CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20768

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: November 21, 1997
From: Randy Levin, M.D., Neurology Team Leader
Subject: Zolmitriptan (NDA 20-768)
To: File

Background:

Prior to an approval action, Dr. Temple and Dr. Leber requested that the sponsor provide a safety update. Specifically, they wanted an update for all deaths and serious adverse events. The sponsor supplied an update that included an accounting of all deaths, serious adverse events and discontinuations from adverse events up to a cut off date of 7/7/97.

Studies covered under the safety update:

Since submission of the NDA, the sponsor has initiated 13 clinical trials. This includes 8 single dose clinical pharmacology studies, one long term open label safety study and 4 patient treatment studies. No safety data was presented for the 4 patient treatment studies since they were ongoing and blinded. The clinical pharmacology studies were single dose and among the 138 subjects enrolled in these studies, there were no discontinuations or serious adverse events reported. The safety update will focus on the long term safety study. This study supports the long term data provided in study 015 that was included in the original NDA.

Study 043:

Design: In the long term safety study, 311CIL/00043, patients treated their first attack with 2.5 mg. If pain persisted, patients were randomized to placebo, 2.5 or 5 mg. Subsequent attacks could be treated with 2.5 or 5 mg.

Exposure and demographics: A total of 2800 patients treated at least one headache. The demographic of the patients in this study was similar to that seen in the other migraine trials.

Deaths: There have been no deaths reported in patients who have been exposed to the drug in any of the trials.

Discontinuations for adverse events: 135 of the 2800 (5%) patients who treated at least one headache discontinued for adverse events. This compares to the 8% discontinuation rate seen with patients in study 015 described in labeling. The most common adverse events leading to discontinuations, dizziness, asthenia, heaviness, somnolence, were similar to those seen in study 015.

Serious adverse events: There were a total of 43 of 2800 patients (1.5%) who reported serious

adverse events. The types of adverse events and the frequency of adverse events were similar to that seen in study 015. As in study 015, most serious adverse events occurred only once and only on occasion, twice. A single case of increased LFTs was reported. This was a 36 year old female who had treated 17 headaches with 37 tablets over one month. She was also on Paxil, Migranal, Fiorinal, Dalmane, Estraderm, Flexeril, Xanax and DHE. She complained of nausea and vomiting and was diagnosed with gastritis. She also complained of right abdominal pain. A work up was negative. Treatment with zolmitriptan was discontinued on April 29th and on April 30th the LFTs were normal. On May 2nd, there was a slight elevation of the ALT and by May 3rd, the ALT peaked at 225 (6 times the ULN). The bilirubin had peaked one day earlier at 20 (normal 0 to 17). The AST was 183 and the ALK PHOS was 315 (upper limit of normal was 280). By May 16th all LFTs were normal except for an ALK PHOS of 116 with a normal range of 31 to 110). Work up was positive for gastritis which was thought to be related to non steroidal anti inflammatory drugs (Fiorinal).

Most common adverse events:

The common adverse event profile in study 043 was similar to that seen in study 015 and in the controlled clinical trials.

Foreign Labeling:

The sponsor also supplied the labeling approved by the Swedish authorities. There were no new contraindications or warnings. There was one new drug interactions reported. For patients on cimetidine, there was an approximately doubling of the AUC and half life of zolmitriptan and the active metabolite following a 5 mg dose. In this labeling, a maximum dose of 5 mg a day was recommended. The labeling states that an interaction with specific inhibitors of CYP 1A2 cannot be excluded and a dosage reduction was recommended with compounds of this type such as fluvoxamine and the quinolones.

After talking with Dr. Baweja and Dr. Tammara, I asked the sponsor to send in the summary report for the interaction study. They reviewed the summary report and concluded that the study was adequate by design to assess the interaction with cimetidine. They recommended that the increase in half life and AUC be added to the drug interaction section of the clinical pharmacology and precautions sections. Dr. Tammara and Dr. Baweja felt that it was not clear which isoenzyme inhibition was responsible for the interaction so the statement regarding an interaction with the specific CYP 1A2 inhibitors was not recommended at this time.

Recommendations:

The safety update did not provide any clear indication of a change in the safety profile for the drug as seen in the NDA and provided in the labeling. The interaction with cimetidine can be added to labeling.

Randy Levin, M.D.
Neurology Team Leader
rl/November 24, 1997

Temple

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 12, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Zomig (zolmitriptan)

TO: File NDA 20-768
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

Introduction

This memorandum conveys my endorsement of the Division review team's recommendation that Zeneca Pharmaceuticals' NDA 20-768, which allows for the use of Zomig (zolmitriptan, aka 311C90) tablets (2.5 mg and 5.0 mg) in the management of acute migraine headaches, be declared approvable. This recommendation is conditioned upon the firm's capacity to meet and/or to agree to the requirements enumerated in the approvable action letter with attached draft labeling being forwarded to the Office for issuance.

Dr. Randy Levin, who heads the Neurology subunit responsible for anti-migraine drug products, provides a more detailed exposition (his 10/27/97 approvable action memorandum) of the information and argument that support the proposed approvable action.

Dr. Levin has lead the negotiations with the firm regarding the form and content of product labeling. The labeling attached to the approvable action letter is presumably acceptable to the sponsor.

The User Fee goal date for this non-priority review ("S") NDA is November 26, 1997.

Zolmitriptan is one of several anti-migraine drug products that share a common set of risks and benefits

Zolmitriptan's capacity to reduce the duration of acute migrainous attacks presumably is mediated through its high affinity binding to 5HT1d and 5HT1b receptors located on intracranial blood vessels and/or sensory neurons innervating the dura. Zolmitriptan's binding to the former presumably leads to the constriction of abnormally dilated vessels (including, in particular, arterio-venous anastomoses); its binding to sensory neurons presumably blocks the release of inflammatory, pain inducing substances.

Several marketed (e.g., Imitrex {sumatriptan}, DHE {dihyroergotamine}), and investigational (e.g., ...) anti-migraine drug products possess nearly identical pharmacologic actions and exhibit (or would be expected to exhibit), clinical benefit and risk profiles that are very similar to those of zolmitriptan.

Although the set of controlled clinical trials necessary to provide a valid assessment of the comparative risks and benefits of all anti-migraine products does not exist, the Division has concluded that there is sufficient theory, preclinical experimental results, and uncontrolled clinical findings to justify treating all anti-migraine drugs with high affinity binding and agonist activity at 5HT1d and 5HT1b receptors as members of a common pharmacological class.

Generic anti-migraine drug product labeling statements apply to Zolmitriptan

Based upon its conclusion that drugs with similar affinities for and actions at 5HT1d and 5HT1b receptors belong to a common pharmacologic/therapeutic class, the Division takes the position that an anti-migraine drug product with these attributes must carry a number of generic statements that apply to all members of the drug class.

Specifically, an anti-migraine drug product of the kind identified would, in the Division's view, <u>be unsafe for use</u> if it were marketed under

product labeling that fails to provide generic statements warning and/or cautioning about the untoward events that are known to be, or are likely to be, associated with the use of drugs within the putative class.

