) | 2 (8%) |
| neck tightness | 1 (<1%) | 0 (0%) | 2 (2%) | 1 (20%) | 9 (5%) | 22 (5%) | 6 (5%) | 3 (13%) |
| nausea | 5 (4%) | 0 (0%) | 2 (2%) | 0 (0%) | 16 (9%) | 34 (8%) | 17 (15%) | 3 (13%) |
| dizziness | 1 (<1%) | 0 (0%) | 7 (7%) | 1 (20%) | 13 (7%) | 28 (7%) | 14 (12%) | 0 (0%) |
| somnolence | 5 (4%) | 1 (5%) | 4 (4%) | 0 (0%) | 22 (12%) | 34 (8%) | 22 (19%) | 9 (38%) |
| paresthesia | 2 (1%) | 1 (5%) | 2 (2%) | 1 (20%) | 7 (4%) | 26 (6%) | 5 (4%) | 2 (8%) |

## *8.5.3 Adverse Events in Placebo Controlled Studies*

A total of 3533 patients participated in the 5 controlled clinical treatment trials contained in this NDA (FDA Table 16: Patient Exposures by Study, page 41). Sponsor Table 19 (ISS, Vol. 211, p. 50) contains the incidence of adverse events in the placebo-controlled treatment studies. Figure 3 (ISS, Vol. 211, p. 50) graphically summarizes the same data. The bar graph shows that all doses of zolmitriptan were associated with higher incidences of AE's, and the incidence increases with increasing doses. The same trend is seen in the individual studies (sponsor Figure 4, ISS Vol. 211, p. 50).

*Table 19: Incidence of AE's in Placebo-Controlled Treatment Studies (006, 008, 017, 018, 042)*

| | PBO n=136 | Zolmitriptan (mg) 1 n=163 | 2.5 n=496 | 5 n=1012 | 10 n=514 | 15 n=215 | 20 n=210 | 25 n=21 | Suma 100 mg n=504 |
|---|---|---|---|---|---|---|---|---|---|
| # (%) Patients with ≥1 AE | 117 (29%) | 68 (42%) | 227 (46%) | 587 (58%) | 359 (70%) | 170 (79%) | 158 (75%) | 17 (81%) | 279 (55%) |
| # (%) Patients with Serious AE's | 1 (<1%) | 0 (0%) | 0 (0%) | 2 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (<1%) |
| # (%) Patients with severe AE's | 20 (5%) | 6 (4%) | 22 (4%) | 71 (7%) | 55 (11%) | 37 (17%) | 39 (19%) | 0 (0%) | 28 (6%) |

*Figure 3: Overall Incidence of Patients with ≥ 1 AE, by Initial Dose, in Placebo-Controlled Treatment Studies - all studies combined*

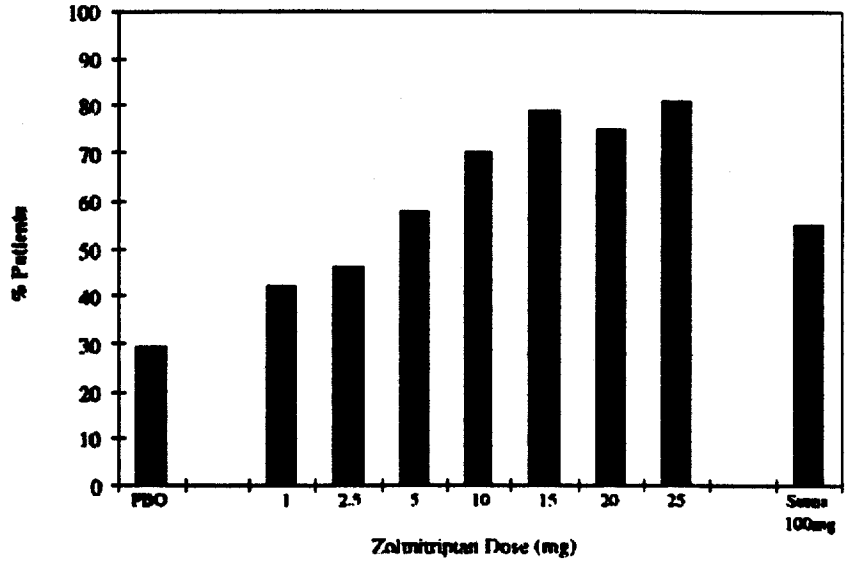
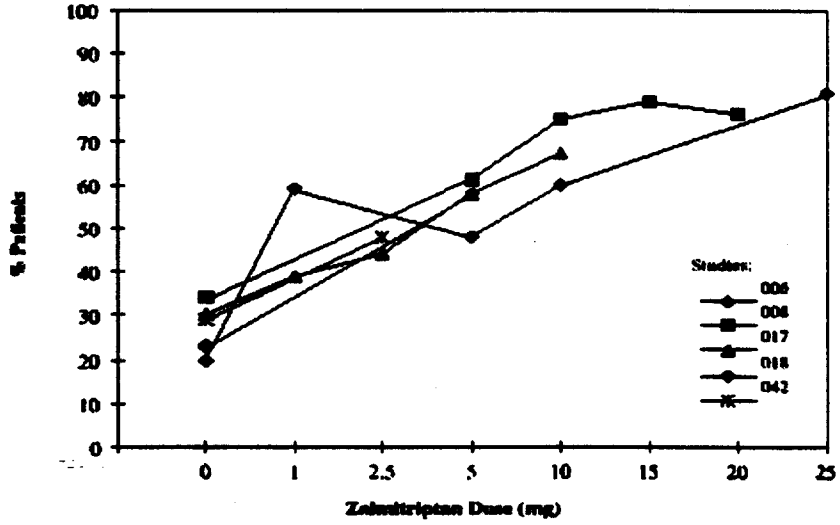



*Figure 4: Incidence of Patients with AE's in Controlled Treatment Studies*




### *8.5.3.1 Incidence of Particular AE's*

Among the patients receiving zolmitriptan in placebo-controlled treatment studies, a total of 25 AE's occurred with an incidence of ≥ 5% in at least one of the seven zolmitriptan dose groups. Of these 25 AE's, the 10 most common, as defined as occurring with the highest incidences in the zolmitriptan 2.5 mg group, are listed in order of decreasing incidence in FDA Table 20.

Most AE's, including the most common AE's, were of mild or moderate intensity. The incidence of severe AE's were ≤ 1% for placebo and also ≤ 1% for zolmitriptan doses of 5 mg or less. For higher doses of zolmitriptan, the incidences of patients with severe AE's ranged up to 3%

*Table 20: The Most Common AE's in Controlled Treatment Studies*

| Adverse Event | Zolmitriptan 2.5 mg N = 497 (%) | Placebo N = 415 (%) |
|---|---|---|
| nausea | 45 (9.0) | 15 (3.6) |
| dizziness | 42 (8.5) | 15 (3.6) |
| somnolence | 30 (6,0) | 12 (2.9) |
| paresthesia | 29 (5.8) | 5 (1.2) |
| warm sensation | 21 (4.2) | 6 (1.5) |
| asthenia | 16 (3.2) | 13 (3.1) |
| dry mouth | 16 (3.2) | 7 (1.7) |
| tightness throat | 13 (2.6) | 3 (0.7) |
| tightness chest | 13 (2.6) | 2 (0.5) |
| heaviness, other than chest or neck | 10 (2.0) | 2 (0.5) |

*8.5.3.2 Selecting Key Adverse Events Tables - 1% Table*

For labeling purposes, data from the patient controlled treatment studies (006, 008, 017, 018, 042) were pooled and the incidence of adverse events were calculated for zolmitriptan doses 2.5 and 5 mg. FDA Table 21 summarizes the adverse events reported in clinical trials.

*Table 21: Adverse Events in Clinical Studies (006, 008, 017, 018, 042) having Incidence > 1% for zolmitriptan 2.5 mg tablet.*

| ADVERSE EVENT (N) | TOTAL 3533 | PBO 415 | % | 1 MG 162 | % | 2.5 MG 497 | % | 5 MG 1011 | % | 10 MG 514 | % | 15 MG 229 | % | 20 MG 220 | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [illegible]EA | 258 | 15 | 3.61 | 6 | 3.7 | 45 | 9.05 | 63 | 6.23 | 41 | 7.98 | 32 | 13.97 | 20 | 9.09 |
| [illegible]ESS | 325 | 15 | 3.61 | 9 | 5.56 | 42 | 8.45 | 96 | 9.5 | 67 | 13.04 | 28 | 12.23 | 34 | 15.45 |
| S[illegible]OLENCE | 266 | 12 | 2.89 | 8 | 4.94 | 30 | 6.04 | 78 | 7.72 | 55 | 10.7 | 20 | 8.73 | 28 | 12.73 |
| PARESTHESIA | 271 | 5 | 1.2 | 8 | 4.94 | 29 | 5.84 | 77 | 7.62 | 56 | 10.89 | 22 | 9.61 | 38 | 17.27 |
| SENSATION WARM | 180 | 6 | 1.45 | 5 | 3.09 | 21 | 4.23 | 52 | 5.14 | 36 | 7 | 19 | 8.3 | 12 | 5.45 |
| ASTHENIA | 328 | 13 | 3.13 | 8 | 4.94 | 16 | 3.22 | 89 | 8.8 | 64 | 12.45 | 36 | 15.72 | 45 | 20.45 |
| DRY MOUTH | 135 | 7 | 1.69 | 8 | 4.94 | 16 | 3.22 | 32 | 3.17 | 25 | 4.86 | 20 | 8.73 | 12 | 5.45 |
| TIGHTNESS THROAT | 95 | 3 | 0.72 | 1 | 0.62 | 13 | 2.62 | 28 | 2.77 | 22 | 4.28 | 9 | 3.93 | 10 | 4.55 |
| TIGHTNESS CHEST | 68 | 2 | 0.48 | 1 | 0.62 | 13 | 2.62 | 15 | 1.48 | 21 | 4.09 | 9 | 3.93 | 1 | 0.45 |
| HEAVINESS OTHER | 193 | 2 | 0.48 | 2 | 1.23 | 10 | 2.01 | 51 | 5.04 | 30 | 5.84 | 36 | 15.72 | 33 | 15 |
| TIGHTNESS NECK | 58 | 1 | 0.24 | 1 | 0.62 | 10 | 2.01 | 18 | 1.78 | 11 | 2.14 | 5 | 2.18 | 5 | 2.27 |
| PAIN LOC SPEC | 92 | 2 | 0.48 | 3 | 1.85 | 9 | 1.81 | 29 | 2.87 | 18 | 3.5 | 12 | 5.24 | 9 | 4.09 |
| SWEAT | 67 | 5 | 1.2 | 0 | 0 | 9 | 1.81 | 25 | 2.47 | 7 | 1.36 | 5 | 2.18 | 4 | 1.82 |
| PRESSURE OTHER | 64 | 1 | 0.24 | 3 | 1.85 | 9 | 1.81 | 15 | 1.48 | 3 | 0.58 | 13 | 5.68 | 5 | 2.27 |
| PAIN NECK | 92 | 4 | 0.96 | 0 | 0 | 8 | 1.61 | 27 | 2.67 | 11 | 2.14 | 8 | 3.49 | 7 | 3.18 |
| DYSPEPSIA | 42 | 2 | 0.48 | 5 | 3.09 | 8 | 1.61 | 10 | 0.99 | 7 | 1.36 | 0 | 0 | 3 | 1.36 |
| NERVOUSNESS | 23 | 1 | 0.24 | 0 | 0 | 7 | 1.41 | 7 | 0.69 | 3 | 0.58 | 1 | 0.44 | 3 | 1.36 |
| THINKING ABNORM | 28 | 2 | 0.48 | 0 | 0 | 6 | 1.21 | 3 | 0.3 | 8 | 1.56 | 3 | 1.31 | 3 | 1.36 |
| MYALGIA | 56 | 1 | 0.24 | 1 | 0.62 | 5 | 1.01 | 17 | 1.68 | 11 | 2.14 | 9 | 3.93 | 8 | 3.64 |
| SENSATION UNUS SPEC | 54 | 1 | 0.24 | 2 | 1.23 | 5 | 1.01 | 14 | 1.38 | 10 | 1.95 | 9 | 3.93 | 6 | 2.73 |
| TIGHTNESS OTHER | 47 | 1 | 0.24 | 4 | 2.47 | 5 | 1.01 | 14 | 1.38 | 9 | 1.75 | 6 | 2.62 | 3 | 1.36 |
| RHINITIS | 32 | 1 | 0.24 | 2 | 1.23 | 5 | 1.01 | 9 | 0.89 | 5 | 0.97 | 2 | 0.87 | 4 | 1.82 |
| TREMOR | 32 | 3 | 0.72 | 1 | 0.62 | 5 | 1.01 | 7 | 0.69 | 5 | 0.97 | 2 | 0.87 | 2 | 0.91 |
| DIARRHEA | 24 | 2 | 0.48 | 1 | 0.62 | 5 | 1.01 | 6 | 0.59 | 4 | 0.78 | 1 | 0.44 | 1 | 0.45 |

In this table, only AE's with incidences greater than 1% for the zolmitriptan 2.5 tablet are listed, and for which the incidence was greater than placebo. The AE's for zolmitriptan 25 mg are not included since the number of exposures to this dose were relatively small (N = 21) The complete list of AE's is found in FDA Table 32, page 79. Most of the adverse event terms are self-explanatory. The term "heaviness other" generally included heaviness in arms, legs, or both. "Pain loc spec" is a heterogeneous category which included reports of pain distributed

to pressure in the head, arms, or abdomen. "Thinking abnorm" generally included concentration difficulties or decreased mental abilities. "Sensation unus spec" is another heterogeneous category which included strange or unusual sensations throughout the body, including the reports affecting the face, arms, back, abdomen, and/or legs.

