

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-231

MEDICAL REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name: ZOMIG - ZMT

Generic Name: zolmitriptan orally disintegrating tablets

Sponsor: AstraZeneca

Indication: 

NDA Number: 21-231

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Clinical Reviewers: Armando Oliva, MD

Review Author: Armando Oliva, MD

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1. Background

The NDA for Zomig tablets was approved for the acute treatment of migraine on 11/26/97. This new application contains information to support the approval of a new formulation of zolmitriptan, an orally disintegrating tablet. The application is provided in electronic format in accordance with the 1999 guidance document. I used these electronic documents for the primary review of the application.

2. Chemistry, Manufacturing and Controls

The formulation is an orally disintegrating tablet containing 2.5mg of zolmitriptan. The drug substance is identical to that contained in the approved zolmitriptan tablet. The orally disintegrating tablet is a round, white, and uncoated. They are ¼ inch in diameter (6.4mm), flat faced with a "Z" on one face and a beveled edge. The tablet is manufactured via a _____ . The manufacturing site is CIMA Labs, in Eden Prairie, MN. The tablets will be packaged into cartons at AstraZeneca in Newark, DE.

According to the sponsor, the tablets have shown good stability after 18 months storage at 30°C and 60% relative humidity and at 25°C and 60% relative humidity and 6 months storage at 40°C and 75% relative humidity.

The Division alerted the sponsor to a potential interaction between aspartame and zolmitriptan (such an interaction was observed between aspartame and rizatriptan in Merck's similar formulation). The sponsor then conducted forced degradation studies. They concluded that aspartame and its major degradation products are compatible with the formulation components.

The investigational formulation used for both the bioavailability study (088) and the efficacy study (107) was the same as the intended marketed formulation.

3. Animal Pharmacology & Toxicology

The application contains no new pre-clinical information and section 5 of the NDA (nonclinical pharmacology and toxicology) references the original Zomig tablet NDA.

4. Clinical Data Sources

The application contains the results from three human studies:

- 311CIL/0088
- 311CIL/0090
- 311CIL/0107

From this point forward, I refer to these three studies as 088, 090, and 107, respectively. Studies 088 and 090 are two PK studies. Study 088 compared the PK of the new formulation and the approved tablet in healthy volunteers. Study 090 compared the subject preferences and PK of two different flavors of the new formulation.

Study 088 demonstrated that the new formulation and the approved tablet shared similar C_{max} and AUC for both parent and active metabolite, but the T_{max} of the parent compound in the new formulation was delayed compared to the tablet (3 hours vs. 1.5 hours). Although an equivalent T_{max} is not normally considered necessary to demonstrate bioequivalence, in the acute treatment of migraine, this may be an important parameter. Therefore, we requested, and the sponsor conducted, a controlled efficacy study, which they did and is submitted as study number 107.

5. Human Pharmacokinetics

In the two PK and bioavailability studies conducted and submitted with this application (studies 088 and 090), zolmitriptan was given to healthy subjects in the fasting state. The orally disintegrating tablets were placed on the tongue and allowed to dissolve without chewing. They were then swallowed with saliva. The conventional tablets (used as control) were swallowed with a drink of water. The results of these studies are summarized below. For detailed reviews of these studies, I refer the reader to the clinical pharmacology / biopharmaceutics review.

Both studies used a single dose of 5mg (2 x 2.5mg tablets). This dose was chosen because the sponsor points out that it can be difficult to measure plasma concentrations of the active metabolite (n-desmethyl zolmitriptan) at doses below 5mg. The active metabolite generally is found at concentrations approximately 60% of parent and the assay is less sensitive for this molecule. Furthermore, there is extensive inter-subject variability.

Study 090 was a randomized, single-blind, crossover study that assessed the palatability of 2 flavors of zolmitriptan (— and orange). It was conducted in healthy male and female volunteers. The study also determined the PK of the 2 different formulations in the same volunteers (phase 2 of the study) by administering two separate oral doses of 5mg (2 x 2.5mg) zolmitriptan (coated or uncoated) on each trial day, in a randomized manner.

Study 088 was an open, randomized, 3-way crossover study to assess whether the two new orally disintegrating tablet formulations (— or uncoated) of zolmitriptan are bioequivalent to the conventional tablet. It was also conducted in healthy male and female volunteers. There was a washout of at least 48 hours between doses.

Blood samples were taken at protocol-designated intervals for up to 15 hours after dosing. Both parent and active metabolite levels were measured.