Because of the potential for the numerical values reported in clinical investigations of anti-migraine drug effects (e.g., percent subjects pain free, etc.) to be misunderstood and/or misrepresented, the Division takes the view that an anti-migraine drug product will be misbranded if its labeling fails to advise that the data adduced in controlled clinical investigations of the drug product cannot be validly compared with that adduced in trials of other anti-migraine drug products. Toward that goal, I crafted the following statement that I propose be included in the Clinical Trials section of all antimigraine drug products.

> "Comparisons of drug performance based upon results obtained in different clinical trials are always of arguable validity and reliability. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study. Accordingly, estimates of treatment effects obtained from a single study or small series of studies have limited value as estimates of the likely effect of a drug in the population as a whole. "

The statement is similar in intent, structure, and argument to that which appears in the introductory paragraph of the ADR section of product labeling of virtually every neurological or psychiatric drug that has been approved for marketing over the last two decades.

Zolmitriptan specific issues

Preclinical Findings

The primary pharm/tox reviewer assigned to the NDA, Dr. John Jessop, has provided written reviews of both the original zolmitriptan IND (6/10/94) and Zomig NDA (9/12/97). Dr. Jessop concludes (see, in particular, pages 186 to 189 of his voluminous and comprehensive review) that zolmitriptan has been adequately evaluated in all tests required to assess it preclinical pharmacology and toxicology, and, in his view, no findings suggest that zolmitriptan is unsafe for use.

Dr. Jessop does recommend, however, that certain preclinical test findings be mentioned in product labeling. (i.e., binding to Melanin-Containing tissues, thyroid follicular cell adenoma in male rats in the life-time CA test, the positive human lymphocyte clastogenicty assay , the positive Ames Test, and the excessive fetal resorptions in rat and rabbit teratogenicity studies.).

Dr. Fitzgerald, the Team leader for Pharmacology, endorses Dr. Jessop's conclusion (her memorandum of 9/25/97) that the NDA be declared approvable under the labeling recommended by Dr. Jessop. Dr. Fitzgerald also provided draft text for sections of the labeling relevant to pharm tox. In agreement with Dr, Jessop, she recommends that the drug be classified as Pregnancy Category C. I agree.

Biopharmaceutics.

Dr. V.K. Tammara conducted the primary biopharm review (9/10/97) for OCPB. OCPB deems the application approvable provided Zomig is marketed under labeling conforming to OCPB's recommendations.

About 40% of an orally administered dose of zolmitriptan becomes systemically bioavailable. The Cmax occurs at about 2 hours. Sex may affect peak levels, but this might be weight related.

Cmax as a function of dose and Sex

Dose administered	Sex	C_{max} ng/ml
2.5 mg	female	~ 4 +/- 2
2.5 mg	male	~ 3.5 +/- 1
5 mg	female	~ 10 +/- 3
5 mg	male	~ 6 +/- 2

Feeding reduces the extent of absorption, lowers Cmax and delays Tmax. In the midst of an acute migraine episode, the extent of absorption and Cmax are reduced and Tmax is delayed.

Protein binding is about 25% and not affected by plasma concentration. Mean apparent Volume distribution is about 7 L/kg

Zolmitriptan is metabolized to 3 major metabolites; one, 183C91, an N-desmethylated metabolite, is 2 to 6 fold more active (as a 5HT1d agonist) than zolmitriptan. Because this metabolite appears in plasma at concentrations said to be about 60% of that of zolmitriptan it must be assumed to make a major contribution to both the product's effectiveness and its potential to cause harm. Were 183C91 eliminated more slowly than zolmitriptan, the potential for accumulation following multiple doses might be a matter of concern. It is claimed, however, that the elimination half-life for 183C91 is about 2 to 3 hours, and, therefore, this concern is largely dismissible, although the Clinical Pharmacology section of labeling should provide this information

Plasma clearance (volume/unit time) is constant (31.5 mL/min/kg) over the dose range of 2.5 to 50 mg. Although about 2/3 of the radioactivity of an orally administered radiolabeled dose of zolmitriptan appears in the urine, metabolism is primarily hepatic. Hepatic disease impairs clearance. Zolmitriptan clearance is also impaired by renal disease.

Drug-Drug Interactions

Concomitant Drug regimen being taken by volunteer	Effect relative to state without drug
fluoxetine 20 mg/d for 4 weeks	none
moclobemide (MAOI-A) 150 mg bid for 1 week	25% increase in Cmax and AUC of Zolmitriptan and 150% increase in Cmax and AUC of 183C91. the active desmethyl metabolite
selegiline (MAOI-B)	none
metaclopromide, 10 mg, one dose	none
APAP, 1 gm, one dose	none
oral contraceptives	Cmax and AUC increased
propranolol	zolmitriptan Cmax, AUC increased, 183C91 Cmax, AUC decreased.

Effectiveness in Use

The primary efficacy data reviews were conducted by Dr. Randy Levin (9/28/97) and Dr. Qing Liu (biometrics. 6/16/97 and 10/2/97). The following table, taken from the sponsor's ISE, summarizes the clinical effectiveness trials conducted by the sponsor.

Table 8.1. Categorization of Zolmitriptan (311C90) Efficacy Studies

Study Category	Study Characteristics	Primary Endpoint	Study Number	311C90 Doses Used (mg)	Number of Unique Patients
PATIENT CONTROLLED STUDIES FOR TREATMENT OF MIGRAINE					
Adequate and Well-Controlled	inpatient, optional 2nd dose, placebo-controlled efficacy, single attack, dose range finding	headache response at 2 hrs	006	1, 5, 25	84
	outpatient, single dose, placebo-controlled efficacy, single attack, dose range finding	headache response at 2 hrs	008	5, 10, 15, 20	951
	outpatient, optional 2nd dose, placebo-controlled efficacy, single attack, dose range finding	headache response at 2 hrs	017	1, 2.5, 5, 10	1144
	outpatient, single dose, placebo-controlled efficacy, single attack	headache response at 2 hrs	042	2.5	301
	TOTAL ADEQUATE AND WELL-CONTROLLED				2480
Active-Controlled	outpatient, single dose, active-controlled efficacy, single attack	[redacted] complete response[redacted]	018	5, 5+100[a]	1058
	TOTAL ACTIVE-CONTROLLED				1058
Non-controlled	outpatient, optional 2nd dose, open-label, long-term efficacy, multiple attacks	headache response at 2 hrs	015	5	112[x]
	inpatient, single dose, open-label, efficacy, PK patients	headache response at 2 hours	012	25	18
			007	10	20
	TOTAL NON-CONTROLLED				150
TOTAL STUDIES FOR TREATMENT OF MIGRAINE					3687
PATIENT CONTROLLED STUDIES FOR TREATMENT OF MIGRAINE HEADACHE					
Controlled	outpatient, optional 2nd dose, placebo-controlled efficacy, single attack, dose range finding	prevention of headache	026	20	30
TOTAL STUDIES FOR PREVENTION OF MIGRAINE					30
TOTAL OF ALL 311C90 EFFICACY STUDIES					3718

[a] 5+100 = sumatriptan 100 mg

The controlled clinical trials conducted by the sponsor document unequivocally that zolmitriptan is an effective anti-migraine drug product.