Sponsor Table 22 summarizes uncommon AE's after 2.5 mg or 5 mg administration. Uncommon is defined as incidence of <1%, which include infrequent (0.1≤AE<1 %) and rare (<0.1%) events.

***Table 22: Uncommon AE's after Zolmitriptan 2.5 mg or 5 mg in Placebo-Controlled Migraine Treatment Studies (Studies 006, 008, 017, 018, 042)***

| | | | |
|---|---|---|---|
| **Body / Back** | **Cardiovascular** | **Nervous / CNS** | **Skin** |
| pain back | arrhythmia | agitation | erythema |
| | hypertension | anxiety | pruritus |
| **Body / General** | hypotension | ataxia | rash |
| chills | QT prolonged | CNS stimulation | rash vesc. bullous |
| fever | tachycardia | confusion | |
| flu syndrome | thrombophlebitis | abnormal coordination | **Special Senses** |
| hypothermia | vasodilation | depersonalization | abn. accommodation |
| infection | | depression | amblyopia |
| accidental injury | **Digestive** | abnormal dreams | diplopia |
| malaise | increased appetite | dystonia | dry eye |
| neoplasm | bloody diarrhea | hyperkinesia | eye disorder |
| pain | flatulence | hypotonia | hyperacusis |
| jaw pain | hematemesis | insomnia | lacrimation disorder |
| throat pain | gum hemorrhage | sleep disorder | ear pain |
| photosensitivity | increased saliva | speech disorder | eye pain |
| throat pressure | thirst | stupor | parosmia |
| reaction unevaluated | | | photophobia |
| jaw tightness | **Hemic / RBC** | **Nervous / PNS** | taste perversion |
| unexpected benefit | cyanosis | paresthesia circumoral | tinnitus |
| facial edema | | unusual sensation unspec. | Abnormal vision |
| headache | **Metabolic / Nutritional** | | visual field defect |
| | edema | **Respiratory** | |
| **Body / Neck** | peripheral edema | bronchitis | **Urogenital / Female** |
| neck heaviness | SGPT increase | bronchospasm | dysmenorrhea |
| neck pressure | | cough increase | uterine hemorrhage |
| | **Musculoskeletal** | epistaxis | vaginal hemorrhage |
| **Body / Thorax** | leg cramps | hyperventilation | menorrhagia |
| chest heaviness | joint disorder | pharyngitis | |
| chest pain | tetany | pneumonia | **Urogenital / Urinary** |
| chest pressure | twitch | sinusitis | hematuria |
| | | voice alteration | urinary tract infection |
| | | yawn | polyuria |
| | | | urine frequency |
| | | | urinary tract disorder |
| | | | urinary urgency |

Nausea is the most common reported AE in the 2.5 mg group. Although nausea is a common symptom of migraine, it was reported more frequently as an adverse event following 2.5 mg administration compared to placebo (9% vs. 3.6%). Although a clear dose/response relationship does not exist across higher doses, all exposures of zolmitriptan greater than 1 mg resulted in an incidence of nausea higher than in the placebo group.

Asthenia, although reported commonly at high doses, appears at an incidence at 2.5 mg comparable to placebo (3.2% vs. 3.1%, respectively). The other AE's listed in Table 21 generally occur at incidences after 2.5 mg exposures of at least twice that of placebo, although numbers are small for many categories.

*8.5.3.3 Additional Analyses and Explorations*

8.5.3.3.1 INCIDENCE OF AE'S IN STUDIES 017 AND 042

Studies 017 and 042 are the only two clinical trials which used the recommended 2.5 mg dose. Therefore, it is useful to pool just these two studies to look at adverse events incidences for the 2.5 mg dose. FDA Table 23 summarizes the AE's occurring with greater than 2% incidence in the zolmitriptan 2.5 mg group. All incidences are greater than placebo. There are 11 AE categories, and these are identical to the top 11 categories in the AE summary table for all clinical studies combined. It is worth noting that asthenia in this analysis does appear at a rate higher than placebo (3.4% vs. 2%).

***Table 23: Adverse Incidences, Studies 017 and 042, Zolmitriptan 2.5 vs. Placebo***

| ADVERSE EVENT | N | PBO N = 241 | % | 2.5 MG N = 497 | % |
|---|---|---|---|---|---|
| DIZZINESS | 156 | 9 | 3.73 | 51 | 10.26 |
| NAUSEA | 109 | 13 | 5.39 | 45 | 9.05 |
| SOMNOLENCE | 100 | 8 | 3.32 | 33 | 6.64 |
| PARESTHESIA | 107 | 5 | 2.07 | 31 | 6.24 |
| SENSATION WARM | 66 | 3 | 1.24 | 22 | 4.43 |
| ASTHENIA | 80 | 5 | 2.07 | 17 | 3.42 |
| DRY MOUTH | 42 | 6 | 2.49 | 17 | 3.42 |
| TIGHTNESS THROAT | 45 | 2 | 0.83 | 14 | 2.82 |
| TIGHTNESS CHEST | 46 | 2 | 0.83 | 13 | 2.62 |
| HEAVINESS OTHER | 33 | 1 | 0.41 | 11 | 2.21 |
| TIGHTNESS NECK | 32 | 1 | 0.41 | 10 | 2.01 |

8.5.3.3.2 INCIDENCE OF AE'S FOLLOWING ONE OR TWO DOSES OF ZOLMITRIPTAN

Patients in study 017 received an initial dose of 1, 2.5, 5, or 10 mg, or placebo, and were allowed to take an optional second dose if the headache persisted. The second dose was randomized to either placebo, or a repeat of the initial dose.

For each dose or dose combination of zolmitriptan evaluated, the overall incidence of AE's in patients who received one or two doses of zolmitriptan (35-74%) was greater than the incidence in patients who received one or two doses of placebo (27-30%). However, none of the zolmitriptan doses evaluated showed a clinically importantly higher overall incidence of patients with AE's in those who receive two doses of zolmitriptan than in those who received a single dose or a single dose followed by placebo. For example, the incidence of side effects in the 2.5 mg groups was 43%, in the 2.5+0 group, 49%, and in the 2.5+2.5 mg group, 44%. No serious AE's were reported in study 017.

Furthermore, the types of AE's were similar in incidence and nature for patients who received two doses of zolmitriptan compared with those who received one dose with or without placebo. There was no indication that a second dose of zolmitriptan consistently resulted in an increased incidence of the most commonly reported AE's.

8.5.3.3.3 SUBGROUP ANALYSIS: GENDER

Females predominated in the zolmitriptan development program. A total of 435 females and 63 males were exposed to zolmitriptan 2.5 mg. The overall incidence of AE's was higher in females than males for doses of 2.5 and 5 mg (48% vs. 30% for the 2.5 mg group, and 59% vs. 51% for the 5 mg group, respectively). The incidence of severe AE's was low in all dose groups and not different between females and males (5% vs. 3% in the 2.5 mg group). None of the eight most common AE's appeared to occur more frequently in either sex.

8.5.3.3.4 SUBGROUP ANALYSIS: AGE

For the age categories with substantial numbers of patients, (*i.e.*, 18-40 and >40-60 yrs), the overall incidence of patients with AE's was approximately the same for young adults and older adults in each treatment group. The overall incidence of severe AE's was not consistently related to age for groups receiving ≤ 5 mg. For the higher doses of 10-20 mg, severe AE's were slightly more frequent in young adults than older adults.

There was no clinically important relationship between age and incidence of the most common AE's for either 2.5 mg 5 mg. The age groups <18 yrs and >60 yrs were very small (17 and 35, respectively) and too small to merit specific discussion of their data.

8.5.3.3.5 SUBGROUP ANALYSIS: BODY WEIGHT

There was no indication of a consistent relationship between body weight and overall incidence of AE's or SAE's , with the exception of the 20 mg zolmitriptan group. At this dose, there was a 2 fold increase in AE's and SAE's in the 50-80 kg compared with the >80 kg group.

For the most common AE's, there was no consistent relationship between incidence and body weight for any dose of zolmitriptan, with the possible exception of increased incidence of asthenia, heaviness other than chest or neck in the 50-80 kg patients exposed to zolmitriptan 10-20 mg.

8.5.3.3.6 SUBGROUP ANALYSIS: RACE

Since 97% of the patients enrolled in the placebo-controlled treatment studies were white, the numbers are too small to draw any meaningful conclusions about racial differences in AE incidences.

8.5.3.3.7 SUBGROUP ANALYSIS: AURA, MENSES, CONCOMITANT MEDICATIONS

The overall incidences of AE's were slightly higher in patients whose headaches were not preceded by aura than in those in whom an aura was present, but the magnitude for these differences was small (*e.g.*, 46% vs. 41% in the 2.5 mg group).

Women experiencing a menstrual migraine were more likely to experience an AE after zolmitriptan (all doses) compared with those who did not experience a menstrual migraine (42% vs. 23%), however, incidences of AE's were similar in the 2.5 and 5 mg treatment groups (*e.g.*, 53% vs. 50%).

A substantial number of patients also received concomitant medications (approximately 10% or greater). The most frequently used medications were analgesics (44-69%). The least frequently used medications were the SSRI's (3-13%). There was no evidence, for either the placebo, 2.5 mg, or 5 mg zolmitriptan groups that the overall incidence of AE's was affected in any systematic manner by the concurrent use of analgesics, antidepressants, SSRI's, other antimigraine drugs, or oral contraceptives.

It is apparent that there is a dose-response relationship between increasing doses of zolmitriptan and the incidence of AE's (although incidence is roughly the same for 1 mg and 2.5 mg, but less than the incidence for 5 mg) Three studies (001, 006, and 007) examined the relationship between AE's and plasma concentrations of zolmitriptan and its metabolites. Overall, there was a tendency towards higher zolmitriptan plasma concentrations with somnolence or asthenia, but there was no direct relationship. There was no relationship between the other frequently reported AE's and either zolmitriptan, or its active metabolite, n-desmethyl zolmitriptan plasma concentrations.

### *8.6 Laboratory Findings*

The sponsor developed a "Normal and Expanded Reference Ranges" for clinical hematology and chemistry laboratory values. This table was discussed with and approved by the Division during the Pre-NDA meeting (Appendix B: Normal and Expanded Laboratory Ranges, page 84). Baseline and post-dosing lab values were classified as either low, normal, or high, based on these ranges. If the post-treatment lab value was outside the expanded normal range, and it differed from the baseline value, then this abnormality was considered treatment emergent. In the case of urine dipstick data, if the result was ≥ 2 units from baseline, then it was considered treatment emergent.

#### *8.6.1 Extent of Laboratory Testing During Development*

Laboratory determinations were made at a variety of time points in the different studies. In the clinical pharmacology studies, lab testing was done at screening, baseline, and, in some studies, at post-treatment. In the clinical trials, lab testing was done at screening, post-treatment, and and/or at follow-up. Clinical labs from unscheduled visits were not included in the safety database. By protocol design, 7 of the 31 studies in the integrated safety database did not collect post-treatment clinical laboratory data. One study (028) of the 31 studies did collect post-treatment labs, but an electronic database was not available. Therefore, lab results from eight studies are not included in this submission.

#### *8.6.2 Selection of Studies for Overall Drug-Control Comparisons*

##### *8.6.2.1 Clinical Pharmacology Studies*

A total of 22 clinical pharmacology studies were done. Sixteen (16) of these studies contain screen/baseline and post-treatment labs. Eight of the 16 were double-blind and 14 involved a cross-over design. Zolmitriptan in the range 0.5 mg to 50 mg was used. Oral, sublingual, intranasal, and intravenous routes were used.

##### *8.6.2.2 Placebo-Controlled Studies*

Six placebo controlled trials (006, 008, 017, 018, 026, 042) have laboratory safety data. Study 026 was the headache prevention study in patients experiencing an aura. All other trials were headache treatment studies. A total of 3068 patients participated in these studies (2679 exposures to zolmitriptan, 405 to placebo). The safety data were pooled from these studies to obtain the integrated laboratory database for the placebo-controlled trials.

#### *8.6.3 Standard Analyses and Explorations of Laboratory Data*

##### *8.6.3.1 Clinical Pharmacology Studies*

Across oral doses of zolmitriptan, the percentages of exposures that were associated with at least one-treatment emergent change in hematology values ranged from 0% to 3%, versus 1% for placebo. The treatment emergent changes following oral zolmitriptan involved three values

eosinophils only. Overall 1.8% (10/543 exposures) of zolmitriptan oral exposures were associated with treatment emergent changes, vs. 1% for placebo.

Treatment emergent changes in chemistry ranged from 0-8% in the zolmitriptan group, vs. 3% for placebo. These changes were in sodium, alkaline phosphatase, ALT, and glucose. For oral doses, the percent exposures associated with a change were comparable, 12/554 (2%) for oral zolmitriptan and 2/78 (3%) for placebo.