In study 090, both (— and orange formulations were well tolerated with regard to taste, and there was no overall preference for either flavor. Orange flavor was selected for further study, as this was considered the more commercially attractive. Both the — and uncoated formulations gave similar PK profiles.

In study 088, both the — and uncoated formulations were found to be bioequivalent with the commercial tablet with respect to C_{max} and AUC of both parent and n-desmethyl

metabolite. However, median T_{max} was later for the orally disintegrating tablets compared to commercial tablet (3 hours vs. 1.5 hours) for the parent drug. T_{max} for the active metabolite was similar at 3 hours for both orally disintegrating tablet. and commercial tablet.

The sponsor argued that the small delay seen in T_{max} of parent was unlikely to be of any clinical significance given that the rapid rise in zolmitriptan plasma concentrations with the orally disintegrating tablets was similar to that seen with the conventional oral tablet. We requested they perform a clinical efficacy trial to confirm this hypothesis. I review the results of that study below.

6. Study 107

6.1 Protocol

This was an international, randomized, placebo-controlled, double blind study to evaluate the efficacy and tolerability of Zomig 2.5mg orally disintegrating tablet in the acute treatment of adult patients experiencing a single migraine.

The study intended to treat approximately 380 migraineurs in approximately 45 centers in Canada, South Africa, and the UK. Patients had to be males and non-pregnant females 18-65 years old with established diagnosis of migraine with or without aura (IHS criteria), age of onset less than 50 years, and migraine frequency at least 1 per month for the previous three months. Those with a history of basilar, ophthalmoplegic, or hemiplegic migraine were excluded, as were those with a history of any serious medical illness (including heart disease, hypertension, severe hepatic impairment). Not allowed during the study was the use of MAO A inhibitors, methysergide, or methylergonovine within 2 weeks. Not allowed within 24 hours of study medication were any 5HT_{1B/1D} agonists or ergot medication. Not allowed within 12 hours were any opiates. Not allowed within 6 hours were any analgesics.

After an initial screening visit, patients took a single 2.5mg zolmitriptan orally disintegrating tablet or placebo for the treatment of an acute moderate or severe migraine in an outpatient setting. A second 2.5mg dose was permitted after 2 hours for persistent pain. Rescue was also permitted 2 hours after study medication. A follow-up visit was to take place as soon as possible after treatment, but no later than 2 weeks. Those who did not treat a migraine within 6 weeks after screening were withdrawn from the trial.

The primary endpoint was the proportion of patients achieving a headache response at 2 hours (i.e., the 2-hour headache response rate). Response was defined as in previous studies: the presence of a mild or no headache in a patient who had a moderate or severe headache at baseline. Secondary endpoints included:

- response rates at 0.5, 1, and 4 hours
- ~~pain-free~~ rates at 1, 2, and 4 hours
- proportion achieving a one point decrease in migraine rating scale (defined as none, mild, moderate, severe) at 0.5 and 1 hour
- patient preference of orally disintegrating tablets vs. normal tablets

Safety monitoring included the incidence and nature of adverse events.

All endpoints except patient medication preference and incidence, intensity, seriousness, and relationship of AE's were formally analyzed by a logistic regression model (with terms for treatment group, center, and baseline intensity) using PROC LOGISTIC in SAS. Results were presented in terms of odds ratios with 95% confidence intervals and p-values using data from the intent-to-treat (ITT) population who treated a moderate or severe headache at baseline. Patients who took a 2nd dose or rescue were considered treatment failures for all assessments after the second treatment. All patients who received at least a single dose of study medication were included in the descriptive safety analysis.

6.2 Study Population

A total of 573 patients were randomized and 471 patients received at least one dose of study medication.¹ Of these, 231 received zolmitriptan and 240 received placebo. One patient randomized to placebo took study medication and then withdrew consent and did not have any post-dose efficacy assessment. Therefore, this patient was excluded from the intent-to-treat (ITT) population.

The ITT population therefore consisted of 231 patients who took zolmitriptan and 239 patients who took placebo. The per-protocol population consisted of 450 patients: 219 on zolmitriptan and 231 on placebo (Table 1, adapted from study report il107.pdf, page 34).

Table 1: Study 107 – Study Population

Population	Zolmitriptan 2.5mg	PBO	Total
Randomized	291	282	573
Treated	231	240	471
Intent-To-Treat	231	239	470
Per-Protocol	219	231	450

The demographic characteristics of the treated population are shown in Table 2 (sponsor Table 3, il0107.pdf, page 27). Approximately 87% were female, which is typical of adult migraine studies of this type. The mean patient age was 41 in the zolmitriptan group and 42 in the placebo group. Ninety-seven percent (97%) were Caucasian, and the mean weight and height were 70kg and 165cm, respectively.