In Dr. Levin's view, Studies 008, 017 and 042, each conducted in an outpatient setting, provide clear evidence of zolmitriptan's effectiveness in use. In each, outcome assessment was based on the proportion of

subjects obtaining pain relief[1] 2 hours following treatment with placebo or one of a number of fixed single doses of zolmitriptan (differing among studies, but ranging from a low of 1 mg to a high of 20 mg)

The dose response profile

Because the risk of experiencing coronary vasoconstriction following treatment with 5HT1d/1b agonists is likely to be dose related, however, it is not enough simply to find a dose of an agonist that is effective in the sense of being statistically significantly superior to placebo. The goal is, rather, to find the lowest dose of the agonist at which meaningful headache relief can be reliably obtained in the patient population treated.

The search for such a dose is problematic, however. Indeed, the very concept of the lowest effective dose for a drug is virtually meaningless in circumstances where there the dose response relationship varies among individuals. Identifying the minimum effective dose as the lowest tested at which a statistically significant difference from placebo has been found has long been used but, because statistical significance is controlled in large measure by sample size, the approach is less than satisfying, even misleading.

Moreover, there are competing interests here. Anyone who sells an anti-migraine drug product in a competitive market would prefer to recommend its drug for use at a dose that will be effective in the largest possible proportion of patients to whom it is administered, provided, of course, that that dose is reasonably far below that likely to cause serious harm to even a very small fraction of the population exposed to that dose. The problem, however, is that the dose response for injury to patients at greatest risk for suffering rare serious events is almost impossible to construct. Accordingly, if ADRs of a less serious kind are not dose limiting, the current practice is to advance the dose no further than is necessary to gain a response reasonably close to what appears to be the maximum quantal dose response plateau (asymptote).

For a number of reasons, the maximum response plateau is not easily

---

[1] defined as no or mild pain having entered with severe or moderate pain

identified and may seem to differ among studies. That acknowledgement notwithstanding, for the studies conducted with Zomig, the plateau (intra-ocular test) seems to be somewhere between 2.5 mg and 5 mg. Some patients, of course, do respond to a dose of 1 mg (studies 006 shows a trend and 017 statistical significance[2]), perhaps less.

Safety for Use [Clinical]

Based upon the Division review team's assessment of the reports submitted to the NDA, Zomig can. within the meaning of the Act, be deemed safe for use as recommended for use in the labeling being forwarded as an attachment to the approvable action letter.

The primary clinical safety review was conducted by Dr. Armando Oliva (5/1/97).

The sponsor's ISS contains a number of tabulations (Table 9.6. 9.8 and 9.9) that enumerate the extent and kind of the clinical experience gained with Zomig over the course of its premarketing testing in migraineurs:

APPEARS THIS WAY
ON ORIGINAL

[2] Dose groups in study 006 are about 1/10 th the size of those in Study 017, a difference, perhaps illustrating the point made earlier in the text about the limitations of statistical significance as an indicator of minimum effective dose

Table 9.6. Summary of the Extent of Exposures to Zolmitriptan in All Patient Studies

Study Category	Study Characteristics	No. of Patients Exposed to 311C90	No. of Patients Treating with:		Total No. of Attacks Treated with 311C90	Total No. of Attacks Treated with:	
			One Dose	Two Doses		One Dose	Two Doses
Patient Studies for the Treatment of Migraine							
Placebo Controlled	Inpatient, optional 2nd dose	79	55	24	79	55	24
	Outpatient, single dose	1,550	1,550	N/A	1,550	1,550	N/A
	Outpatient, optional 2nd dose	1,004	789	215	1,004	789	215
Uncontrolled	Outpatient, multiple attack, opt 2nd dose	2,058	463	1,595	31,579	17,140	14,439
	Inpatient, single dose	38	38	N/A	38	38	N/A
Total for Treatment Studies		4,729	2,895	1,834	34,250	19,572	14,678
Patient Study for the Prevention of Migraine Headache							
Placebo Controlled	Outpatient, two attack, opt 2nd dose	30	17	13	46	33	13
All Patient Studies							
Total for all Patient Studies		4,759	2,912	1,847	34,296	19,605	14,691

Across all Patient studies, a total of 34,296 attacks were treated with zolmitriptan. The vast majority of these (31,579; 92%) were treated in Study 015. Of the 34,296 treated attacks, 19,605 were treated with one dose of zolmitriptan, and 14,691 were treated with two doses (Table 9.6).

Table 9.8. Distribution of Patient Exposures By Initial Dose of Zolmitriptan in Patient Studies

Study Category	Study Characteristics	PBO	Initial Dose of Zolmitriptan							
			1	2.5	5	10	15	20	25	Total
Patient Studies for the Treatment of Migraine										
Placebo Controlled	Inpatient, optional 2nd dose	5	22		21	15			21	79
	Outpatient, single dose	256		200	711	214	215	210		1,550
	Outpatient, optional 2nd dose	140	141	298	280	285				1,004
Uncontrolled	Outpatient, multiple attack, opt 2nd dose				2,058					2,058
	Inpatient, single dose					38			18	56
Total for Treatment Studies		401	163	498	3,070	552	215	210	39	4,747
Patient Study for the Acute Prevention of Migraine Headache										
Placebo Controlled	Outpatient, two attack, opt 2nd dose	4						46		46
All Patient Studies										
Total for all Patient Studies		405	163	498	3,070	552	215	256	39	4,793

Patients received zolmitriptan over the dose range of 1 to 25 mg. The majority of exposures were at 5 mg (3,070 of 4,793; 64%) as this was the dose used in

Table 9.9. Summary of Long-Term Exposure To Zolmitriptan For Patients Treating Two or More Migraine Attacks Per Month in Study 015

Treatment Duration	Number of Patients
> 3 Months	809
> 6 Months	669
Approximately 1 Year[1]	137

1 >11 months

In sum, the extent of exposure gained (i.e., ~ 4000 subjects) during premarket development of Zomig is more than sufficient, under current agency policies and guidance, to assess risks of use of that occur at an

incidence ordinarily identified prior to marketing of almost any commercial drug product.

Risks of use assessed

Deaths

No deaths were reported during clinical testing.

Serious Untoward Events

Four "serious" clinical events deemed by Dr. Oliva to be possibly related to zolmitriptan use are identified; none of the 4 would seem a signal of a unique risk of the product.

Untoward Events associated with Discontinuations

In controlled trials, there were but a handful of dropouts.