*8.6.3.2 Placebo-Controlled Studies*

The percentage of patients exposed to zolmitriptan who developed a treatment emergent hematology abnormality was 1% (26/2558) vs. <1% for placebo (2/387). The abnormalities were evenly distributed "above" and "below" the expanded reference values and were distributed among almost all hematological parameters (hemoglobin, platelet count, WBC, etc., except basophils).

The overall percentage of patient exposures that were associated with a treatment-emergent change in chemistry was comparable between zolmitriptan (43/2581, <2%) vs. placebo (3/392, <1%). The abnormalities seen were scattered among 9 of the 10 chemistry parameters measured. The only exception was creatinine.

The overall percentage of patients with at least one dipstick urinalysis value that was 2 or more units over baseline were comparable between zolmitriptan (163/2617, 6%) and placebo (21/394, 5%). Most of these were in urinary blood values.

*8.6.3.3 Long-Term Study (015)*

A total of 2058 patients treated multiple migraine attacks for up to one year. Labs were collected at screening and every three months. The analysis was limited to visits 2-7, when sample size was high enough (n>50) to make analyses meaningful.

Fewer than 1% of the patients had abnormalities in any one hematological parameter. The abnormalities were distributed among 8 of the 9 parameters tested (expect monocytes). The number of abnormalities decreased across visits, with no abnormalities reported after visit 7.

Fewer than 1% of patients had treatment emergent abnormalities in chemistry values. The abnormalities were distributed among all chemistry parameters tested except creatinine and alkaline phosphatase. No abnormalities were reported after visit 8.

Less than 1% had changes in urinary protein values, in contrast, 5-7% had post-treatment changes in urinary blood. This may be due to urine sample collection during menses (9-11% of samples were collected during this period).

*8.6.3.4 Summary of Laboratory Data*

Based on the available laboratory data, the following conclusions are possible:

- Zolmitriptan does not appear to have any clinically significant effects on standard measures of clinical chemistry, hematology, or urinalysis. The incidence of treatment-emergent abnormalities was low and comparable to placebo.
- The treatment-emergent changes in urinary blood values are likely due to the predominantly female population and collection of urine specimens during menses.
- Most of the abnormalities seen occurred sporadically and no dose-related effects were

### *8.7 Vital Signs*

Based on experience with sumatriptan, and with pre-clinical zolmitriptan studies, some effect on the cardiovascular system is a likely class effect of $5HT_{1D}$ agonists. As a result, blood pressure and heart rate were monitored in all volunteers for a period of 10-24 hours, depending on the individual study design. The most accurate assessment come from placebo-controlled, double-blind studies. Threshold BP and HR values were established prospectively (Table 24) and values which exceeded threshold formed the basis for analysis.

***Table 24: Threshold BP and HR Changes Compared to Baseline, by Age***

| Age | Systolic BP | Diastolic BP | HR |
|---|---|---|---|
| ≥ 18 yrs | ≤90 or ≥180 mm<br>& ≥ Δ20 mm | ≤50 or ≥105 mm<br>& ≥ Δ15 mm | ≤50 or ≥120 bpm<br>& ≥Δ15 bpm |
| 16-17 yrs | ≤90 or ≥149 mm<br>& ≥ Δ20 mm | ≤50 or ≥97 mm<br>& ≥ Δ15 mm | ≤50 or ≥120 bpm<br>& ≥Δ15 bpm |
| 13-15 yrs | ≤90 or ≥143 mm<br>& ≥ Δ20 mm | ≤50 or ≥91 mm<br>& ≥ Δ15 mm | ≤50 or ≥120 bpm<br>& ≥Δ15 bpm |
| 12 yrs | ≤90 or ≥133 mm<br>& ≥ Δ20 mm | ≤50 or ≥89 mm<br>& ≥ Δ15 mm | ≤50 or ≥120 bpm<br>& ≥Δ15 bpm |

#### *8.7.1 Clinical Pharmacology Studies*

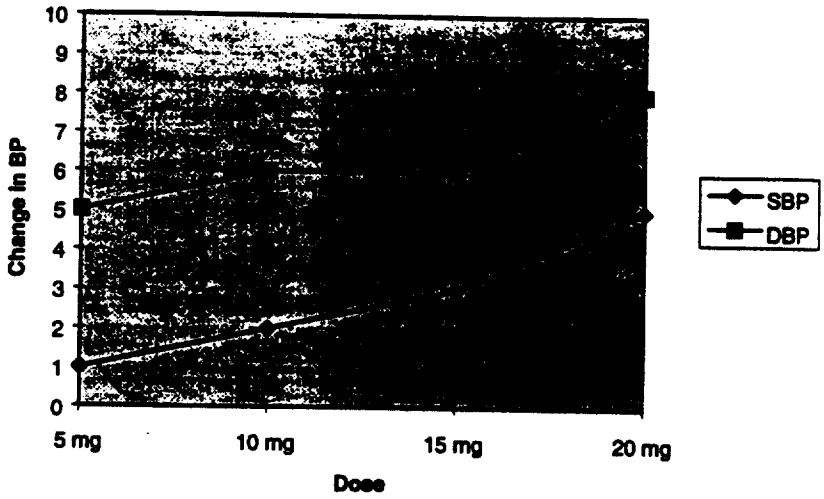
In study 001, doses as high as 50 mg were administered. BP increases were observed, particularly at the higher doses. The mean maximum systolic and diastolic BP changes from baseline were 9 and 12 mm Hg, respectively, after zolmitriptan 25 mg, and 15 and 15 mm Hg respectively, after zolmitriptan 50 mg. The maximum change was 30 mm Hg systolic and 35 mm Hg diastolic after zolmitriptan 50 mg, compared with 25 mm Hg systolic and 15 mm Hg diastolic increased for placebo. Based on these results, the effects of zolmitriptan on BP were assessed in four placebo-controlled, double-blind trials: 010, 012, 013, 023. Doses of 5, 10, 15, and 20 mg were used. Zolmitriptan is associated with mean peak systolic and diastolic blood pressure increases. These are shown in FDA Table 25 and graphically in Figure 5.

***Table 25: Mean Peak Systolic and Diastolic BP Increases in Double-blind, Placebo Controlled Clinical Pharmacology Trials (010, 012, 013, 023)***

| Treatment | N | Mean systolic BP increase (95% CI) | Mean diastolic BP increase (95% CI) |
|---|---|---|---|
| 5 mg | 29 | 1 (-2, 4) | 5 (3,7) |
| 10 mg | 30 | 2 (-1, 5) | 6 (3,8) |
| 15 mg | 24 | 3 (-1, 7) | 6 (3,8) |
| 20 mg | 30 | 5 (2,7) | 8 (6,11) |

The increase in systolic BP was slightly greater in elderly patients, but there was no age-related difference in diastolic BP changes. Normotensive volunteers experienced slightly greater increases in diastolic BP compared to hypertensive volunteers (by 1-5 mm). These differences were minor and not clinically significant. Renal failure patients had higher baseline BP's compared to normal volunteers, and they experienced a higher rise in systolic blood pressures.

*Figure 5: Mean Systolic and Diastolic Blood Pressure Changes, Studies 010, 012, 013, 023*




BP changes were also studied in the combination drug trials with fluoxetine, pizotifen, moclobemide, selegiline, dihydroergotamine, and propranolol. The BP changes seen in these settings were similar to the BP effects seen with zolmitriptan alone.

Heart rate has been monitored in the clinical pharmacology studies, and no effects attributable to zolmitriptan have been detected.

*Figure 6: Mean HR, Placebo(○), 5 mg (●), 10 mg (□) or 15 mg (■) Zolmitriptan in Elderly*

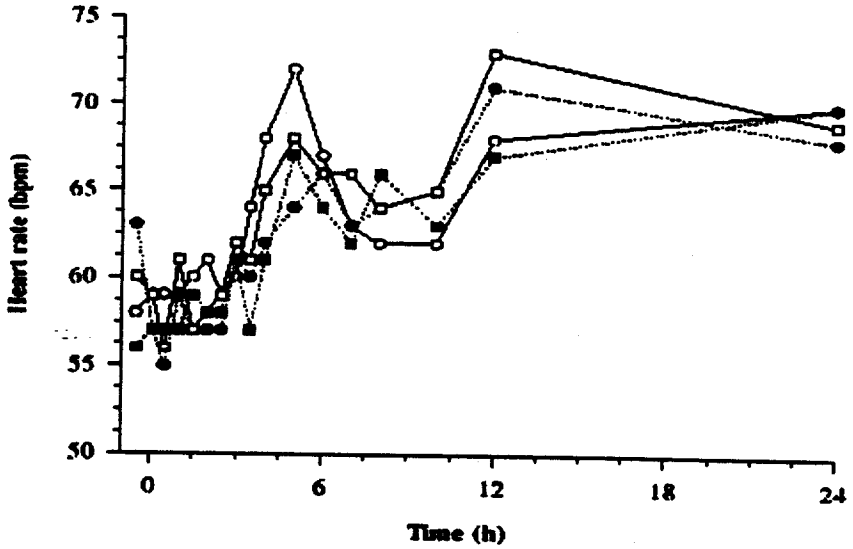



Figure 6 illustrates the relationship between HR and dose in elderly patients. No consistent pattern is present. A similar pattern exists for young patients. No relationship between heart rate and treatment dose was apparent in subgroups analyses according to age, pre-existing hypertension, renal failure, or in the drug interaction studies.

In the clinical pharmacology studies, there were few reported cases of treatment emergent BP

Four (4) were of syncope (5 mg x 2, 10 mg, 15 mg) and two of these resulted in withdrawal. The other two were unrelated to treatment (one occurred after venipuncture, the other 24 hours after treatment). There was one report of palpitations.

The two patients withdrew as a result of BP/HR associated adverse events. One was a 28 year old female who experienced hypotension and syncope 6 hours after a 5 mg dose. The second was a 72 year old female who had a syncopal episode 26 hours after receiving a single 15 mg dose (this case was previously described in section 8.4.5, Other Significant Adverse Event: Syncope, page 40).

*8.7.2 Patient Studies*

Of the 5 placebo-controlled treatment studies, only one (006) was an inpatient study and thus included baseline and period vital signs and ECG findings. The remaining 4 studies were outpatient studies in which patients administered drug outside of a clinic setting. For these studies, vitals signs were only recorded at screening since vital signs taken many hours to days after treatment would be of little clinical value. This was also the case for study 026, the outpatient migraine headache prevention study.

Patients in study 006 were randomized to placebo, zolmitriptan 1, 5, or 25 mg (n=20-25 per arm). There were no significant changes in mean systolic or diastolic BP at 0.5, 1, or 2 hours after dosing in any treatment group. Only one of 79 patients treated with zolmitriptan had a change in diastolic blood pressure which exceeded threshold. This was a change from a baseline DBP of 90 mm to a zolmitriptan 25 mg post-treatment DBP of 110 mm Hg at 0.5, 1, and 4 hour assessments.

Baseline and post-treatment BP and HR recordings were also recorded in two uncontrolled patient trials, 007 and 015. In study 007, 20 patients received zolmitriptan 10 mg for the treatment of a single migraine attack. Eighteen of the 20 received a second dose during a migraine-free period. BP and HR were measured at 15, 30, 45, 60, 90, 120, 180, and 240 min post dose. No HR measurements exceeded threshold. Five of 38 patient exposures exceeded BP threshold. Three had decreases in SBP (80, 90, and 90 mm), one had an increase in SBP (190 mm), and one had an increase in DBP (105 mm). None resulted in withdrawal and none resulted in an adverse event.

Study 015 was the open label, long term safety study using zolmitriptan 5 mg. Of the 2,058 patients who received zolmitriptan at least once, 98 (5%) had one or more threshold values for BP or HR. Most of these were decreases in BP and all but one were decreases in HR. Two patients led to withdrawal because of diastolic hypertension (see section 8.4.4, Adverse Events Associated with Dropouts, page 40)

***8.8 Electrocardiogram***

*8.8.1 Clinical Pharmacology Studies*

Two lead 24 hour Holter recordings were done the majority of the clinical pharmacology studies (except 023, 024, 025, 041, 044, and 045). There were no zolmitriptan associated effects on heart rate, ECG morphology, PR, QRS, QT/QTc intervals, nor on ST segments. A comparison of ST segments in the double blind studies (001, 009, 010, 012, 014, 032) was done. An ST segment event was defined as a 1 mm deviation for 1 minute relative to baseline. It is noted that these changes may represent artifact in the vast majority of recordings, but an

asymptomatic coronary vasospasm. The actual incidence of ST segment events was 10% on active drug and 13% on placebo.

Asymptomatic rhythm disturbances were seen in 7 subjects tested. One was associated with placebo, two were associated with vomiting and likely represent increased vagal tone. The other 4 were unsustained ventricular tachycardia associated with 5 mg (1 case) and 10 mg (3 cases. The number of beats ranged between 5-14 beats. None had the morphology of Toursade de Pointe. and none had prolonged QTc intervals. The incidence represents 0.6% of all Holter monitors analyzed, which is similar to the rate of idiopathic ventricular tachycardia in the general population (1%), according to a consulting cardiologist, Dr. Camm, St. Georges Hospital, London. He also reviewed the tapes and agrees they probably have a benign, idiopathic origin.