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¹ The planned sample size was 380. The sponsor states that over-enrollment occurred, in part, because of delayed recruitment at some sites that resulted in excessive enrollment near the end, and by noncenter-specific labeling of trial medication that allowed centers to recruit more than the expected number of patients.

Table 2: Study 107 – Demographics

Characteristic	Zolmitriptan 2.5mg n=231	PBO n=239
Age (y)		
Mean	41	42
SD	9.9	10.2
Range	18 - 62	18 - 62
Age distribution; number (%)^a of patients		
18 to 39 y	98 (42)	90 (38)
40 to 65 y	133 (58)	149 (62)
Sex; number (%)^a of patients		
Male	27 (12)	33 (14)
Female	204 (88)	206 (86)
Weight (kg)		
Mean	70	70
SD	15.1	16.0
Range	41 - 125	42 - 164
Height (cm)		
Mean	165	165
SD	8.9	8.4
Range	142 - 192	145 - 189
Race; number (%) of patients		
Caucasian	223 (97)	231 (97)
Other ^b	8 (3)	8 (3)

SD standard deviation

^a percentages based upon the number of patients in the ITT population

^b others include Afro-Caribbean, Asian, Oriental, Mixed, and not otherwise classified.

Table 3 (adapted from sponsor table 4, il0107.pdf, page 30) summarizes the baseline headache characteristics of the ITT population. Approximately 70% of patients reported treating a moderate pain at baseline. About a quarter of patients had an aura. Slightly over half experienced nausea. Approximately 80% had photophobia and a lower percentage (62% for zolmitriptan and 82% for placebo) had phonophobia at baseline. All characteristics were reasonably balanced between the two groups with the exception of phonophobia at baseline, which was more common in the placebo group.

Table 3: Study 107 – Baseline Headache Characteristic

	Zolmitriptan 2.5mg n=231	PBO n=239
Headache pain at baseline		
Mild	1 (<1)	0 (0)
Moderate	167 (72)	168 (70)
Severe	63 (27)	71 (30)
Aura at baseline; number (%) of patients		
Yes	52 (23)	56 (24)
No	172 (77)	180 (76)
Nausea at baseline; number (%) of patients		
Yes	128 (56)	130 (54)
No	100 (44)	109 (46)

	Zolmitriptan 2.5mg n=231	PBO n=239
Photophobia at baseline; number (%) of patients		
Yes	179 (78)	195 (82)
No	51 (22)	44 (18)
Phonophobia at baseline; number (%) of patients		
Yes	143 (62)	167 (70)
No	88 (38)	70 (30)

Number of patients with response may be less than total number of randomized patients

One-hundred two (102) patients withdrew from the study before treating a migraine: 60 in the zolmitriptan and 42 in the placebo group.

No patient was excluded from the efficacy analysis because of a major protocol violation. Twenty patients were excluded from the per-protocol analysis because of major protocol violations: 12 in the zolmitriptan and 8 in the placebo groups. Twelve (12) missed assessments due to sleep, 5 were not free from headache pain 24 hours after their last attack, two took their first and second doses simultaneously, and one treated a mild headache at baseline.

6.3 Efficacy Results

The main efficacy results are summarized in Table 4 (sponsor table 1, il0107.pdf, page 9). The two hour headache response rates were 63% for zolmitriptan and 22% for placebo. This difference was highly significant at $p < 0.0001$.

Table 4: Study 107 – Summary of Efficacy Results

Time (hr)	Zolmitriptan (n=231)		PBO (n=239)		Odds ratio	95% CI	p-value
	N	Resp n(%) ^a	N	Resp n(%) ^a			
Headache Response							
0.5	227	36 (16)	237	23 (10)	1.7	1.0, 3.1	0.0538
1	224	101 (45)	232	45 (19)	3.5	2.3, 5.3	<0.0001
2 ^b	220	138 (63)	236	53 (22)	6.1	4.0, 9.3	<0.0001
4	226	115 (51)	239	34 (14)	6.3	4.0, 9.8	<0.0001
Pain-Free							
0.5	228	3 (1)	237	1 (<1)	NC	NC	NC
1	225	17 (8)	232	6 (3)	3.1	1.2, 7.9	0.0207
2	221	59 (27)	236	17 (7)	4.7	2.6, 8.4	<0.0001
4	227	84 (37)	239	26 (11)	4.9	3.0, 8.0	<0.0001
Improved Headache							
0.5	228	51 (22)	237	36 (15)	1.7	1.0, 2.7	0.0385
1	225	115 (51)	232	67 (29)	2.7	1.8, 3.9	0.0001
2	221	146 (66)	236	70 (30)	NC	NC	NC
4	227	117 (52)	239	40 (17)	NC	NC	NC