Table 9.41. AEs Leading to Withdrawal from Study 015

AEs Leading to Withdrawal	N	% of Patients Based on Total Number Treating a Migraine	% of Patients Based on Total Number Withdrawing Because of AEs
AE(s) leading to withdrawal not specified 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	11	<1%	7%
heaviness other than chest or neck	10	<1%	6%
somnolence	10	<1%	6%
warm sensation	9	<1%	5%

[a] Body location other than chest or neck.

In open studies,about 8% of patients discontinued treatment prematurely, but none for a reason that would suggest a unique, product specific risk, beyond those seen with other 5HT1d/1b agonists. The kind of event associated with discontinuation is well illustrated by those reported (See sponsor's ISS Table 9.41 above) by the 167 who withdrew for an

BEST POSSIBLE COPY

adverse clinical event in Study 015, an open, multiple attack, trial reporting upon the experience of >1500 migraineurs who treated 2 or more headaches with zolmitriptan. These appear to be more or less identical to those reported in association with the use of other 5HT1d/1b antimigraine drug products.

Common ADRs

Table 9.37. Most Common[a] AEs in International, Long-Term, Multiple Attack Uncontrolled Study for Treatment of Migraine

# (%) Patients with:	Zolmitriptan Dose			
	5 mg (n=1858)		5+5 mg (n=1995)	
asthenia	264	(14%)	220	(11%)
pain ± location specified[b]	128	(7%)	99	(6%)
heaviness other than chest or neck	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 of zolmitriptan.

[b] Body location other than chest or neck.

The commonly reported ADRs, (e.g., see ISS Table 9.37) are again, essentially identical to those reported with other 5 HT1d/1b agonist anti-migraine drug products.

The incidence of ADRs of any kind increases among patients as a function of dose.

Safety Update

The SUD based on a cut off date of 12/15/96 provides no finding that would cause the Division to rescind or modify its conclusions about Zomig.

BEST POSSIBLE COPY

Labeling/Recommendations for dosing

The product labeling being forwarded as an attachment to the approvable action letter represents a synthesis of 5HT1d /1b class labeling statements and zolmitriptan specific information. It is my understanding, based on my conversations with Dr. Levin that the firm will accept the labeling largely as developed by the Division.

Dosing

Conclusions

Zomig has, within the meaning of the Act, been shown to be safe for use and effective in use as an anti-migraine drug product if marketed under the conditions of use recommended in the draft labeling attached to the approvable action letter being forward to the Office for issuance.

Recommendation.

Issue the approvable action letter.

Paul Leber, M.D.
November 12, 1997

NDA 20-768
cc
HFD-101
Temple
HFD-120
Katz
Levin
Oliva
Fitzgerald
Guzewska
Heimann
Chen
HFD-710
Sahlroot
Liu
HFD-860
Baweja

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-5437

ZOMIG™ (zolmitriptan) Tablets

ITEM 13: Pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG.

1. Active ingredients(s):

   (S)-4-[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone.

2. Strength(s):

   2.5 mg and 5 mg

3. Trade Name:

   ZOMIG™ (zolmitriptan) Tablets

4. Dosage Form, Route of Administration:

   Tablet, Oral

5. Applicant Firm Name/Holder of the New Drug Application:

   IPR Pharmaceuticals Inc.
   Carolina, Puerto Rico

   US Agent:
   Zeneca Pharmaceuticals
   A Business Unit of Zeneca Inc.
   1800 Concord Pike
   Wilmington, DE 19850-5437

6. NDA Number:

   20-768

7. Approval Date:

N/A

8. Applicable Patents

(i) US Patent No. 5,466,699

(a) Expiration Date:

November 14, 2012

(b) Type of Patent:

The patent claims the drug product as a compound per se, a method of using the compound and a pharmaceutical composition containing the compound.

(c) Name of Patent Owner:

Zeneca Limited
Macclesfield, Cheshire, England

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

Cushman, Darby and Cushman,
Intellectual Property Group of
Pilsbury, Madison and Sutro, LLP
1100 New York Avenue
Washington, DC 20005-3918

(e) Original Declaration:

The undersigned declares that US Patent No. 5,466,699 covers the formulation, composition, and/or method of use of ZOMIG™ (zolmitriptan) Tablets. This product is the subject of this application for which approval is being sought.

RUTH H. NEWTSON
CHIEF IP COUNSEL
PHARMACEUTICALS

NDA:	**20-768**
Trade Name:	**Zomig**
Generic Name:	**zolmitriptan**
Applicant Name:	**Zeneca**
Division:	**HFD-120**
Project Manager:	**Lana Y. Chen, R.Ph.**
Approval Date:	November 25, 1997

PART I

IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a. Is it an original NDA? — Yes

   b. Is it an effectiveness supplement? — No
   If yes, what type? (SE1, SE2, etc.)

   c. Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") — Yes

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. — N/A

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: — N/A

   d. Did the applicant request exclusivity? — Yes

   If the answer "yes," how many years of exclusivity did the applicant request? — 5 yrs

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? No

If yes, what is NDA number

If yes, what is Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? No

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

   Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   No

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

   If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

   N/A

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

1) If yes, explain:

2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

If yes, explain:

If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

      Investigation #1

      Investigation #2

      Investigation #3

      If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

      NDA: Study:

      NDA: Study:

      NDA: Study:

   b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

      Investigation #1

      Investigation #2

      Investigation #3

      If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

      NDA: Study:

      NDA: Study:

NDA: Study:

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #: Study #:

Investigation #: Study #:

Investigation #: Study #:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND#: Explain:

Investigation #2
IND#: Explain:

Investigation #2
IND#: Explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
Explain:

Investigation #2
Explain:

Investigation #3
Explain:

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

If yes, explain:

Lana Y. Chen, R.Ph.
Project Manager
DNDP, HFD-120

Paul Leber, M.D.
Director
DNDP, HFD-120

c:\wpfiles\zomig.nda\ae\exclusiv.sum
Final: June 25, 1997

cc:
Original NDA
Division File
HFD-120/Chen
HFD-85/Holovac

B. EXCLUSIVITY INFORMATION

Applicant claims an exclusivity period of five years from the date of approval of this New Drug Application pursuant to 21 CFR 314.108(b)(2). To the best of Applicant's knowledge or belief, a drug has not been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act which contains any active moiety in ZOMIG™ (zolmitriptan) Tablets, the drug for which Applicant is seeking approval.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-768 Trade (generic) names Zomig (zolmitriptan) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

__✓__ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

__✓__ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

R. L.
Signature of Preparer

10/27/97
Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437
Telephone (302) 886-2132
Fax (302) 886-2822

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

NOV 2 6 1996

Re: ZOMIG™ (zolmitriptan)
NDA 20-768

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc., that we did not and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

William J. Kennedy, Ph.D.