There were few treatment-emergent 12 lead ECG changes: 6% on placebo, 5% at 2.5 mg, 9% at 5 mg, 2% at 5-10 mg, and 11% at doses above 10mg. The 2% at 5-10 mg represents the greatest number of subject exposures (6/343). There were no patterns of abnormalities and none were of clinical concern. None resulted in adverse experiences or withdrawals.

### *8.8.2 Patient Studies*

#### *8.8.2.1 Methods*

Standard 12 lead ECG's were performed at baseline and periodically acute post-dose in study 006, the placebo controlled inpatient study, and in study 007, the uncontrolled inpatient PK study. These are the only patient studies in which ECG data are available acutely during treatment. Therefore, these are the tracings that are most likely to detect acute electrocardiographic changes that may result from treatment.

Pre- and post-treatment ECG's were also collected in the placebo controlled outpatient studies (008, 017, 018, 042), and in the acute prevention of migraine headache during aura study (026). In the long term safety study (015), ECG's were collected at baseline, every three months, and at discharge. Since these ECG's were performed in the vast majority of cases many days after therapy, they are less useful than the ECG's from studies 006 and 007, but nonetheless can provide information about chronic, long-term or permanent ECG's changes resulting from treatment.

All 12 lead ECG's were reviewed by 1 of 2 independent cardiologists who were blinded to treatment but not to the sequence of ECG tracings (baseline vs. post-baseline). ECG's from studies 006, 017, 018, 042, and 015 were sent to Dr. Galen Wagner at Duke University Medical Center. Study 008 tracings were reviewed by a consultant cardiologist (Dr. Ward) in London.

The CRF recorded the following ECG parameters:

- ventricular rate
- status of the ECG (normal, normal variants present, abnormalities present, or normal variants and abnormalities present)

The independent cardiologist was able to compare baseline to post-baseline tracings. He reported whether there was a significant change, and whether, in his opinion, the change potentially represented an ischemic event.

In addition, for study 006 only, PR, QRS, QT, and QTc intervals were recorded and summary statistics were tabulated for data obtained during the first 2 hours following treatment (PBO, 1, 5, and 25 mg)

The NDA includes individual patient narratives for any patient with ECG findings who 1) were reported as treatment emergent AE which resulted in withdrawal, or 2) were judged by the consulting cardiologist to represent a significant change from baseline, or 3) were judged to be potentially ischemic by the consulting cardiologist.

*8.8.2.2 Results*

In study 006, 8/78 (10%) zolmitriptan treated patients and 1/5 (20%) placebo treatment patients had treatment emergent ECG changes. One of the 8 zolmitriptan treated patients actually exhibited the ECG changes after treatment with placebo but before treatment with zolmitriptan. Two others had the same abnormalities noted at baseline, but had been checked "normal variant" at baseline, which resulted in the same abnormalities being classified as "treatment emergent" when they in fact were not. Individual review of all cases fail to reveal distinctive ischemic changes. In particular, no ST segment elevations or depressions were reported. The abnormalities detected are shown in sponsor Table 26 (ISS, Vol. 211, pg. 134). Two of the 5 true emergent ECG abnormalities associated with zolmitriptan were 1st degree AV blocks.

***Table 26: Treatment Emergent ECG abnormalities, Study 006***

| PTID | 1st Dose | Opt. 2nd Dose | Assessment[1] | ECG Abnormality |
|---|---|---|---|---|
| 006-001-001039 | PBO | 10 | 1:00 | SVT |
| 006-001-001041 | 25 | no | 1:00 | left axis deviation |
| 006-001-001045 | PBO | no | 4:00 | sinus bradycardia < 50 |
| 006-001-001049 | 25 | no | 1:00; 2:00 | 1st degree AV Block |
| 006-001-001060 | 5 | 20 | 2:00 | NS ST-T wave changes |
| 006-001-001072 | 1 | no | 0:30; 1:00 | sinus bradycardia < 50 |
| 006-001-001081 | 1 | 15 | 2:30 | 1st degree AV Block |
| 006-001-001059 | 1 | 15 | 3:00 | left axis deviation, RBBB[2] |
| 006-001-001074 | 1 | no | 4:00 | incomplete RBBB[2] |

[1] the optional second dose was given at 2 hours
[2] these were also present at baseline and were judged not to have true treatment emergent changes

Study 006 was the only study that measured PR, QRS, QT, and QTc intervals. For each of these ECG parameters, no clinically significant changes in median values from baseline to 2 hours following the first dose of study drug were observed for any treatment group.

In study 007, a total of 20 patients had baseline and acute post-treatment ECG's done. All 20 patients received zolmitriptan 10 mg for the acute treatment of a migraine headache, and 18 subsequently received 10 mg during a headache free period. There were no treatment emergent ECG changes.

A total of 2,512 zolmitriptan treated patients, and 387 placebo treated patients and 495 sumatriptan treated patients underwent baseline and post-baseline ECG's in placebo controlled outpatient studies (008, 017, 018, 042). Treatment emergent ECG abnormalities were 2-3% in the zolmitriptan groups, 2% in placebo group, and 4% in sumatriptan group. In general, these were mild and of doubtful clinical significance. In many cases, the abnormalities were present at screening but had been noted as "normal variant"

Six of the 2,512 zolmitriptan treated patients and 1 of the 495 sumatriptan treated patients had ECG changes rated as a significant change from baseline, as rated by the independent cardiologist. Three of these patients (2 for zolmitriptan, and the one sumatriptan treated patient) had ECG's rated as "potentially ischemic." These are described below.

8.8.2.2.1 SIGNIFICANT ECG CHANGES RATED AS POTENTIALLY ISCHEMIC

In one patient (008-034-034003), a 36 year old female, the ischemic changes were noted at screening (flattened T waves) but were absent on a subsequent post-treatment (zolmitriptan 10 mg) tracings. This patient enrolled in the long term safety study (015) and treated 32 headaches over 10 months and ECG's remained normal.

The second patient (017-026-026032) was a 60 year old female who had non specific ST-T wave changes at screening. She received zolmitriptan 1 mg (+ placebo as the second dose). Five days later, her post-treatment ECG showed T wave inversion in the lateral leads in addition to the previously seen non specific ST-T wave changes. This change prompted further cardiac evaluation, resulting in a normal Thallium stress test and echocardiography. As a result, the cardiologist deemed the findings of "no clinical importance."

The third patient (018-222-000765) was a 43 year old female who used sumatriptan 100 mg and experience chest pain 90 minutes later, lasting 5 minutes. The post-treatment ECG one week later had ST depression in $V_2$, $V_3$, and $V_4$, suggestive of ischemia by the independent cardiologist. A follow-up ECG was normal.

8.8.2.2.2 SIGNIFICANT ECG CHANGES RATED AS NON-ISCHEMIC

The remaining three patients had significant ECG changes rated as non-ischemic by the independent cardiologist.

The first patient (018-221-221751) was a 44 year old female who treated a single migraine with zolmitriptan 5 mg. The screening ECG had non-specific ST-T wave changes and T wave inversions. Thirteen days after treatment, the post-treatment ECG had upright T waves. The clinical significance of this change was unknown, however the patient enrolled in study 015 and treated 17 headaches over nine months with zolmitriptan 5+5 mg. She had one episode of palpitations 30 minutes after a 5 mg dose, lasting 10 minutes. No significant ECG changes were found.

The second patient (017-001-001010) was a 56 year old female who received a single zolmitriptan 5 mg dose. The screening ECG had inverted T waves in $V_1$ and $V_2$ and was judged normal. The post-treatment ECG 5 days later had non specific ST-T wave changes in addition to the inverted T waves. The independent cardiologist considered the change benign and consistent with "late transition". The patient entered study 015 and treated 46 migraines with zolmitriptan 5+5 mg over 12 months. The eight ECG's during that study were variable with T waves in $V_3$ being inconsistently inverted. Both the investigator and independent cardiologists interpreted the changes as lacking clinical importance.

The third patient (017-024-024039) was a 52 year old female who received a single zolmitriptan 10 mg dose. The screening ECG was normal. The post-treatment ECG 6 days later showed Q waves inferiorly indicative of an old myocardial infarction. Subsequent reviews of old ECG which pre-dated study participation by about 5 years also showed small Q waves inferiorly. The investigator and independent cardiologist judged the small Q waves to be normal variants.

#### 8.8.2.2.3 ECG ABNORMALITIES REPORTED AS ADVERSE EXPERIENCES

Across all patient studies, ECG abnormalities were reported as AE's in 9 patients. None were rated as serious, but 6 led to withdrawal. All were associated with zolmitriptan 5 mg ingestion in study 015. Two consisted of QT prolongation, however in one of these cases, the independent cardiologist felt the QTc intervals were within the range of normal. The other AE's were due to extrasystole (1), 1st degree AV block (1), T wave changes (1), and non-specific ECG changes (4).

## *8.9 Summary of Cardiovascular Safety Data*

### *8.9.1 Clinical Pharmacology Studies*

Oral zolmitriptan 0.5-50 mg resulted in small transient increases in blood pressure. There appeared to be no clinically significant drug interactions. In studies of patients with controlled hypertension or renal failure, zolmitriptan ingestion did not result in significant differences in peak blood pressures and effects over time compared to young, healthy controls.

Heart rate was monitored in all clinical pharmacology studies and no effects attributable to zolmitriptan ingestion were detected. A small number of transient asymptomatic rhythm disturbances recorded by 2–lead ECG Holter tapes occurred (one with placebo) and are thought to be consistent with the incidence in a normal healthy adult population.

Across all clinical pharmacology studies there were few treatment–emergent 12–lead ECG abnormalities. The incidence of treatment–emergent abnormalities was not dose–related. Administration of zolmitriptan has not been associated with any effect on ECG morphology or PR, QRS, QT or QTc intervals. Furthermore, there is no evidence of ST segment depression attributable to zolmitriptan administration.

### *8.9.2 Patient Studies*

The small pressor effect observed in volunteers who received zolmitriptan in clinical pharmacology studies has not been observed in patients with migraine headaches. In the placebo–controlled inpatient study for the treatment of migraine headache (Study 006), in which 84 patients were randomly assigned to receive placebo, 1, 5, or 25 mg zolmitriptan during a migraine attack, no significant changes in mean SBP, DBP, or HR were observed in any treatment group. The single patient who had a post–baseline BP value which met the threshold criteria for increased DBP received 25 mg zolmitriptan. Few patients had BP or HR values which met the threshold criteria in the other 2 studies in which baseline and post–baseline BP and HR were evaluated (these were Study 007, the uncontrolled inpatient pharmacokinetic and safety study, and Study 015, the long–term study). Similarly, few patients across all patient studies had treatment–emergent adverse experiences potentially related to BP or HR. Patients were rarely withdrawn from the long–term study for AE's potentially related to BP or HR.

Baseline and post–baseline 12–Lead ECG's were obtained in all but one patient study. QRS complex and PR, QRS, QT and QTc intervals were measured in the inpatient treatment study (Study 006). No clinically significant changes in median values from baseline to 2 hours following the first dose of study drug were observed in any treatment group.

Few treatment–emergent ECG abnormalities were reported across all patient studies. The incidence of treatment–emergent abnormalities was not dose–related and in the placebo–

patients who received zolmitriptan in the long–term study were withdrawn based on an investigator evaluation of an ECG abnormality. None of the ECG abnormalities were considered to be serious.

ECG's from most Patient studies were reviewed by an independent cardiologist. None of the ECG's from patients in Study 006 were judged to be representative of a significant change from baseline by the central cardiologist. Only 6 of 2,512 zolmitriptan–treated patients in the placebo–controlled outpatient studies for the treatment of migraine headache had an ECG judged by a central cardiologist to represent a significant change from baseline. The change was judged to be potentially representative of an ischemic event in only 2 zolmitriptan–treated patients (one on a screen ECG before administration of zolmitriptan and one on an ECG obtained after administration of zolmitriptan). Thorough review of all ECG data for these patients indicates that the changes described are unlikely representative of true ischemia. Eleven of 6,689 post–screen ECG's from Study 015 were evaluated by the central cardiologist as having a significant change from baseline. None of these changes were considered to potentially represent an ischemic event.

One patient for whom the independent cardiologist did not report a significant change comparing baseline to any post–baseline ECG, had an ECG abnormality reported as an adverse experience (T wave change – coronary ischemia). The patient had a follow–up evaluation including an exercise stress ECG which was reported to be normal. All ECG's for this patient were subsequently re–reviewed by the central cardiologist. He reported that it was highly unlikely' that the ECG abnormality represented an ischemic event.

### *8.10 Long Term Safety*

Study 015 contains long term safety data for zolmitriptan. It was the open label, international (20 countries), multicenter study whose primary objective was to evaluate the long term safety of multiple administrations. Duration of the study was one year. According to ICH guidelines, safety should be established in 300 patients taking zolmitriptan for six months and in 100 patients for one year. Headache frequency should average 2 headaches per month per patient.

FDA Table 27 summarizes the exposures to zolmitriptan in study 015. It enrolled 2296 patients. A total of 2058 patients treated at least one migraine attack. Each attack was treated with 5 mg, and an optional 2$^{nd}$ 5 mg dose was permitted for headache recurrence after 2 hours. Six hundred seventeen (617) had headache frequencies of 2 or more headaches per month for at least six months, and 126 had 2 or more headaches per month for at least 12 months. These numbers satisfy ICH criteria.