^a percentages based on total number of patients in the ITT population reporting at each time interval

^b Primary efficacy parameter

CI confidence interval

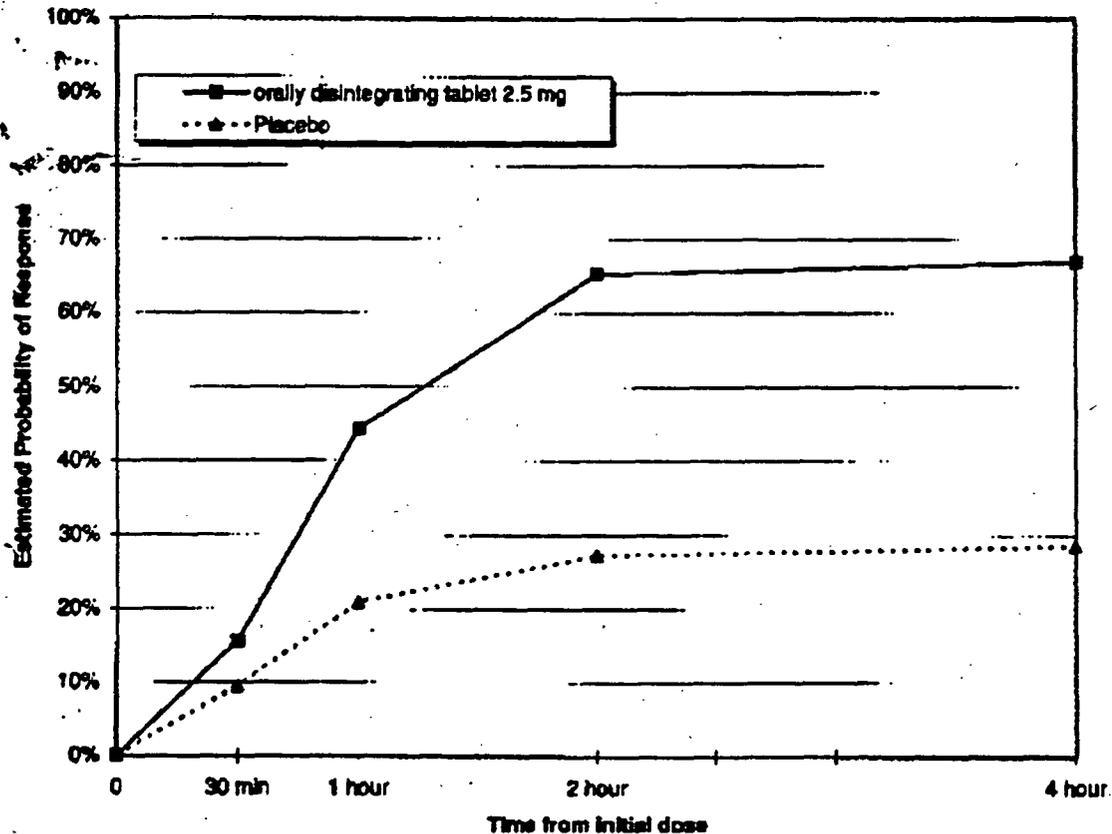
NC not calculated

Pain-free rates at 2 hours were also in favor of drug (27% vs. 7%, $p < 0.001$), as were response rates at 1, 4 hours, pain-free rates at 4 hours, and improved headache rates at 1

hour (p values were not calculated for the latter at 2 and 4 hours although the percentages were numerically also in favor of drug).

The estimated probability of achieving a response within 4 hours is shown in Figure 1 (Kaplan-Meier method, sponsor figure 2, il0107.pdf, page 37). It shows that patients treated with zolmitriptan 2.5mg had a greater probability of achieving a headache response within 4 hours, compared to placebo.