WJK/lmc/24671/118

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: **10/27/97**
From: **Randy Levin, M.D., Neurology Team Leader**
Subject: **NDA 20-768 Zolmitriptan**
To: **file**

Background:

This NDA is for Zolmitriptan, a 5 HT1 agonist for the acute treatment of migraines. The IND was submitted on 4/28/94 and the NDA was received by the Agency from Zeneca on 11/29/96. The NDA review team included Dr. Martha Heimann (chemistry), Dr. John Jessop/Dr. Glenna Fitzgerald (nonclinical pharmtox), Dr. VJ Tammara (biopharm), Dr. Armando Oliva (clinical safety), and Dr. Liu Qing (statistical consultant).

I have reviewed the efficacy portion of the application as well as the evaluations submitted by the review team and conclude that the application is approvable. The following is a summary of information from the NDA reviews on which I based my decision.

Chemistry:

Conclusion: The sponsor plans on supplying zolmitriptan as a 2.5 mg (yellow) or 5.0 mg (pink) tablet. After review of the NDA and response to chemistry deficiencies, Dr. Martha Heimann concluded that the drug was approvable but could not recommend that the drug be approved with the following issues being addressed.

Non clinical pharmacology and toxicology:

Conclusions: Following review of the non clinical pharmacology and toxicology section of the NDA, both Dr. Jessop and Dr. Fitzgerald concluded that the information provided was adequate to support the approval of zolmitriptan. They have provided recommendations for labeling.

Zolmitriptan pharmacologic action is similar to sumatriptan. Zolmitriptan binds with high affinity to 5HT1D and 5HT1B receptors and with modest affinity for 5HT1A receptors. It does not bind with significant affinity to other receptors.

The carcinogenicity studies have been reviewed by the Carcinogenicity Assessment Committee. The studies were found to be adequate. There was an increase in thyroid follicular adenomas. The mechanism is not known. The Ames test was positive in two assay but negative in others. The division's consultant recommended that the positive test be included in labeling. Zolmitriptan was clastogenic in the human lymphocyte assay.

At high exposures, zolmitriptan was associated with embyrolethality in both rats and rabbits. In rabbits, there was an increase in rib malformations and variations of major blood vessels. This led the reviewers to conclude that the drug be classified as category C for pregnancy rather than category B proposed by the sponsor.

The toxicology studies included a 6-month rodent and 1-year non-rodent oral study to support chronic use. Dr. Jessop concluded in his review that the finding in the study were "quite adequate to support the administration of the drug to humans". There appeared to increase blood pressure and heart rate with potency about 2-3-fold greater than sumatriptan on dose per dose basis. In anesthetized animals, there appeared to be no effect on conductance to myocardium, coronary vasculature, subregions of the brain or pulmonary vasculature. There did appear to be a decrease in renal blood flow and conductance as well as ocular, splanchnic and stomach vascular conductance. In vitro studies on human coronary artery did show dose-related contraction (37% of the maximum caused by serotonin).

Biopharm:

Conclusions: Following review of the biopharm section of the NDA, both Dr. Tammara and Dr. Baweja concluded that the information provided was supportive of approval provided that the sponsor incorporate labeling suggestions. They also recommended on the basis of the dissolution tests that the biowaver for the 5 mg tablet be granted.

From Dr. Tammara's review the following information was provided:

Parameter	Result
Bioavailability	40%
Absorption -Cmax	2.5 mg (male/female) - 3.5/4.1 ng/mL 5 mg (male/female) - 5.9/9.7 ng/mL
Absorption -Tmax	30 minutes to 6 hours
Absorption - AUC	2.5 mg (male/female) - 18.4/23.1 ng*hr/mL 5 mg (male/female) - 32.7/60.2 ng*hr/mL
Food effect	15% decrease in AUC and Cmax, 30 minute increase in Tmax
Metabolism	Route of metabolism is hepatic with three major metabolites, N desmethylate (183C91), N oxide analog and indole acetic acid. 183C91 was active as a 5 HT1 agonist.
Interaction in vitro	at therapeutic doses, the drug is unlikely to affect the CYP 450 metabolism of coadministered drugs. No inhibitory effect on MAOA or B.
Elimination half life	3 hours
Protein binding	25%
Dose proportionality	Linear kinetics from 2.5 to 10 mg
Multiple dose kinetics	No accumulation
Hepatic impairment	Following dosing with 10 mg, there was an increase in the Cmax and AUC by 50%. There was an increase in the AUC by 2 times and a three fold increase in the half life. This was associated with a decrease in the 183C91 metabolite.
Renal impairment	No change in PK
Age effect	No differences in PK in young and elderly
Race	No differences in the metabolism in Japanese and Caucasian
Hypertension	Both systolic and diastolic BP increased in a linear fashion with dose in both normotensive and hypertensive patients. There was no difference in both the Cmax and AUC.

Safety:

Conclusions: The safety data support the safety of single zolmitriptan doses from 1 mg to 5 mg, two 5 mg doses for the treatment of a single headache and chronic use of 5 mg doses in otherwise healthy migraine patients. The potential for serious cardiac and cerebrovascular events have not been eliminated by this data base which consists of mostly healthy migraine patients. Labeling contraindications, warnings and precautions similar to those used for Imitrex should be applied to this 5HT1 agonist.

Exposure: The sponsor evaluated doses of 1 to 25 mg in the controlled clinical trials. There were an adequate number of patients treated with single doses of 5 mg, two doses of 5 mg for the treatment of a single headache and long term use of 5 mg to reasonably assess the safety of zolmitriptan.

For drugs indicated for acute treatment for migraines, the division has asked sponsors to provide safety data on at least 1500 patients who used the drug at least once, greater than 300 patients who used the drug at least twice per month, on average for 6 months and greater than 100 patients who used the drug at least twice a month, on average, for 12 months These numbers are based on ICH guidance for safety data base size for drugs used intermittently for a chronic condition.

The sponsor has exceeded the recommended numbers. In the placebo controlled clinical trials, approximately 2600 patients received at least a single dose of zolmitriptan. 94% of the patients given zolmitriptan received single doses of ≥ 2.5 mg and 75% received single doses of ≥ 5 mg.

In two placebo controlled clinical trials and in a long term open label trial, patients who did not have complete relief of their headache or had a recurrence of pain were allowed to repeat a dose 4 hours after the initial dose. Approximately 1800 patients treated a single headache with 2 doses with over 1500 using 5 mg individual doses for a total of 10 mg used in a 24 hours period.

The sponsor conducted an open label study to evaluate the long term safety of the 5 mg dose of the drug. In this study 2,068 patients were treated with at least one 5 mg dose of zolmitriptan. 669 of these patients treated on average more than 2 migraines per month over 6 months with 137 treating, on average, 2 migraines per month over one year.

Demographics: The demographics of the population studied was similar in age

and sex to the demographics of patients with migraines. Patients of races other than caucasian were under represented in the safety data base. In the controlled clinical trials, approximately 85% of the patients were female, The average age was about 40 with 17 patients under the age of 18 and 35 patients over the age of 60. Over 95% were white.

Adverse events in the controlled clinical trials:

The adverse event profile of zolmitriptan was similar to other 5HT1 agonists including sumatriptan including nausea, dizziness, chest/throat tightness and warm sensation. Other adverse events with zolmitriptan that appear more prominent than seen with sumatriptan including asthenia and somnolence.