*Table 27: Study 015, Long Term Exposure to Zolmitriptan*

| Population | N | Duration in Study (months) | | No. of Headaches Treated per Pt. | | Headache Frequency (has/mo) | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean | SD |
| All Patients | 2296 | 7.8 | 3.4 | 15.3 | 15.2 | 1.8 | 1.7 |
| ≥ 6 mos | 1584 | 9.7 | 1.9 | 19.3 | 15.7 | 1.9 | 1.4 |
| ≥ 12 mos | 209 | 12.5 | 0.4 | 30.7 | 17.9 | 2.4 | 1.4 |
| ≥ 6 mos and ≥ 2 has/mo | 617 | 10.4 | 1.8 | 33.9 | 14.0 | 3.3 | 1.2 |
| ≥ 12 mos and | 126 | 12.5 | 0.4 | 42.0 | 13.6 | 3.4 | 1.1 |

The numbers differ from the sponsor generated numbers because the sponsor has used the time between first and last headaches as the duration of exposure, as opposed to the actual duration in the study, which is used here. The sponsor's values result in higher headache frequencies but fewer numbers of exposures at 6 and 12 months. Patients could treated as many migraines as desired.

The 2,058 patients treated a total of 31,579 attacks, and reported 16,248 AE's. On average, each patient treated 15 attacks and approximately 50% of patients were exposed for 6-12 months. Fifty-four percent (54%) of the attacks were treated with one dose, and 46% were treated with 2 doses. Of the 31,579 attacks, 7,921 (25%) had an associated AE. The number of attacks associated with at least one AE was evenly distributed between the 5 mg (26%) and the 5+5 mg (24%) groups.

The majority of AE's were mild or moderate in intensity (94%), of short duration (54% < 2 hours), and had an onset within 2 hours of taking zolmitriptan (59%). There were virtually no difference in the AE characteristics between the 5 mg and 5+5 mg groups. Thirty-nine (39) patients reported a total of 43 SAE's. These are covered in the SAE section (8.3 Serious Adverse Events, page 38).

The common AE's reported are summarized in sponsor Table 28 and were similar to those reported in the placebo-controlled clinical trials. Incidences were higher, probably due to the multiple exposures. As in the case for the placebo controlled trials, AE's were more common in females than in males.

*Table 28: Most Common[a] AE's in Long Term Treatment Study (015)*

| | Zolmitriptan Dose | | | |
|---|---|---|---|---|
| | 5 mg (N=1858) | | 5+5 mg (N=1595) | |
| asthenia | 264 | 14% | 220 | 14% |
| pain-location specified[b] | 128 | 7% | 99 | 6% |
| heaviness, other than chest or neck[c] | 113 | 6% | 100 | 6% |
| throat tightness | 112 | 6% | 92 | 6% |
| nausea | 214 | 12% | 134 | 8% |
| dry mouth | 81 | 4% | 75 | 5% |
| somnolence | 194 | 10% | 161 | 10% |
| dizziness | 207 | 11% | 142 | 9% |
| hyperesthesia | 85 | 5% | 70 | 4% |
| paresthesia | 206 | 11% | 156 | 10% |
| warm sensation | 117 | 6% | 93 | 6% |

[a] defined as occurring with an incidence of ≥ 5% for one or both doses
[b] includes pain in face, back, abdomen, arms, legs
[c] usually arms and/or legs

There was a general trend towards a lower incidence of AE's in patients who treated a higher number of attacks; *i.e.*, proportionately fewer AE's were reported as the number of treated attacks increased.

### *8.11 Safety Data from Other Studies*

#### *8.11.1 Uncontrolled Studies - 002, 007*

Two uncontrolled single migraine treatment studies (002, and 007) were conducted. Each study employed a dose higher than the recommended dose (25 mg and 10 mg, respectively).

*8.11.2 Placebo-Controlled Migraine Headache Prevention Study (026)*

In this study, patients with migraine headache preceded by an aura were enrolled and asked to take either zolmitriptan 20 mg or placebo during the aura phase. The objective was to evaluate the ability of zolmitriptan to prevent the onset of the headache. An optional 2nd dose of either 20 mg (if the first dose was placebo) or 5 mg (if the first dose was 20 mg) was permitted.

There was a small number of placebo patients (n=4) reflecting the fact that most patients who received placebo initially opted for a second dose, which always was active medication. A total of 46 patients were exposed to study medication. Seventy-eight percent (78%) reported at least one AE, which is reflection of the high dose of zolmitriptan used. No SAE's were reported. The most common AE's were paresthesia, nausea, dizziness, somnolence, asthenia, and heaviness other than chest or neck, and were similar to the AE's seen at lower doses in the controlled studies. Also reported were neck tightness, confusion, abnormal coordination, and pharyngitis.

***8.12 Cognitive Effects***

Multiple standard psychometric tests were used to assess cognitive function in study 023, which compared zolmitriptan to lorazepam. Significant impairments were seen with lorazepam, but not with zolmitriptan . Zolmitriptan did produce mild, transient, dose-related increases in subjective ratings of mental and physical sedation The ratings of sedation were minimal at the 5 mg dose. This was confirmed in the clinical pharmacology study 012 which compared psychometric function in the young and elderly. Mild, transient, dose-related subjective feelings of sedation were following zolmitriptan administration in both age groups.

***8.13 Drug-Drug Interactions***

Seven clinical pharmacology drug-drug interactions studies were performed. All were conducted in non-patient volunteers using 10 mg or 20 mg oral dose of zolmitriptan. A brief summary of each drug studied is included below. All studies were small, with 11-18 subjects per treatment arm.

*8.13.1 Ergotamine (Cafergot) - Study 010*

There were four treatment arms: placebo, Cafergot alone, zolmitriptan 20 mg alone, or the two in combination. Cardiovascular measurements were performed up to four hours after dosing. The combination of zolmitriptan and Cafergot was tolerated as well as zolmitriptan alone and there were no significant effects on cardiovascular parameters, vital signs, or AE reporting.

*8.13.2 Dihydroergotamine - Study 039*

There were two treatment arms: DHE 10 mg p.o. daily (divided BID) for 10 days or placebo. All subjects received zolmitriptan 10 mg on day 10. There were no significant effects noted on the AE profile, BP, or other cardiovascular parameters.

*8.13.3 Acetaminophen and Metoclopramide - Study 033*

There were five treatment arms: zolmitriptan 10 mg alone, acetaminophen 1 g alone, zolmitriptan 10 mg + acetaminophen 1 g, zolmitriptan 10 mg + metoclopramide 10 mg, zolmitriptan 10 mg + acetaminophen 1 g + metoclopramide 10 mg. There were no significant changes in AE profile, BP, or PK of zolmitriptan. However, acetaminophen absorption was lower when given with zolmitriptan compared to when given alone (AUC 11% lower, $C_{max}$ 31% lower, $T_{max}$ 0.8 vs. 3.0 hours). These data suggest that zolmitriptan delays the rate and extent of acetaminophen absorption.

*8.13.4 Propranolol - Study 021*

There were two treatment arms: Inderal LA 160 mg/d for seven days or placebo. All subjects received zolmitriptan 10 mg concomitantly. The $C_{max}$, AUC, and $T_{1/2}$ for zolmitriptan were all significantly higher (37%, 56%, 32%, respectively) when co-administered with propranolol, however the $C_{max}$ and AUC for the active metabolite, n-desmethyl zolmitriptan, were lower (24%, and 21%, respectively). These data suggest that propranolol inhibits the metabolism of zolmitriptan to the active metabolite, n-desmethyl zolmitriptan. These changes in PK parameters were not associated with any clinically relevant events.

*8.13.5 Pizotifen - Study 034*

Pizotifen is a non-specific 5-$HT_2$ receptor antagonist approved in Europe for migraine headache prophylaxis. There were two treatment arms: pizotifen daily for 8 days or placebo. All subjects received zolmitriptan 10 mg on the last day of dosing. Pizotifen produced a small (16%) and not-statistically significant increase in the AUC of the active metabolite (n-desmethyl zolmitriptan). No clinically significant effects on AE or BP were seen.

*8.13.6 Fluoxetine - Study 035*

There were two treatment arms: fluoxetine 20 mg/d for 28 days or placebo. All subjects received zolmitriptan 10 mg on the last day of dosing. There were no clinically significant differences on the AE profile, vitals signs, or BP. The PK of zolmitriptan were similar with and without the presence of fluoxetine (all changes were 16% or less).

*8.13.7 MAO Inhibitors - Study 038*

There were three treatment arms: moclobemide 150 mg BID for 7 days, selegiline 10 mg/d for 7 days or placebo. All subjects received zolmitriptan 10 mg on the last day of dosing. Patients were monitored for 24 hours. Selegiline had no effect on the PK or PD of zolmitriptan. Moclobemide produced a 26% increase in zolmitriptan AUC and a 23% increase in the mean $C_{max}$. $CL_R$ was 15% lower. There were also increases (3 and 2.5 fold in AUC and mean $C_{max}$, respectively) of the active metabolite, n-desmethyl zolmitriptan. Concentrations of the inactive metabolites were significantly reduced. These data suggest that ***MAO-A inhibitors significantly decrease the conversion of the active metabolite, n-desmethyl zolmitriptan to the inactive products. This results in a three fold increase in the plasma concentrations of the active metabolite.***

*8.13.8 Experience from Clinical Trials*

There was no evidence that the overall number of patients with ≥1% incidence of AE's was affected in any systematic manner by the concomitant use of analgesics, antidepressants, SSRI's, other migraine drugs, or oral contraceptives.

***8.14 Drug-Disease Interactions***

Three special population studies were done to evaluate the effects of zolmitriptan in hypertension, renal failure, and hepatic failure.

*8.14.1 Hypertension - Study 013*

There were two treatment arms: stable mild to moderate hypertensives (n=16, on HCTZ) and normal volunteers (n=17) each received single oral doses of 5, 10, and 20 mg zolmitriptan. Zolmitriptan plasma concentrations were similar in hypertensive and normotensive subjects, but at 20 mg zolmitriptan, the AUC was 50% higher in hypertensive patients. This dose is not proposed for marketing, therefore this interaction should not be clinically important.

*8.14.2 Renal Failure - Study 024*

There were two treatment arms: severe renal failure (n=16, mean creatinine clearance 21.5 mL/min) and normal volunteers (n=15, mean creatinine clearance 87.6 mL/min). All received a single 10 mg oral dose of zolmitriptan. Plasma concentrations were similar in both groups, although the $T_{1/2}$ was longer in the renal failure subjects (2.9 vs. 2.2 hours). Furthermore, the active metabolite, n-desmethyl zolmitriptan exhibited a higher AUC (35%), $C_{max}$ was higher (17%), and $T_{1/2}$ was 0.9 hours longer (3.2 vs. 2.3 hours). $CL_R$ was lower by 80-90% for zolmitriptan and all its metabolites in the renal failure subjects. There were no pharmacodynamic or BP events associated with the changes in PK parameters observed.

*8.14.3 Hepatic Failure - Study 030*

There were three treatment arms. Group 1: patients with moderate liver disease (n=10); Group 2: patients with severe liver failure (n=10), and Group 3: normal healthy volunteers matched in age, sex, and smoking status (n=10). Metabolism of zolmitriptan was reduced in patients with liver disease, resulting in higher $C_{max}$ (approximately 50%, 31 ng/mL vs. 21 ng/mL), increased AUC (226%) and prolonged $T_{max}$ (12 hours vs. 4.7 hours) in severe liver disease (less so with moderate disease). Therefore, the dose may need to be reduced in this population. Zolmitriptan 10 mg was generally well tolerated in volunteers and patients.

***8.15 Drug-Demographic Interactions***

The majority of the patients studied were female between the ages of 18 and 60. A review of the data collected in the zolmitriptan clinical development programs provided no evidence for any prominent interaction between zolmitriptan and any particular demographic subgroup in the populations treated. It should be noted that the sample sizes for some of the demographic categories were too small to provide meaningful conclusions.

*8.15.1 Study Location*

The sponsor analyzed the safety data for the potential effect of study location (US vs. non-US). No clinically significant differences were detected in the overall frequency of adverse experiences as a consequence of study location.

*8.15.2 Gender*

A formal statistical comparison between the genders was made in four studies (012, 013, 016, and 045). In addition, data from healthy male and female volunteers from the other studies were included in cross-study comparisons of the effect of gender and oral contraceptives.

*8.15.2.1 Gender Data from Clinical Pharmacology Studies*

In study 012, across the dose range of 5-15 mg, zolmitriptan AUC and $C_{max}$ in young females were approximately twice those in your males. This difference was not seen in elderly volunteers. In all four groups, there was a 2 to 4-fold variability between individuals that resulted in an overlapping of ranges of values among the groups. Across the dose range of 5-10 mg in study 013, plasma concentrations were similarly approximately 2 fold higher in females.

After I.V. dosing in study 016, plasma concentrations of zolmitriptan were about 25% higher in females, but this was not statistically significant. After a 10 mg oral dose, AUC values were 2 fold higher in females. $C_{max}$ was also higher, but did not reach statistical significance.

In study 045, there were no gender differences observed for the 2.5 mg dose, but at 5 mg

The cross study comparison indicated that AUC was increased 30-50% and CL/F decreased approximately 30% in women taking oral contraceptives compared to those who were not. This suggests that oral contraceptives contribute to the overall effect of gender on the PK of zolmitriptan.