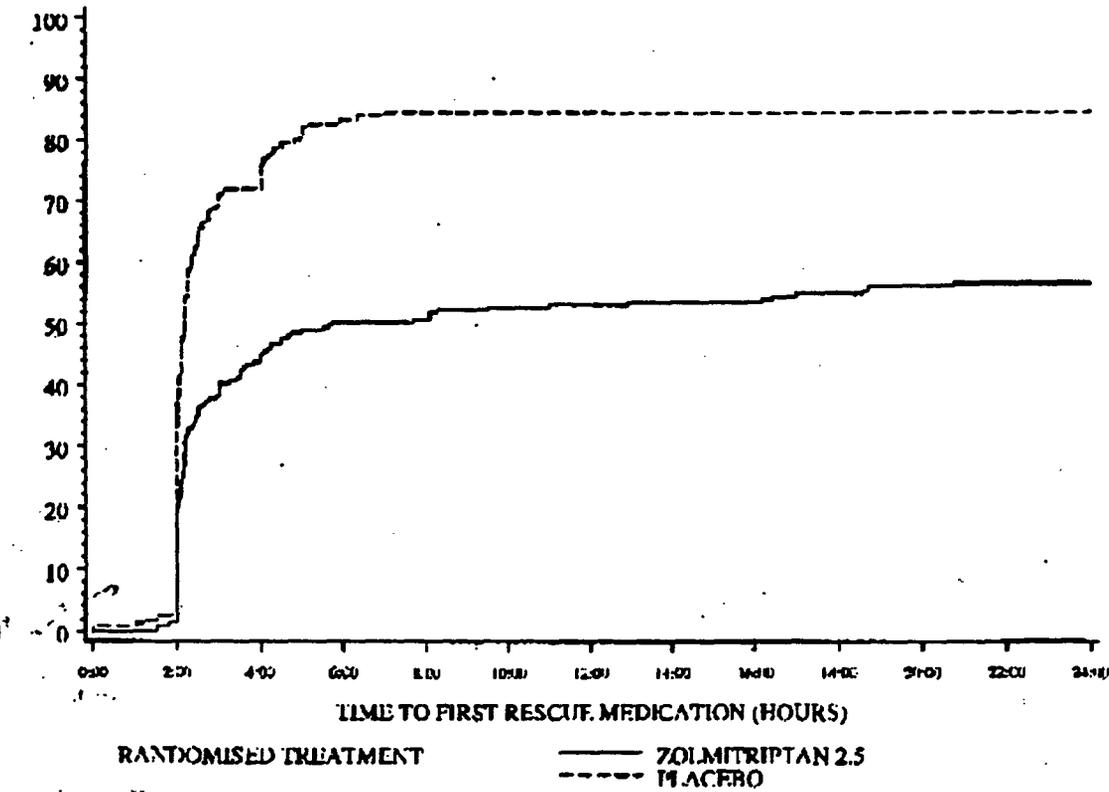
Figure 1: Study 107 – Estimated Probability of Achieving a Headache Response



One hundred forty-nine (149, or 65%) of the 231 patients in the ITT population randomized to zolmitriptan took only 1 tablet vs. 99 (41%) of patients randomized to placebo. The percentage who took two tablets were 35% for zolmitriptan and 59% for placebo. Of those who took only one tablet, 33% of zolmitriptan patients took rescue, vs. 64% of placebo patients who took rescue. Of those who took 2 tablets of study medication 24% of zolmitriptan patients took rescue, vs. 51% of placebo patients.

The estimated probability of needing a second treatment (either second dose or rescue) is shown in Figure 2 (Kaplan-Meier method, sponsor figure 3, il0107.pdf, page 40). Patients treated with zolmitriptan 2.5mg had lower probabilities of needing a second treatment, compared to placebo.

Figure 2: Study 107 – Estimated Probability of Remedication



Headache response rates at 2 hours were summarized by age group, gender, menses, weight group, intensity of headache pain at baseline, pre-treatment headache duration, migraine onset while waking or sleeping, baseline aura, baseline nausea, baseline photophobia, and baseline phonophobia. No significant differences in headache response between subgroups were observed except for baseline intensity and baseline photophobia. These are summarized in Table 5 (adapted from sponsor tables T21.1 through T21.11, il0107.pdf, pages 116-126).