Some adverse events appear to be dose related, increasing in frequency and severity with higher doses. The increased frequency of adverse events with increasing doses of zolmitriptan is illustrated in figure 3 from the ISS. Patients on 1 mg, in general, had fewer adverse events compared to patients on 2.5 mg who, in turn, had fewer events than patients on 5 mg. For the most common AE, nausea, dizziness, somnolence, paresthesia, warm sensation and asthenia, the incidence increased with increasing doses. The incidence of AEs occurring in at least 1% of patients on 2.5 mg with a greater frequency in patients on placebo is in Dr. Oliva's table 21.

There did not appear to be an increase in incidence of AEs in patient who took 1 dose compared to those who took two doses to treat a single headache. The age or sex of the patient did not appear to change the incidence of AEs.

The severity of the adverse events also increased with increasing doses. The incidence of severe AEs was < 1% for all dose groups up to 5 mg. For the 15 and 20 mg doses, the incidence of severe asthenia and somnolence was up 3%. This not only included the more common events of asthenia and somnolence but also a more potentially serious adverse events, hypertension. There was a small change (1 mm Hg in mean systolic pressure and 5 mm Hg in diastolic BP) in patients treated with zolmitriptan which increased with higher doses; 5 mm Hg in systolic pressure and 8 mm Hg in diastolic pressure for the 20 mg dose. There was no associated change in pulse rate. In a study in patients with liver dysfunction, 7 of 20 patients treated with 10 mg had elevations of BP; two with significant elevations of 20 to 80 mm Hg increases in either the systolic or diastolic BP.

For the other few serious adverse events seen, no dose response was seen.

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

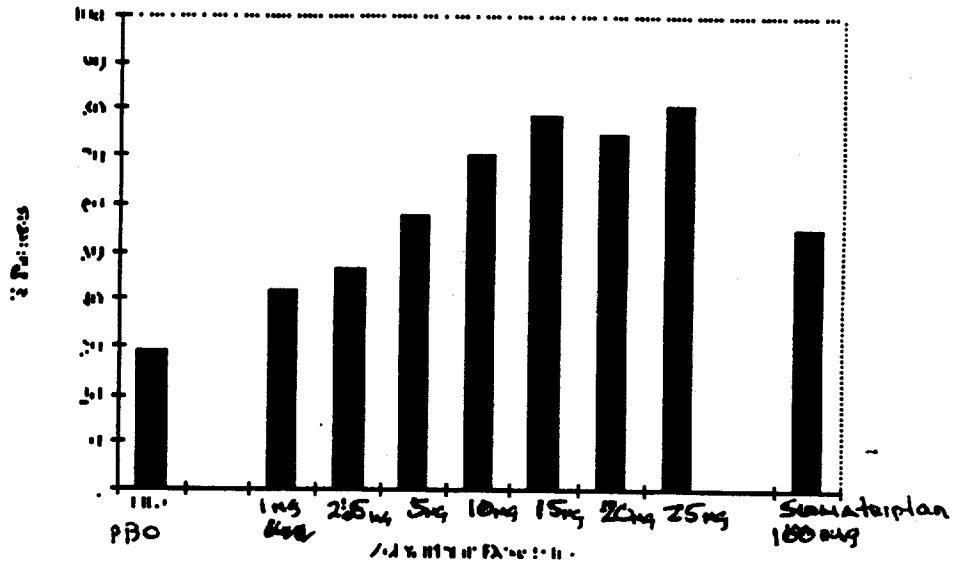

Table 21: Adverse Events in Clinical Studies (006, 008, 017, 018, 042) having Incidence > 1% for zolmitriptan 2.5 mg tablet.

ADVERSE EVENT (N)	TOTAL 3533	PBO 417	%	1 MG 162	%	2.5MG 487	%	5 MG 1011	%	10 MG 514	%	15MG 229	%
NAUSEA	258	15	3.61	6	3.7	45	9.05	93	6.23	41	7.98	32	13.97
DIZZINESS	325	15	3.61	9	5.56	42	8.66	96	9.5	67	13.04	28	12.23
SOMNOLENCE	256	12	2.89	8	4.94	30	6.04	76	7.26	55	10.7	20	8.73
PARESTHESIA	271	5	1.2	8	4.94	29	5.84	77	7.62	56	10.89	22	9.61
SENSATION WARM	180	6	1.44	5	3.09	21	4.23	52	5.14	36	7	19	8.3
ASTHENIA	328	13	3.13	8	4.94	16	3.22	69	6.8	64	12.45	35	15.72
DRY MOUTH	135	7	1.69	8	4.94	16	3.22	32	3.17	25	4.86	20	8.73
TIGHTNESS THROAT	93	3	0.72	1	0.62	13	2.62	28	2.77	22	4.28	9	3.93
TIGHTNESS CHEST	68	2	0.48	1	0.62	13	2.62	15	1.48	21	4.09	9	3.93
HEAVINESS OTHER	193	2	0.48	2	1.23	10	2.01	91	9.04	30	5.84	36	15.72
TIGHTNESS NECK	58	1	0.24	1	0.62	10	2.01	16	1.78	11	2.14	5	2.18
PAIN LOC SPEC	92	3	0.48	3	1.85	9	1.81	29	2.87	18	3.5	12	5.24
SWEAT	67	5	1.2	0	0	9	1.81	25	2.47	7	1.36	5	2.18
PRESSURE OTHER	64	1	0.24	3	1.85	9	1.81	13	1.49	3	0.58	13	5.68
PAIN NECK	92	4	0.96	0	0	8	1.61	27	2.67	11	2.14	8	3.49
DYSPEPSIA	42	2	0.48	5	3.09	9	1.81	19	0.99	7	1.36	0	0
NERVOUSNESS	23	1	0.24	0	0	7	1.44	7	0.69	3	0.58	1	0.44
THINKING ABNORM	28	2	0.48	0	0	6	1.21	3	0.3	8	1.56	3	1.31
MYALGIA													

Discontinuations, serious adverse events and deaths: The safety data base for zolmitriptan did not include evidence for serious adverse events that are more significant than that seen with the currently marketed 5 HT1 agonists, sumatriptan and dihydroergotamine. No events of cardiac ischemia were documented. No cerebrovascular events were reported.

There were 43 patients with serious adverse events in the clinical trials with 38 occurring in patients enrolled in the long term safety study. 25 events occurred only once and 10 occurred twice. The events occurring twice include, overdose, accidental injury, ovarian disorder, unevaluated reaction, neoplasm, pain in the abdomen, back pain, pyelonephritis and syncope.