In summary, plasma concentrations of zolmitriptan were approximately 2 fold high in females compared to males. The differences is due, in part, to reduced first pass metabolism in the females. Considerable variability (2-4 fold) exists within the populations leading to overlap in PK parameters between the sexes.

*8.15.2.2 Gender Data from Clinical Trials*

In the 2.5 mg zolmitriptan dose groups, females did have more AE's than males (48% vs. 30%) but the difference was less in the 5 mg group (59% vs. 51%). It should be noted that females reported more AE's in the placebo group as well (30% vs. 24%). Adverse events rated as severe appeared to be twice as prevalent in females than males in both the placebo and the zolmitriptan groups.

*8.15.3 Age*

There were two treatment arms in study 012: one group consisted of healthy elderly volunteers (n=12, ages 65-76), and the other consisted of young volunteers (n=12, ages 18-39). Both groups received zolmitriptan 5mg, 10 mg, and 15 mg at various times in a balanced, cross-over design. In general, PK parameters for zolmitriptan and its active metabolite were similar. $CL_R$ were generally lower in the elderly, reflecting decreasing renal function with age. In clinical trials, there was no indication of a relationship between age and incidence of AE's.

*8.15.4 Weight*

In clinical trials, there did not appear to be any indication of a relationship between body weight and AE incidence rates.

*8.15.5 Race*

Approximately 97% of the patients were white. Therefore there are insufficient data to draw conclusions about racial differences in the tolerability of zolmitriptan.

***8.16 Class Effect of $5HT_{1D}$ Agonists***

Eight AE's occur at an incidence of ≥5% in at least three of the zolmitriptan dose groups. A comparison of these eight AE's with the AE's that are commonly associated with sumatriptan indicate some similarities that are likely indicative of a class effect of $5HT_{1D}$ agonists.

Atypical sensations such as feelings of heaviness, feeling of tightness, pressure sensation, tingling and warm/hot sensations are a constellation of AE's that occur more frequently following sumatriptan administration as well. It would appear that paresthesia, feeling of heaviness and warm sensation are commonly occurring class effects related to $5HT_{1D}$ agonists. In addition to the most frequently occurring AE's, other AE's that are classified as "frequent" (*i.e.*, occurring in > 1% of patients) in the sumatriptan labeling include chest discomfort, chest pressure/heaviness and chest tightness. Review of Table 21: Adverse Events in Clinical Studies (006, 008, 017, 018, 042) having Incidence > 1% for zolmitriptan 2.5 mg tablet., on page 45, indicate that similar AE's also occur following zolmitriptan administration.

Study 018 is the only clinical study in the NDA that compared zolmitriptan to sumatriptan. These doses produced roughly equivalent efficacy results. This analysis may be especially relevant since AE's related to both were collected under similar conditions. Sponsor Table 29 summarizes these adverse events.

*Table 29: Most Frequent (≥5%) AE's - Zolmitriptan, Sumatriptan, and Placebo (Study 018)*

| AE | Zolmitriptan 5 mg (N=491) | Sumatriptan 100 mg (N=504) | Placebo (N=56) |
|---|---|---|---|
| asthenia | 11% | 11% | 5% |
| dizziness | 7% | 7% | 2% |
| paresthesia | 6% | 7% | 0% |
| heaviness other than chest or neck | 6% | 5% | 0% |
| nausea | 6% | 7% | 2% |
| somnolence | 8% | 6% | 4% |
| warm sensation | 5% | 6% | 2% |
| neck pain | 3% | 5% | 2% |

This comparison helps confirms the concept of these "$5HT_{1D}$ class effects." Other possible AE's in this list, which are not included in the sponsor's table, include chest pain, chest pressure, chest heaviness, and chest tightness. These occur in both the zolmitriptan and sumatriptan treatment groups, although at lower incidences (0-2%).

Table 30 lists these putative $5HT_{1D}$ class effects, although additional comparisons with other $5HT_{1D}$ agonists are needed to establish the validity of such a list.

*Table 30: Adverse Events associated with $5HT_{1D}$ Agonist Class Effect*

| | |
|---|---|
| asthenia | nausea |
| dizziness | somnolence |
| paresthesia | warm sensation |
| heaviness other than chest or neck (usually arms/legs) | neck pain, tightness |
| | chest pain, pressure, heaviness, tightness |

### *8.17 Withdrawal Phenomenon and Abuse Potential*

The withdrawal potential from zolmitriptan is difficult to assess since the drug is administered on an intermittent basis. The single migraine studies provide no meaningful information on withdrawal effects since patients administered only one or two doses. One potential concern related to withdrawal effects of $5HT_{1D}$ agonists is the development of rebound headaches following prolonged, repeated use. Study 015, the open-label long-term safety study, allowed patients to treat as many migraines as desired for a period up to one year. In this study, there was only 1 report, which was a serious adverse event, consistent with rebound headaches (this was previously described in section 8.3, Serious Adverse Events, page 38). This isolated case does not raise clinical concerns regarding withdrawal effects from zolmitriptan.

There were no studies in the clinical development program of zolmitriptan to specifically assess abuse potential. However, the abuse potential was evaluated by examining the integrated database for adverse events that could be related to subjective effects that may be indicative of abuse potential. Among all zolmitriptan treated patients enrolled in placebo controlled trials (N=2633) there were four reports of CNS stimulation (<1%), five reports of euphoria (<1%), and three reports of stupor (<1%). The incidence was not dose related. For the placebo treated patients (N=400), there was one report of CNS stimulation (<1%), no reports of euphoria, and

patients reported hallucinations, three reported stupor, and two reported CNS stimulation. All of these AE's occurred at an incidence of <1%. These low incidences suggest that the abuse potential for zolmitriptan is minimal.

### *8.18 Human Reproduction Data*

There were a total of 11 pregnancies reported during clinical development. Ten occurred in study 015, the long term safety study. One occurred in study 018. Of the 11 pregnancies, there have been 5 live births with normal infants (three normal vaginal deliveries, two cesarean section). There were four elective terminations with no fetal abnormalities reported. Two spontaneous abortions occurred prior to the eighth week of gestation. There was no apparent relationship between dose(s) of zolmitriptan taken after the last menstrual period and spontaneous abortions. Specifically, both spontaneous abortions occurred with doses of 1 x 5 mg and 0 mg, respectively, following the last menstrual period, whereas patients having normal infants had exposures up to 4 x 5 mg following the last menstrual period.

### *8.19 Overdose*

The initial dose-range finding study in normal volunteers (001) indicated that acute oral doses up to 50 mg were well tolerated. The escalation was stopped at this dose because of the high incidence of somnolence (6/7, 86%). However there were no ECG, BP, or laboratory findings or other AE's indicative of clinical safety concerns. All other studies used doses of 25 mg or less.

Study 014 used multiple oral doses (5 and 10 mg every 6 hours for a total of 5 doses) and suggested that zolmitriptan was well tolerated following multiple doses.

Three clinical migraine studies (006, 026, and 017) permitted the use of a second dose of zolmitriptan as early as 2-4 hours after the first dose, with the cumulative dose not exceeding 25 mg. The second dose of zolmitriptan was not associated with any additional safety concerns.

Study 015, the long-term safety study, was the only study in which accidental or intentional overdose could occur, since patients were dispensed with up to 120 mg of zolmitriptan at a clinic visit to treat up to 12 migraines over the next 3 months. This study reported 4 overdoses (Table 31). All the exposures were 30 mg or less over 2-3 days. The only adverse event reported was thirst in one patient.

In summary, the available information indicate that doses up to 50 mg in volunteers and 25 mg in migraine patients are well tolerated.

*Table 31: Overdoses, Study 015*

| Patient ID | Overdose | AE reported |
|---|---|---|
| 015-081-081503 | 25 mg over 3 days | none |
| 015-051-051507 | 20 mg over 3 days | none |
| 015-160-160511 | 20 mg over 2 days | thirst |
| 015-220-220511 | 30 mg over 2 days | none |

### *8.20 Summary of Key Adverse Events*

The overall incidences of patients with ≥ 1 AE for doses of 1 to 25 mg zolmitriptan were higher than for placebo. The incidences were in general dose-dependent. The incidences were comparable for patients receiving 1 and 2.5 mg and less than that for patients receiving 5 mg

moderate in intensity. SAE's were reported in <1% of patients receiving zolmitriptan or placebo.

The most commonly reported AE's in the placebo controlled studies were nausea, dizziness, somnolence, paresthesia, warm sensation, asthenia, dry mouth, tightness in throat, tightness in chest, heaviness other than chest/neck (usually arms/legs).

In general, the pattern and incidence of AE's in these studies did not appear to be influenced by age, or weight. The small sample size prevented any determination of racial differences in safety or tolerability. The overall incidence of AE's was slightly higher for females than males, but the small proportion of males in the program limits interpretation of this observation.

The incidences of patients with AE's among those receiving zolmitriptan did not appear to be affected by the concurrent use of analgesics, antidepressants, SSRI's, other acutely or prophylactically administered antimigraine agents, or oral contraceptives. MAO-A inhibitors increase the plasma levels of the active metabolite, n-desmethyl zolmitriptan by about 2-3 fold. Patients not experiencing an aura with their migraine headache were only slightly more likely to experience AE's than those who experienced an aura. There was no indication that AE's were more common in patients experiencing a menstrual migraine.

## 9. Four Month Safety Update

On 12/13/96, Zeneca requested a waiver from the requirement to submit a safety update 4 months following the original application submission (11/26/96). The waiver was granted on 2/19/97. However, the Division suggested an abbreviated safety update of limited scope be provided instead, the contents of which are described below. Also in the submission are two study reports: the safety, tolerability, and PK study in liver disease (030), and a bioequivalence study (091).

Finally, the sponsor submits comparative dissolution data on tablets manufactured at the IPR Pharmaceuticals, Inc. factory in Puerto Rico and the GlaxoWellcome facility in Dartford, UK. This dissolution report is not reviewed here.

### *9.1 Safety Data Presented*

The current update contains information for patients whose previously unreported AE's meet the following criteria: death, serious adverse events, or withdrawals due to adverse events. The data submitted have a cutoff date of 12/15/96 and they originate from information gathered since the ISS cutoff date of 8/22/96. The studies contributing to the report are:

- 091 - bioequivalence study (completed)
- 093 - drug interaction study with rifampicin (completed)
- 094 - drug interaction study with cimetidine (completed)
- 030 - hepatic failure study (completed)
- 092 - PK adolescent study (ongoing)
- 043 - long term treatment study (ongoing)

Study 091 was conducted in the UK. It compared the tablets manufactured by Zeneca with those manufactured by GlaxoWellcome. Twenty (20) volunteers participated.

Study 093 and 094 were two-way crossover studies to assess the effects of an enzyme inducer, rifampicin, and enzyme inhibitor cimetidine. They enrolled 14, and 16 volunteers, respectively.

Study 030 is described in section 7.5.2, page 35.

Study 092 compares the PK and tolerability of zolmitriptan 5 mg in adolescents and adults. Thirty-nine (39) volunteers enrolled.

Study 043 is a long-term efficacy and safety study which is evaluating the effects of a second 2.5 or 5 mg dose in persistent headache. A total of 3,000 patients will enroll. As of 12/15/96, a total of 850 patients had been recruited.

### *9.2 Deaths*

No deaths have been reported in the interim 8/22/96-12/15/97.

### *9.3 Adverse Events Leading to withdrawal*

No non-serious adverse events leading to withdrawal have been reported in the interim 8/22/96-12/15/97.

### *9.4 Serious Adverse Events*

Six (6) SAE's have been reported in the interim 8/22/96-12/15/97. All have been reported from trial 043. None appear to be likely due to zolmitriptan ingestion.

1. A 29 year old female experienced sinus tachycardia (130 BPM), left sided chest pain, shortness of breath, dizziness 16 days after zolmitriptan 2.5 mg ingestion. She had received 3 previous doses of zolmitriptan to treat migraine headaches on other occasions. Seven days prior to the SAE, her verapamil dose had been increased from 40 mg to 120 mg/day. Although the event occurred 16 days after zolmitriptan, the investigator could not exclude it as a possible contributing factor and recommended withdrawal from the study.

2. A 54 year old male suffered chest pain three days after zolmitriptan 2.5 mg ingestion. He was admitted to the hospital, where ECG, echocardiogram, CPK were normal. The cardiologist considered the chest pain due to pre-existing chronic bronchitis. Zolmitriptan causality is unlikely.

3. A 45 year old female experienced abdominal pain and rectal bleeding 6 days after zolmitriptan 2.5 ingestion. Evaluation lead to a diagnosis of sigmoid colitis. Zolmitriptan causality appears unlikely.

4. A 44 year old female with essential hypertension felt lightheaded and was admitted for observation during the pre-trial screening period. She had not received zolmitriptan.

5. A 36 year old male with a history of surgical repair for idiopathic hypertrophic sub-aortic stenosis presented 23 days after zolmitriptan 5 mg ingestion with weight loss, anemia, hematuria, and was diagnosed with post-streptococcal glomerulonephritis and bacterial endocarditis with streptococcus viridans. Echocardiogram showed a ventricular septal defect, aortic stenosis, tricuspid insufficiency, and valvular vegetations. He went on to renal failure during treatment. He was withdrawn from the trial due to co-existing medical illness. Association with zolmitriptan appears unlikely.

6. A 48 year old female experienced a painful ovarian cyst during the pre-trial screening period and before treatment with study medication. Zolmitriptan causality is impossible.