Table 5: Study 107 – Two-Hour Response Rates in Various Subgroups

Subgroup	Zolmitriptan 2.5mg (%)	PBO (%)
Aura		
Present	62.5	28.6
Not Present	63.0	20.9
Menses		
Present	57.1	21.1
Not Present	62.2	23.4
Sex		
Female	61.7	23.2
Male	70.4	18.2
Age		
18-39	58.9	24.4
40-65	65.4	21.2

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Subgroup	Zolmitriptan 2.5mg (%)	PBO (%)
Baseline Nausea		
Present	59.3	17.8
Absent	67.4	28.0
Baseline Intensity		
Moderate	68.1	25.3
Severe	48.3	15.7
Migraine on Awakening		
Yes	62.2	21.6
No	63.5	23.4
Weight		
<50kg	60	12.5
50-80kg	62.2	20.1
>80kg	66.0	30.5
Baseline Photophobia		
Present	58.7	22.9
Absent	76.6	20.5
Baseline Phonophobia		
Present	59.3	18.7
Absent	68.2	30.9
Untreated Migraine Duration		
0-30 min	53.8	22.6
<30 min - 1 hr	56.5	34.2
>1 - 2 hrs	59.6	19.1
>2 - 4 hrs	69.2	20.3
>4 hrs	78.3	16.7

6.4 Reviewer's Efficacy Analysis

The sponsor submitted the efficacy data. It contained information on all 573 randomized patients. I removed all records for patients who failed to take study medication (n=102). This modified dataset contained efficacy data on 471 patients (zolmitriptan=231, placebo=240). One patient who took placebo (ID 0505, 48 year old female) did not record any post-treatment efficacy data. I removed her from the analysis. This resulted in 470 patients available for analysis in the ITT population (zolmitriptan=231, placebo=239), exactly the number described in the sponsor's ITT analysis.

The pain assessment scores at time points 0.5-4 hours were recorded in the variable PAINASSA. The baseline pain scores were recorded in the variable PAINBASE. There was one patient (ID 0851, 30F who took zolmitriptan 2.5mg) who treated a mild pain at baseline. All other patients treated a moderate or severe pain at baseline. I considered this patient a non-responder at all future time points since the definition of a response requires that the pain be moderate or severe at baseline.²

² As it turns out, this patient's pain increased at 0.5-4 hours to moderate. Therefore, she would not have been classified as a responder in any case at any of those time points, even if she had treated a moderate/severe pain at baseline.

The distribution of missing pain scores 0.5 – 4 hours is shown in Table 6. There were 27 missing pain scores (12 in the zolmitriptan group and 15 in the placebo group). Whenever possible, I used a post-treatment last observation carried forward approach to impute missing pain assessment scores.

Table 6 (RA): Study 107 – Missing Pain Scores in the ITT Population

Scheduled Time Point (hr)	Missing	Zolmitriptan 2.5mg	PBO
0	0	0	0
0.5	1	0	1
1	4	1	3
2	5	2	3
4	17	9	8
All	27	12	15

Using this approach, I was able to impute all but 3 of the missing scores (one each at 0.5, 1, and 2 hours – all on placebo). I defined a response at each time point using the traditional definition. A headache response was defined as a moderate or severe headache at baseline and a mild or no headache at the specified time point.

The headache response rates at 0.5-4 hours are shown in Table 7. The p-values shown are merely descriptive, as I did not perform the protocol specified analysis, which was logistic regression. I refer the reader to the statistical review for their analysis. At two hours, the response rates were 64% for zolmitriptan 2.5mg and 24% for placebo. I point out that this analysis does not take into account the use of remedication (either a second dose or rescue).

Table 7 (RA): Study 107 – Headache Response Rates Regardless of Remedication

Time Point (hr)	Zolmitriptan 2.5mg	PBO	p-value*
0.5	37/231 (16%)	24/239 (10%)	0.056
1	102/231 (44%)	47/239 (20%)	<0.0001
2	147/231 (64%)	57/239 (24%)	<0.0001
4	177/231 (77%)	86/239 (36%)	<0.0001

* Fisher's exact test

In Table 8, I modified the definition of a responder to add the additional requirement that the patient did not remedicate prior to the assessment in order to be classified as a responder. My numbers are very similar to the sponsor's analysis, which I present below for comparison. They very clearly support the efficacy of the formulation.