In the controlled clinical trials, no patients discontinued for adverse events. Since these were single dose studies, a discussion of discontinuations is not as meaningful as in studies where patients are subjected to multiple dosing. 12 subjects out of 347 in the phase 1 trials discontinued for adverse events. In the long term study, 167, approximately 8%, discontinued for adverse events from the long term study. The AEs associated with discontinuation included: dizziness, nausea, paresthesia, asthenia, pain , reaction aggravated, heaviness other than chest or neck, somnolence, warm sensation. Each of these events occurred in 9 to 14 patients. Two patients withdrew due to diastolic hypertension (105 and 110 mm hg). No events of cardiac ischemia were reported.

Labs: No lab abnormalities were associated with use of the drug.

ECG: 24 hour Holter monitoring was performed in 6 phase 1 studies and no abnormalities were found. ECGs were obtained in the long term clinical trial and in the placebo controlled clinical trials. Since the ECGs were taken usually many days after treatment, conclusions regarding the cardiac safety of the drug is limited. No changes were noted including ST segment changes.

Other data: There were 11 pregnancies during the study with 5 live births with normal infants, 4 elective terminations without fetal abnormality and 2 spontaneous abortions. 4 patients took extra doses with 20 to 30 mg taken over 2 to 3 days. This did not result in any AEs.

4 month safety update: The sponsor submitted a safety update with a cutoff date of 12/15/96. The update reported on phase 1 studies and one ongoing long term study. In the long term, as of 12/15/96, 850 patients of 3,000 planned were enrolled. 6 serious AEs were reported. All occurred many days after treatment. No new AEs were noted in this update.

Efficacy:

Conclusions: The sponsor has demonstrated in more than one adequate and well controlled study that doses of 1 to 25 mg of zolmitriptan is effective for the acute treatment of migraine headaches. There was a statistically significant increase in efficacy in patients treated with doses ≥ 2.5 mg compared to those receiving 1 mg. There was no statistically significant difference between the 2.5 mg dose and higher doses (5, 10, 15 and 25 mg).

Pivotal studies:

The sponsor has provided 5 studies (6, 8, 17, 18, and 42) that are adequate by design to provide evidence for efficacy of the drug in the acute treatment of migraines. Three studies, 8, 17 and 42, had similar designs. In study 6, patients were treated in a clinic setting whereas in studies 8, 17 and 42, patients treated their headache on their own. This design difference may lead to differences in the types of headaches treated and the timing of treatment which may result in differences in headache response. Study 18 was a comparison trial with sumatriptan and excluded patients who had experience with sumatriptan. This criteria was not a part of the other studies and may results in a different patient population being enrolled. All studies are capable by design for demonstrating evidence for efficacy but because of the differences in design, I have chosen, not to combine the results from studies 6 and 18 with studies 8, 17 and 42.

Not all of the studies evaluated the same doses. Two studies evaluated a single 1 mg dose, two studies evaluated the 2.5 mg dose, four studies evaluated dose of 5 mg and three studies looked at doses > 5 mg.

All studies allowed either a second dose and/or rescue treatment after an initial observation period of 2 to 4 hours. In one study, patients were randomized to receive either placebo or active drug for the second dose. Headache pain severity, secondary symptoms and use and/or time to rescue were recorded.

All studies enrolled adults under the age of 65. In study 17, 14 patients out of the 1144 enrolled were between the ages of 12 and 17.

Response rate: The sponsor's prospectively defined measure of efficacy was the response rates 2 hours following treatment with response defined as a reduction in headache pain severity from moderate or severe to mild or no pain. While Dr. Liu questioned this measure as a clinically valid outcome measure based on the statistical analysis of the studies, the outcome measure is widely excepted by

experts in the field as a valid measure of the efficacy of the drug and is used in all of the most recent migraine studies. This is based, in part, on the clinical opinion that movement on the scale from severe to moderate pain was not considered to be a clinically relevant change but a change from moderate to mild pain is considered clinically relevant. This essentially changes the scale from a 4 point scale to a dichotomous scale where severe and moderate pain are grouped together as well as mild or no pain. Dr. Liu found that the evidence supports the efficacy of the drug when using either the 4 point scale or the dichotomous scale.

In each study, there was a statistically significant increase in headache response rates in patients treated with the drug compared to those patients treated with placebo. The finding were consistent across studies.

The following is a brief summary of the results of the headache response rates for the efficacy studies:

Study 42, evaluated the efficacy of the 2.5 mg dose and found that there were statistically significant difference in the response rate at 2 and 4 hours following dosing.

Study 42: Percent of patients with relief (no or mild pain) following the initial treatment *p< 0.05		
Hours post dose	Placebo (relief/N)	2.5 mg (relief/N)
1	26% (26/100)	33% (66/198)
2	35% (35/100)	60%* (119/197)
4	35% (32/94)	68%* (126/184)

Study 17 evaluated doses of 1, 2.5, 5 and 10 mg and found statistically significant differences at all dose groups. The differences were statistically significant at 1 hour for the 2.5, 5 and 10 mg dose and at 2 hours for the 1 mg dose. There was a statistically significant difference between the 1 mg dose and doses ≥ 2.5 mg.

Study 17: Percentage of patients with headache response					
Hours after dosing	Placebo (N=139)	1 mg (N=140)	2.5 mg (N=297)	5 mg (N=279)	10 mg (N=283)
0.5 hours	14%	14%	16%	20%	20%
1 hour	24%	33%	43%*	44%*	50%*
2 hours	32%	50%*	63%*#	65%*#	65%*#
4 hours [a]	28%	52%*	70%*#	69%*#	70%*#

* p value < 0.05 when compared to placebo
# p value < 0.05 when compared to 1 mg
[a] 78 patients took escape medication prior to the 4 hour time point (17 on placebo, 10 on 1 mg, 18 on 2.5 mg, 20 on 5 mg, 13 on 10 mg)

Study 18 compared placebo, 5 mg and 100 mg of sumatriptan. The response rate for the 5 mg dose and the 100 mg dose of sumatriptan was statistically better than the placebo but not different from each other.

Study 18: Headache relief rates (*comparison with placebo p value < 0.05)			
Time post dose	0 mg N=55	5 mg N=495	Sumatriptan N=503
60 minutes	20	34	35*
120 minutes	44	59*	62*
240 minutes	40	73*	77*

Study 8 evaluated doses of 5, 10, 15 and 25 mg. The response rates for all doses were statistically better than placebo but no different from each other.

Study 008: Percentage of patients with headache relief *P value < 0.05					
Hours after dosing	Placebo (N=99)	5 mg (N=213)	10 mg (N=213)	15 mg (N=215)	20 mg (N=209)
1 hour	16%	44%	40%	42%	50%
2 hours	21%	61%*	67%*	67%*	74%*

Study 6 was the only inpatient study. This small study evaluated 1, 5 and 25 mg. There was a statistically significant difference in response rates for the 5 and 25 mg groups but placebo and 1 mg were not different statistically.