In addition, there have been 12 subjects who have exceeded pre-defined threshold values for vitals signs or laboratory measurements. None of these were serious adverse events or led to study withdrawal, however some of them were significant changes. All occurred in study 030, and involved significant increases (+20 to +80 mm from baseline) in systolic and/or diastolic BP in the liver disease patients only (7 out of 20) after receiving zolmitriptan 10 mg. One was accompanied with chest pain.

One liver disease patient (030-01-0111) experienced increases of +60 to +80 mm in systolic BP from a baseline of 120 mm. This was seen at 1, 2, 3, and 4 hours post-treatment.

Another liver disease patient (030-004-0403) exhibited an increase in systolic BP of +60 mm from a baseline of 140 mm at 0.5 post-treatment (10 mg). SBP remained elevated +40 mm from baseline at 4 hours. He experienced sub-sternal chest pain at 4 hours, lasting 2 hours.

A total of 7 (of 20) liver disease patients had increases in SBP and/or DBP (though none as prominent as the two described above). It should be noted that all received 10 mg, which is not recommended for treatment, and the PK results of the study indicate that the dose in liver disease patients should be decreased due to diminished conversion of zolmitriptan to its inactive metabolites in patients with liver impairment. There was no control group (*i.e.*, no patients with liver disease received placebo) so it is not known how much of the increase can be attributed to zolmitriptan.[4]

## 10. Labeling Review

A comprehensive review of the proposed labeling beginning with "Indications and Usage" is provided below. Sponsor proposed labeling is presented in standard text. Strike-through text indicates text which, in this reviewer's opinion, should be deleted. My recommended additions to labeling are underlined. I have used the Division's most recently updated sumatriptan labeling as a template.

[4] However, based on the known PK and PD of zolmitriptan, both in normal volunteers and in patients with

9 pages

PURGED

Draft Labeling

## 11. Conclusions

1. The zolmitriptan safety database contains a large number of patient exposures at clinically relevant doses for up to one year resulting in an appropriate evaluation of the drug's safety profile.
2. Orally administered zolmitriptan was generally well tolerated when used for treatment of migraine headaches. Most AE's were of mild to moderate intensity, short duration, did not require intervention or treatment. Few patients necessitated discontinuation. Less than 1% of the study population experienced serious adverse events.
3. The most commonly reported AE's are similar to those reported by other $5HT_{1D}$ agonists (namely sumatriptan) and are supportive of certain "class effect" for this group of drugs. The overall incidence of AE's was dose-dependent.
4. The overall incidence of AE's is higher in females that in males, both in zolmitriptan and placebo treated patients.
5. No significant drug interactions with other drugs studied were noted, with the exception of the MAO-A inhibitor.
6. Zolmitriptan did not produce any significant changes on serum chemistry, hematology, or urinalysis.
7. Small increases in BP were seen in normal volunteers and migraine patients. These are probably not significant for the vast majority of individuals.
8. Patients with hepatic failure showed significant and clinically alarming increases in blood pressure at the dose tested (10 mg). No significant safety concerns were seen in other disease populations studied (renal failure, hypertension).
9. Zolmitriptan was generally well-tolerated in the long-term (up to 1 year) safety study. ICH guidelines to demonstrate long-term safety have been met.

## 12. Recommendation

Based on the overall review of the safety data presented, zolmitriptan can be used safely on an intermittent, outpatient basis for the acute treatment of migraine attacks with or without aura. In the opinion of this reviewer, NDA 20-768 is approvable from a safety standpoint. However, appropriate changes to proposed labeling, as discussed in section 10, page 68, are recommended.

AOliva

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R. Li (See memo)

ao 5/1/97
cc:
HFD-120
NDA 20-768

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## Appendix A - Adverse Event Incidence Table in Placebo Controlled Trials