Table 8 (RA): Study 107 – Headache Response Rates¹

Time Point (hr)	Zolmitriptan 2.5mg	PBO	p-value*
0.5	37/231 (16%)	24/239 (10%)	0.056
1	102/231 (44%)	47/239 (20%)	<0.0001
2	147/231 (64%)	55/239 (23%)	<0.0001
4	119/231 (52%)	34/239 (14%)	<0.0001

¹ a patient who re-medicated (either 2nd dose or rescue) prior to the assessment is counted as a non-responder in this analysis
 * Fisher's exact test

(sponsor's analysis, from Table 4, page 8)

Time (hr)	Zolmitriptan (n=231)		PBO (n=239)		Odds ratio	95% CI	p-value
	N	Resp n(%) ^a	N	Resp n(%) ^a			
Headache Response							
0.5	227	36 (16)	237	23 (10)	1.7	1.0, 3.1	0.0538
1	224	101 (45)	232	45 (19)	3.5	2.3, 5.3	<0.0001
2	220	138 (63)	236	53 (22)	6.1	4.0, 9.3	<0.0001
4	226	115 (51)	239	34 (14)	6.3	4.0, 9.8	<0.0001

The sponsor did not analyze the associated migraine symptoms of nausea, photophobia, and phonophobia, although these symptoms were captured in the case report form. I performed my own analysis of these symptoms at baseline and at two hours. Because there were so few missing assessments for each parameter across all time points recorded (15 for nausea, 12 for photophobia, and 16 for phonophobia), I did not use any imputation algorithm for missing scores. The results are shown in Table 9. There was a baseline imbalance with regard to phonophobia—a higher percentage of placebo patients had this symptom at baseline compared to drug. This is an imbalance which the sponsor has already recognized and reported (Table 3, page 7). At two hours, zolmitriptan was associated with nominally significant lower incidences of all three migraine associated symptoms, compared to placebo (this was true even when the 2-hour phonophobia analysis was stratified by baseline phonophobia). I conclude that zolmitriptan orally disintegrating tablet is effective for the acute treatment of migraine.

Table 9 (RA): Study 107 – Incidence of Migraine Associated Symptoms

Symptom	Zolmitriptan 2.5mg	PBO	p-value*
Baseline			
Nausea	128/228 (56%)	130/239 (54%)	0.711
Photophobia	179/230 (78%)	195/239 (82%)	0.311
Phonophobia	143/231 (62%)	167/237 (70%)	0.051

Symptom	Zolmitriptan 2.5mg	PBO	p-value*
Two-Hours			
Nausea	70/229 (31%)	104/238 (44%)	0.004
Photophobia	98/229 (43%)	153/238 (64%)	<0.0001
Phonophobia	68/229 (30%)	132/238 (55%)	<0.0001#

* Fisher's exact test unless otherwise stated; # this p-value is Cochran-Mantel-Haenszel test stratified by baseline phonophobia.

6.5 Safety Results

Twenty percent (20% or n=92) of the 471 patients exposed to study medication reported at least one adverse event (n=63 or 27% in the zolmitriptan group vs. n=29 or 12% in the placebo group). The majority of adverse events were mild or moderate in intensity.

There were no deaths within 30 days of study conclusion. No patient was withdrawn due to an adverse event, although the opportunity to withdraw was quite limited in this single attack study.

There were two serious adverse events reported in two patients. Neither occurred within 24 hours of dosing. One patient reported moderate myalgia 6 days after treating a migraine with zolmitriptan after falling from a tree, and one patient was hospitalized with moderate abdominal pain 16 days after treatment with placebo. Neither of these events was considered related to study treatment by the investigator.

The most frequently reported adverse events (>2%) were asthenia, tightness, somnolence, dizziness, paresthesia, hyperesthesia, pharyngitis, and nausea. Those occurring with more frequency in the zolmitriptan group (compared to placebo) were asthenia, tightness, dizziness, hyperesthesia, and pharyngitis. Those receiving zolmitriptan were more likely to report moderate adverse events compared to placebo (13% vs. 2%). The incidence of mild AE's were 11% and 6%, respectively, and the incidence of severe AE's were 3% and 4%, respectively. The most commonly reported adverse events are shown in Table 10 (sponsor table 16, il0107.pdf, page 47).

Table 10: Study 107 – Adverse Events Incidence Table (>2%)

	Zolmitriptan N=231		PBO N=240	
	N	%	N	%
at least 1 adverse event	63	27	29	12
Body as a whole				
Asthenia	8	3	3	1
Tightness	8	3	1	<1
Digestive				
Nausea	5	2	3	1

	Zolmitriptan N=231		PBO N=240	
	N	%	N	%
Nervous				
Dizziness	6	3	2	1
Hyperesthesia	5	2	0	0
Paresthesia	6	3	4	2
Somnolence	7	3	4	2
Respiratory				
Pharyngitis	5	2	0	0

6.6 Sponsor's Conclusion

- Zolmitriptan 2.5mg orally disintegrating tablet showed significantly greater efficacy than placebo (2-hr headache response rate 63% vs. 22% for placebo)
- The safety and tolerability was consistent with that previously described for the conventional oral tablet: asthenia, tightness, dizziness, hyperesthesia, and pharyngitis occurred more frequently among patients randomized to zolmitriptan relative to placebo.
- Overall, zolmitriptan 2.5 mg orally disintegrating tablets are safe and effective in the treatment of acute migraine in adults. It is expected that the widespread use of the orally disintegrating tablet formulation of zolmitriptan will not differ from that of the conventional oral tablet.

7. Labeling Review

The sponsor provides one professional labeling for both zolmitriptan tablets and orally disintegrating tablets. It is, therefore, similar to the labeling currently approved for rizatriptan (MAXALT) and the approach is acceptable. The draft labeling originally did not contain approved changes to labeling, as a result of the approval of the labeling supplement S-003, dated (approval letter dated 5/1/2000) since this supplement was approved after the NDA was submitted.³ The sponsor subsequently submitted draft labeling that included these changes (in a Word file with date stamp 9/20/2000).

7.1 Description

This section contains modifications to the tablet description, and the new description of the ZMT formulation. I have no comments and defer to the chemistry review for any recommended changes to this section.

7.2 Clinical Pharmacology: Clinical Pharmacokinetics and Bioavailability

The sponsor has rewritten this section to adopt the ADME format. It also includes PK information of the ZMT formulation. I have no comments and defer to the biopharmaceutics review for any recommended changes to this section.

7.3 Clinical Pharmacology: Clinical Studies

This section now contains efficacy information from study 107. It is included at the end of the section, similar to rizatriptan labeling. I recommend minor editorial changes to their text, in order to more closely resemble the approved rizatriptan labeling, which I use

³ S-003 strengthened the labeling with regard to cardiovascular safety, as a result of post-marketing reports.

as a template. Furthermore, I recommend they alter their Kaplan-Meier time to response figure from a 4-hour interval to a 2-hour interval (as was done for rizatriptan, since the time interval 2-4 hours is confounded by the use of rescue and/or a second dose).

Specifically, I recommend the following revision to their proposed text:

ZOMIG-ZMT Orally Disintegrating Tablets

The efficacy of ZOMIG-ZMT 2.5 mg was demonstrated in a randomized, placebo-controlled trial that was similar in design to the trials of ZOMIG Tablets. Patients were instructed to treat a moderate to severe headache. Of the 471 patients treated in the study, 87% were female and 97% were Caucasian, with a mean age of 41 years (range 18-62).

At 2 hours post-dosing, response rates in patients treated with ZOMIG-ZMT 2.5 mg was 63% compared to 22% in the placebo group. This difference was statistically significant. The estimated probability of achieving an initial headache response by 2 hours following treatment with ZOMIG-ZMT Tablets is depicted in Figure 3.

Since the tablet portion of labeling also displays a 0-4 hour time point in the corresponding Kaplan-Meier graph, I recommend that figure also be modified to show only 0-2 hours. The reason behind this change is that the 2-4 hour time interval is confounded by the use of rescue medication and/or a second dose (as specified by protocol). We have restricted similar figures in other recent triptan labeling to include only time intervals where remedication was not permitted (i.e., 0-2 hours).

7.4 Warnings, Precautions

The sponsor recommends adding a statement to the precautions section alerting phenylketonurics that the ZMT formulation contains phenylalanine. It also describes how to handle the ZMT formulation in order to maintain potency. I agree with these changes.

7.5 Adverse Events

This section contains a statement that the adverse events seen with the ZMT are similar to those seen with the tablet. I agree with that comment. Rizatriptan labeling contains a

similar statement. I don't see the need to include a separate AE table for the ZMT formulation. I also add additional changes as recommended in my 11/2/99 review.

7.6 Dosage and Administration

This section includes editorial changes to describe which instructions pertain specifically to the conventional tablet. It also contains instructions on taking the ZMT formulation. I agree with the proposed changes and they are similar to what is contained in currently approved rizatriptan labeling.

7.7 How Supplied, Patient Information

This section now contains information about the ZMT formulation. I agree with the comments.

8. Conclusions

From the data presented, zolmitriptan 2.5mg orally disintegrating tablet appears to be both safe and effective for the acute treatment of migraine in adults.

9. Recommendations

From a clinical standpoint, I recommend approval of the NDA, with the recommended changes in labeling as described above.

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Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. _____

ao 1/10/01
cc:
HFD-120
NDA 21-231

**APPEARS THIS WAY
ON ORIGINAL**