*Table 32: Adverse Events in Clinical Studies (006, 008, 017, 018, 042)*

| ADVERSE EVENT | TOTAL | PBO | % | 1 MG | % | 2.5 MG | % | 5 MG | % | 10 MG | % | 15 MG | % | 20 MG | % | 25 MG | % | Suma 100 MG | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (N) | 3533 | 415 | | 162 | | 497 | | 1011 | | 514 | | 229 | | 220 | | 21 | | 503 | |
| NAUSEA | 258 | 15 | 3.61 | 6 | 3.7 | 45 | 9.05 | 63 | 6.23 | 41 | 7.98 | 32 | 13.97 | 20 | 9.09 | 0 | 0 | 35 | 6.96 |
| DIZZINESS | 325 | 15 | 3.61 | 9 | 5.56 | 42 | 8.45 | 96 | 9.5 | 67 | 13.04 | 28 | 12.23 | 34 | 15.45 | 1 | 4.76 | 33 | 6.56 |
| SOMNOLENCE | 266 | 12 | 2.89 | 8 | 4.94 | 30 | 6.04 | 78 | 7.72 | 55 | 10.7 | 20 | 8.73 | 28 | 12.73 | 5 | 23.81 | 29 | 5.77 |
| PARESTHESIA | 271 | 5 | 1.2 | 8 | 4.94 | 29 | 5.84 | 77 | 7.62 | 56 | 10.89 | 22 | 9.61 | 38 | 17.27 | 1 | 4.76 | 33 | 6.56 |
| SENSATION WARM | 180 | 6 | 1.45 | 5 | 3.09 | 21 | 4.23 | 52 | 5.14 | 36 | 7 | 19 | 8.3 | 12 | 5.45 | 0 | 0 | 29 | 5.77 |
| ASTHENIA | 328 | 13 | 3.13 | 8 | 4.94 | 16 | 3.22 | 89 | 8.8 | 64 | 12.45 | 36 | 15.72 | 45 | 20.45 | 4 | 19.05 | 53 | 10.54 |
| DRY MOUTH | 135 | 7 | 1.69 | 8 | 4.94 | 16 | 3.22 | 32 | 3.17 | 25 | 4.86 | 20 | 8.73 | 12 | 5.45 | 2 | 9.52 | 11 | 2.19 |
| TIGHTNESS THROAT | 95 | 3 | 0.72 | 1 | 0.62 | 13 | 2.62 | 28 | 2.77 | 22 | 4.28 | 9 | 3.93 | 10 | 4.55 | 0 | 0 | 8 | 1.59 |
| TIGHTNESS CHEST | 68 | 2 | 0.48 | 1 | 0.62 | 13 | 2.62 | 15 | 1.48 | 21 | 4.09 | 9 | 3.93 | 1 | 0.45 | 0 | 0 | 6 | 1.19 |
| HEAVINESS OTHER | 193 | 2 | 0.48 | 2 | 1.23 | 10 | 2.01 | 51 | 5.04 | 30 | 5.84 | 36 | 15.72 | 33 | 15 | 2 | 9.52 | 27 | 5.37 |
| TIGHTNESS NECK | 58 | 1 | 0.24 | 1 | 0.62 | 10 | 2.01 | 18 | 1.78 | 11 | 2.14 | 5 | 2.18 | 5 | 2.27 | 0 | 0 | 7 | 1.39 |
| PAIN LOC SPEC | 92 | 2 | 0.48 | 3 | 1.85 | 9 | 1.81 | 29 | 2.87 | 18 | 3.5 | 12 | 5.24 | 9 | 4.09 | 1 | 4.76 | 7 | 1.39 |
| SWEAT | 67 | 5 | 1.2 | 0 | 0 | 9 | 1.81 | 25 | 2.47 | 7 | 1.36 | 5 | 2.18 | 4 | 1.82 | 1 | 4.76 | 10 | 1.99 |
| PRESSURE OTHER | 64 | 1 | 0.24 | 3 | 1.85 | 9 | 1.81 | 15 | 1.48 | 3 | 0.58 | 13 | 5.68 | 5 | 2.27 | 1 | 4.76 | 13 | 2.58 |
| PAIN NECK | 92 | 4 | 0.96 | 0 | 0 | 8 | 1.61 | 27 | 2.67 | 11 | 2.14 | 8 | 3.49 | 7 | 3.18 | 1 | 4.76 | 24 | 4.77 |
| DYSPEPSIA | 42 | 2 | 0.48 | 5 | 3.09 | 8 | 1.61 | 10 | 0.99 | 7 | 1.36 | 0 | 0 | 3 | 1.36 | 0 | 0 | 7 | 1.39 |
| VOMIT | 57 | 10 | 2.41 | 1 | 0.62 | 7 | 1.41 | 15 | 1.48 | 8 | 1.56 | 6 | 2.62 | 2 | 0.91 | 0 | 0 | 8 | 1.59 |
| NERVOUSNESS | 23 | 1 | 0.24 | 0 | 0 | 7 | 1.41 | 7 | 0.69 | 3 | 0.58 | 1 | 0.44 | 3 | 1.36 | 0 | 0 | 1 | 0.2 |
| THINKING ABNORM | 28 | 2 | 0.48 | 0 | 0 | 6 | 1.21 | 3 | 0.3 | 8 | 1.56 | 3 | 1.31 | 3 | 1.36 | 0 | 0 | 3 | 0.6 |
| SENSATION COLD | 67 | 8 | 1.93 | 4 | 2.47 | 5 | 1.01 | 19 | 1.88 | 11 | 2.14 | 7 | 3.06 | 4 | 1.82 | 1 | 4.76 | 7 | 1.39 |
| MYALGIA | 56 | 1 | 0.24 | 1 | 0.62 | 5 | 1.01 | 17 | 1.68 | 11 | 2.14 | 9 | 3.93 | 8 | 3.64 | 0 | 0 | 3 | 0.6 |
| SENSATION UNUSUAL SPEC | 54 | 1 | 0.24 | 2 | 1.23 | 5 | 1.01 | 14 | 1.38 | 10 | 1.95 | 9 | 3.93 | 6 | 2.73 | 1 | 4.76 | 6 | 1.19 |
| TIGHTNESS OTHER | 47 | 1 | 0.24 | 4 | 2.47 | 5 | 1.01 | 14 | 1.38 | 9 | 1.75 | 6 | 2.62 | 3 | 1.36 | 0 | 0 | 5 | 0.99 |
| RHINITIS | 32 | 1 | 0.24 | 2 | 1.23 | 5 | 1.01 | 9 | 0.89 | 5 | 0.97 | 2 | 0.87 | 4 | 1.82 | 1 | 4.76 | 3 | 0.6 |
| TREMOR | 32 | 3 | 0.72 | 1 | 0.62 | 5 | 1.01 | 7 | 0.69 | 5 | 0.97 | 2 | 0.87 | 2 | 0.91 | 0 | 0 | 5 | 0.99 |
| DIARRHEA | 24 | 2 | 0.48 | 1 | 0.62 | 5 | 1.01 | 6 | 0.59 | 4 | 0.78 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 3 | 0.6 |
| HYPESTHESIA | 63 | 2 | 0.48 | 1 | 0.62 | 4 | 0.8 | 24 | 2.37 | 9 | 1.75 | 5 | 2.18 | 9 | 4.09 | 2 | 9.52 | 7 | 1.39 |
| PHARYNGITIS | 36 | 2 | 0.48 | 0 | 0 | 4 | 0.8 | 8 | 0.79 | 10 | 1.95 | 3 | 1.31 | 6 | 2.73 | 0 | 0 | 3 | 0.6 |
| ARTHRALGIA | 31 | 2 | 0.48 | 0 | 0 | 4 | 0.8 | 11 | 1.09 | 4 | 0.78 | 6 | 2.62 | 1 | 0.45 | 0 | 0 | 3 | 0.6 |
| REACT AGGRAV | 29 | 4 | 0.96 | 2 | 1.23 | 4 | 0.8 | 7 | 0.69 | 5 | 0.97 | 3 | 1.31 | 2 | 0.91 | 0 | 0 | 2 | 0.4 |
| TINNITUS | 24 | 2 | 0.48 | 0 | 0 | 4 | 0.8 | 9 | 0.89 | 3 | 0.58 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 4 | 0.8 |
| CONFUS | 15 | 0 | 0 | 0 | 0 | 4 | 0.8 | 3 | 0.3 | 4 | 0.78 | 1 | 0.44 | 3 | 1.36 | 0 | 0 | 0 | 0 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRURITUS | 12 | 0 | 0 | 1 | 0.62 | 4 | 0.8 | 5 | 0.49 | 1 | 0.19 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| PAIN ABDO | 64 | 7 | 1.69 | 2 | 1.23 | 3 | 0.6 | 13 | 1.29 | 16 | 3.11 | 5 | 2.18 | 4 | 1.82 | 0 | 0 | 14 | 2.78 |
| MYASTHENIA | 56 | 1 | 0.24 | 0 | 0 | 3 | 0.6 | 19 | 1.88 | 9 | 1.75 | 8 | 3.49 | 9 | 4.09 | 1 | 4.76 | 6 | 1.19 |
| HYPERESTHESIA | 38 | 0 | 0 | 0 | 0 | 3 | 0.6 | 12 | 1.19 | 7 | 1.36 | 6 | 2.62 | 7 | 3.18 | 0 | 0 | 3 | 0.6 |
| CHILLS | 29 | 6 | 1.45 | 0 | 0 | 3 | 0.6 | 8 | 0.79 | 5 | 0.97 | 2 | 0.87 | 1 | 0.45 | 0 | 0 | 4 | 0.8 |
| TASTE PERVERS | 29 | 2 | 0.48 | 4 | 2.47 | 3 | 0.6 | 7 | 0.69 | 4 | 0.78 | 1 | 0.44 | 4 | 1.82 | 0 | 0 | 2 | 0.4 |
| TACHYCARDIA | 25 | 2 | 0.48 | 0 | 0 | 3 | 0.6 | 9 | 0.89 | 7 | 1.36 | 1 | 0.44 | 2 | 0.91 | 0 | 0 | 1 | 0.2 |
| PARESTH CIRCUMORAL | 11 | 0 | 0 | 0 | 0 | 3 | 0.6 | 4 | 0.4 | 1 | 0.19 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| PHOTOPHOBIA | 8 | 2 | 0.48 | 1 | 0.62 | 3 | 0.6 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| REACT UNEVAL | 8 | 0 | 0 | 0 | 0 | 3 | 0.6 | 0 | 0 | 1 | 0.19 | 2 | 0.87 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| CRAMPS LEG | 4 | 0 | 0 | 0 | 0 | 3 | 0.6 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| THIRST | 28 | 0 | 0 | 0 | 0 | 2 | 0.4 | 10 | 0.99 | 5 | 0.97 | 2 | 0.87 | 4 | 1.82 | 0 | 0 | 5 | 0.99 |
| TIGHTNESS JAW | 17 | 2 | 0.48 | 3 | 1.85 | 2 | 0.4 | 4 | 0.4 | 2 | 0.39 | 4 | 1.75 | 0 | 0 | 0 | 0 | 0 | 0 |
| INFECT | 7 | 0 | 0 | 1 | 0.62 | 2 | 0.4 | 1 | 0.1 | 2 | 0.39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HYPERACUSIS | 6 | 1 | 0.24 | 0 | 0 | 2 | 0.4 | 2 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| CNS STIMULAT | 5 | 1 | 0.24 | 0 | 0 | 2 | 0.4 | 0 | 0 | 2 | 0.39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| COUGH INC | 5 | 0 | 0 | 1 | 0.62 | 2 | 0.4 | 1 | 0.1 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| FLATUL | 5 | 0 | 0 | 0 | 0 | 2 | 0.4 | 1 | 0.1 | 1 | 0.19 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| DYSMENORRHEA | 4 | 1 | 0.24 | 0 | 0 | 2 | 0.4 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DRY EYE | 3 | 0 | 0 | 0 | 0 | 2 | 0.4 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| EPISTAXIS | 3 | 0 | 0 | 0 | 0 | 2 | 0.4 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EYE DISORDER | 2 | 0 | 0 | 0 | 0 | 2 | 0.4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PALPITAT | 51 | 3 | 0.72 | 0 | 0 | 1 | 0.2 | 22 | 2.18 | 6 | 1.17 | 7 | 3.06 | 2 | 0.91 | 1 | 4.76 | 9 | 1.79 |
| PRESSURE CHEST | 37 | 1 | 0.24 | 0 | 0 | 1 | 0.2 | 8 | 0.79 | 8 | 1.56 | 3 | 1.31 | 3 | 1.36 | 2 | 9.52 | 11 | 2.19 |
| PAIN CHEST | 33 | 1 | 0.24 | 1 | 0.62 | 1 | 0.2 | 8 | 0.79 | 6 | 1.17 | 2 | 0.87 | 6 | 2.73 | 0 | 0 | 8 | 1.59 |
| DYSPNEA | 30 | 1 | 0.24 | 1 | 0.62 | 1 | 0.2 | 12 | 1.19 | 4 | 0.78 | 2 | 0.87 | 3 | 1.36 | 0 | 0 | 5 | 0.99 |
| HEADACHE | 29 | 2 | 0.48 | 0 | 0 | 1 | 0.2 | 6 | 0.59 | 4 | 0.78 | 3 | 1.31 | 4 | 1.82 | 0 | 0 | 8 | 1.59 |
| PRESSURE THROAT | 25 | 0 | 0 | 1 | 0.62 | 1 | 0.2 | 4 | 0.4 | 5 | 0.97 | 5 | 2.18 | 5 | 2.27 | 1 | 4.76 | 3 | 0.6 |
| PAIN | 23 | 1 | 0.24 | 0 | 0 | 1 | 0.2 | 8 | 0.79 | 5 | 0.97 | 1 | 0.44 | 2 | 0.91 | 0 | 0 | 5 | 0.99 |
| DEPERSONAL | 15 | 1 | 0.24 | 1 | 0.62 | 1 | 0.2 | 5 | 0.49 | 5 | 0.97 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| HEAVINESS CHEST | 14 | 0 | 0 | 1 | 0.62 | 1 | 0.2 | 4 | 0.4 | 3 | 0.58 | 2 | 0.87 | 3 | 1.36 | 0 | 0 | 0 | 0 |
| PAIN JAW | 13 | 0 | 0 | 1 | 0.62 | 1 | 0.2 | 3 | 0.3 | 3 | 0.58 | 1 | 0.44 | 0 | 0 | 0 | 0 | 3 | 0.6 |
| VISION ABNORM | 13 | 0 | 0 | 1 | 0.62 | 1 | 0.2 | 2 | 0.2 | 4 | 0.78 | 2 | 0.87 | 0 | 0 | 0 | 0 | 3 | 0.6 |
| URIN FREQUENCY | 12 | 2 | 0.48 | 0 | 0 | 1 | 0.2 | 1 | 0.1 | 3 | 0.58 | 4 | 1.75 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| PAIN BACK | 11 | 0 | 0 | 0 | 0 | 1 | 0.2 | 2 | 0.2 | 2 | 0.39 | 2 | 0.87 | 2 | 0.91 | 0 | 0 | 1 | 0.2 |
| POLYURIA | 11 | 1 | 0.24 | 0 | 0 | 1 | 0.2 | 2 | 0.2 | 1 | 0.19 | 3 | 1.31 | 2 | 0.91 | 0 | 0 | 1 | 0.2 |
| DREAM ABNORM | 8 | 3 | 0.72 | 0 | 0 | 1 | 0.2 | 0 | 0 | 2 | 0.39 | 0 | 0 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| YAWN | 8 | 0 | 0 | 0 | 0 | 1 | 0.2 | 2 | 0.2 | 2 | 0.39 | 2 | 0.87 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| INSOMNIA | 7 | 2 | 0.48 | 0 | 0 | 1 | 0.2 | 2 | 0.2 | 2 | 0.39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PAIN EAR | 6 | 1 | 0.24 | 0 | 0 | 1 | 0.2 | 2 | 0.2 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| HEMORR VAGINAL | 5 | 3 | 0.72 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| SPEECH DISORDER | 5 | 0 | 0 | 0 | 0 | 1 | 0.2 | 1 | 0.1 | 2 | 0.39 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AMBLYOPIA | 4 | 0 | 0 | 0 | 0 | 1 | 0.2 | 2 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| APPETITE INC | 3 | 0 | 0 | 1 | 0.62 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| HYPERVENTIL | 3 | 0 | 0 | 0 | 0 | 1 | 0.2 | 1 | 0.1 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| URIN URGENCY | 3 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 1 | 0.19 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| ATAXIA | 2 | 0 | 0 | 0 | 0 | 1 | 0.2 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BRONCHOSPASM | 2 | 0 | 0 | 0 | 0 | 1 | 0.2 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEMATEMESIS | 2 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LACRIMATION DISORDER | 2 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| VASODILAT | 2 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| VOICE ALTERAT | 2 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| DIARRHEA BLOODY | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EDEMA | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEMORR GUM | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEMORR UTER | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MENORRHAGIA | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PHOTOSENSITIVITY | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| RASH VESIC BULL | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SGPT INC | 1 | 0 | 0 | 0 | 0 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| VERTIGO | 61 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 1.48 | 6 | 1.17 | 10 | 4.37 | 17 | 7.73 | 0 | 0 | 13 | 2.58 |
| DYSPHAGIA | 41 | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 1.78 | 10 | 1.95 | 3 | 1.31 | 6 | 2.73 | 0 | 0 | 4 | 0.8 |
| PAIN THROAT | 28 | 1 | 0.24 | 0 | 0 | 0 | 0 | 9 | 0.89 | 4 | 0.78 | 3 | 1.31 | 6 | 2.73 | 1 | 4.76 | 4 | 0.8 |
| PRESSURE NECK | 19 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0.49 | 4 | 0.78 | 1 | 0.44 | 4 | 1.82 | 0 | 0 | 5 | 0.99 |
| SENSATION UNUSUAL UNSP | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0.59 | 3 | 0.58 | 1 | 0.44 | 0 | 0 | 0 | 0 | 4 | 0.8 |
| COORDINAT ABNORM | 13 | 2 | 0.48 | 0 | 0 | 0 | 0 | 3 | 0.3 | 1 | 0.19 | 1 | 0.44 | 5 | 2.27 | 0 | 0 | 1 | 0.2 |
| ANXIETY | 12 | 2 | 0.48 | 0 | 0 | 0 | 0 | 4 | 0.4 | 3 | 0.58 | 0 | 0 | 1 | 0.45 | 0 | 0 | 2 | 0.4 |
| HEAVINESS NECK | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0.49 | 4 | 0.78 | 0 | 0 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| HICCUP | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0.78 | 3 | 1.31 | 4 | 1.82 | 0 | 0 | 0 | 0 |
| SINUSITIS | 11 | 1 | 0.24 | 0 | 0 | 0 | 0 | 3 | 0.3 | 6 | 1.17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DEPRESSION | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.2 | 1 | 0.19 | 1 | 0.44 | 3 | 1.36 | 0 | 0 | 2 | 0.4 |
| EDEMA PERIPH | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0.3 | 4 | 0.78 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| MALAISE | 9 | 1 | 0.24 | 0 | 0 | 0 | 0 | 6 | 0.59 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.4 |
| EUPHORIA | 8 | 0 | 0 | 1 | 0.62 | 0 | 0 | 0 | 0 | 2 | 0.39 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 3 | 0.6 |
| AGITATION | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0.49 | 0 | 0 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| PAIN EYE | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0.49 | 0 | 0 | 2 | 0.87 | 0 | 0 | 0 | 0 | 0 | 0 |
| SALIVA INC | 7 | 1 | 0.24 | 0 | 0 | 0 | 0 | 2 | 0.2 | 1 | 0.19 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| ANOREXIA | 6 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0.78 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| UNEXPECTED BENEFIT | 6 | 0 | 0 | 1 | 0.62 | 0 | 0 | 1 | 0.1 | 2 | 0.39 | 0 | 0 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| ACCOMMODATION ABNORM | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 2 | 0.91 | 0 | 0 | 1 | 0.2 |
| EDEMA TONGUE | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 1 | 0.44 | 2 | 0.91 | 0 | 0 | 1 | 0.2 |
| ERYTHEMA | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 1 | 0.44 | 2 | 0.91 | 0 | 0 | 1 | 0.2 |
| HYPERKINESIA | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0.3 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| SLEEP DISORDER | 5 | 1 | 0.24 | 0 | 0 | 0 | 0 | 3 | 0.3 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUPOR | 5 | 1 | 0.24 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| HYPOTONIA | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| UNKNOWN | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EDEMA FACE | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| FLU SYND | 3 | 1 | 0.24 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HYPOTENS POSTURAL | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 1 | 0.44 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| INFECT URIN TRACT | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| INJURY ACCID | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| PAROSMIA | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| RASH | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 2 | 0.39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TONGUE DISORDER | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 2 | 0.67 | 0 | 0 | 0 | 0 | 0 | 0 |
| TOOTH DISORDER | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| APATHY | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| BRONCHITIS | 2 | 1 | 0.24 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EAR DISORDER | 2 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ERUCTAT | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| FEVER | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| HYPERTENS | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HYPOKINESIA | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 1 | 0.2 |
| MENS DISORDER | 2 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| MYDRIASIS | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| PLEURAL DISORDER | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 1 | 0.45 | 0 | 0 | 0 | 0 |
| PNEUMONIA | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| TWITCH | 2 | 1 | 0.24 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| VISUAL FIELD DEFECT | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AKATHISIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ARRHYTHMIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BILIRUBINEM | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| BREAST FBRCYST | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| CYANOSIS | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DIPLOPIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DYSTONIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EMOTION LABIL | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 |
| EXTRASYSTOLES | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| GAIT ABNORM | 1 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GI DISORDER | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4.76 | 0 | 0 |
| HEMATURIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEMOPTYSIS | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEMORR | 1 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HEPATITIS | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HYPOTENS | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HYPOTHERMIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JOINT DISORDER | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| LIVER TENDER | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| MIGRAINE | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 | |
| NAIL DISORDER | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 |
| NEOPL | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| NEUROSIS | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| PAIN BREAST | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 | |
| PAIN CHEST SUBSTRN | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.2 | |
| PAIN EARS | 1 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| PRESSURE JAW | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.44 | 0 | 0 | 0 | 0 | 0 | 0 | |
| QT PROLONGED | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| RECTAL DISORDER | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0 | 0 | 0 | 0 | |
| STOOL ABNORM | 1 | 1 | 0.24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| TETANY | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| THROMBOPHLEB | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| ULCER MOUTH | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| ULCER ST HEMORR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| URIN TRACT DIS | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| URTICARIA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4.76 | 0 | 0 | |

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# Appendix C - List of Tables and Figures

## Tables



## Figures