Study 006: Percentage of patients with headache relief * P value < 0.05				
	Placebo (N=20)	1 mg (N=22)	5 mg (N=21)	25 mg (N=21)
1 hour	15	9	24	43
2 hours	15	27	62*	81*

Dose effect: Using the efficacy criteria of headache response at 2 or 4 hours, there were statistically significant differences from placebo for all doses tested (range 1 mg to 25 mg). Only in study 6 was there a non statistically significant difference between the active treatment and placebo. This was in the comparison of the 22 patients in the 1 mg dose group and 20 patients in the placebo dose group. The 1 mg group was numerically better than the placebo group but the difference did not reach statistical significance. This is in contrast to the results in study 17 were the comparison between 140 patients in the placebo and 1 mg groups was statistically significant. In other outcome measures, such as associated symptoms, estimated probability of headache response and estimated probability of remedication, the 1 mg dose is superior to placebo.

There is evidence for a greater effect with higher doses. In study 17, there was a statistically significant difference between the response rates in the 1 mg dose and the higher doses including 2.5 mg. In no other study was there a statistically significant difference between treatment groups. In regards to other outcome measures, such as incidence of associated symptoms and use of rescue, the 1 mg group numerically falls in between placebo and the higher doses. The higher doses are similar in regards to the secondary outcome measures.

The drug is effective and the results from the studies provide evidence for efficacy for doses of 1 mg and above and as well as evidence that dose $\geq$ 2.5 mg are more effective than doses of 1 mg. There is no evidence that doses of $\geq$ 5 mg are any more effective than 2.5 mg.

Onset of effect: Response rates were evaluated as early as 30 minutes following treatment. In study 17, a statistically significant difference in response rates were seen as early as 1 hour for doses $\geq$ 2.5 mg and 2 hours for the 1 mg dose. Time to effect was not directly addressed by the studies. To illustrate the time to response, we have used a Kaplan Meier plot of the estimated probability of achieving a headache response over the 4 hours following treatment as an illustration of the time to effect.

Duration of effect for the treatment of a single headache: From experience with sumatriptan, an acute treatment for a migraine headache may not lead to complete resolution of the headache. Patients who have mild or no pain at 2 or 4 hours may have recurrent pain and/or require additional treatments. We have used a Kaplan Meier plot of the estimated probability of the using additional treatments for migraine over the 24 hour period following treatment to illustrate the illustrate this problem.

Efficacy of the second dose: The efficacy of the second dose was only assessed in study 017. The design allowed patients to be treated with a second dose for persistent headaches as well as recurrent headaches. Patients were allowed to take rescue medication instead of a second dose. For patients failing to respond to the initial dose of 2.5 mg, the response rate 2 hours following the second dose of 2.5 mg was higher than patients who were randomized to placebo for the second dose though the difference did not reach statistical significance.

At this time, the results of the study does not provide sufficient evidence to support the claim of efficacy of a second dose of 2.5 mg. The failure to detect a difference with the 2.5 mg dose may be a result of a number of factors including a lack of power, continued effect of the initial dose, etc.

Associated migraine symptoms: Though not a primary outcome measure, the studies show a consistent reduction in the incidence in the secondary outcome measures of nausea, photophobia and phonophobia in patients treated with the active treatment compared to those treated with placebo.

Long term benefit: The ability of zolmitriptan to effectively treat migraine headaches repeatedly over time was not evaluated in a controlled clinical trial. Because of the variability of response and potential for placebo effect, conclusions drawn from uncontrolled clinical trials may not be valid. In study 015, the sponsor evaluated the long term safety of the drug in an open label study. Headache response was determined after each headache treatment. While the findings in this study suggest that the benefit of the drug does not dissipates over time, it has limited use in describing efficacy of the drug.

Effects related to sumatriptan: The study comparing the effects of sumatriptan and zolmitriptan was not adequate by design to demonstrate a difference between the two treatments. The dose used in this trial did not cover the entire range of effective doses for either drug. While the results showed a significant difference for both dose groups compared to placebo, it failed to show a significant difference between the treatments.

Subgroup analyses: There were insufficient numbers of patients in each group to determine the effect of race or age < 18 on the efficacy results. The efficacy of did not appear to be affected by the presence or absence of aura or by age, gender, weight, menstrual cycle, or the duration of migraine attack.

Comments:

The nonclinical toxicology and pharmacokinetics reviewers have recommended approval of their sections with acceptable labeling. The chemistry reviewers have noted that prior to approval, additional commitments and information from the sponsor are required. Dr. Heimann has outlined these commitments and information in her review.

In regards to the clinical safety and efficacy, doses of 1, 2.5 and 5 mg were found to be safe and effective. There is additional safety information that is being generated from an ongoing study but since there was safety data from an adequate number of patients exposed to the drug in the NDA and 4 month safety update, I suggest that the additional safety information is not necessary for an approval action.

Overall, I find the application approvable. Prior to approval, the sponsor needs to adequately address the chemistry requirements as outlined by Dr. Heimann, agree to score the 2.5 mg tablet in phase 4 and make changes to the draft labeling.

In the package is my version of draft labeling which is based on the recently approved labeling for Imitrex Nasal Spray. One difference from the Imitrex labeling is the inclusion of a discussion of discontinuations from the open label trial. Since the placebo controlled clinical trials all only involved the treatment of a single headache, there was very little chance for discontinuation. The sponsor included a discussion of discontinuations from the open label study which provides insight into the tolerability of the drug.

From the safety and efficacy data, I have concluded that the 1 mg is a safe and effective dose. While the safety data did not necessarily demonstrate a significant difference in safety profile between the 1 and 2.5 mg doses, there is sufficient evidence for dose related side effects, blood pressure changes for example, that I think that it is reasonable to conclude that the 1 mg dose would be less likely to result in adverse effects. Since the sponsor does not have a 1 mg dosage form, they suggest that a lower dose can be achieved by manually breaking the 2.5 mg dose in half. I have obtained samples of the 2.5 mg and even though the tablet is

not scored, it does break easily and cleanly into two separate halves. I feel that this is an acceptable compromise to the 1 mg tablet. While the dose is more than 1 mg, it provides the benefit of being lower than 2.5 mg and is effective. As part of a phase 4 committment, in subsequent batches, the sponsor can provide a scored 2.5 mg tablet.

Randy Levin, M.D.
Neurology Team Leader

cc:
Original NDA
rl/October 27, 1997

Consult #814 (HFD-120)

ZOMIG zolmitriptan tablets

The Committee found no look-alike/sound-alike conflicts or misleading aspects with the proposed proprietary name.

The Committee had no reason to find the proposed name unacceptable.

D Goring 7/16/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

(014)

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Neuropharmacological Drug Products/ Paul Leber, MD x	HFD-120
Attention: [illegible]	Phone: (301) 594-2280
Date: May 1, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Zomig	**NDA/ANDA#** 20-768
Established name, including dosage form: Oral Tablets	
Other trademarks by the same firm for companion products: n/a	
Indications for Use (may be a summary if proposed statement is lengthy): Migraine Headache	
Initial Comments from the submitter (concerns, observations, etc.): Possible therapeutic claim: "mig" incorporated in the trade name.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-768; HFD-120/division file; HFD-120/lyc; HFD-120/Heimann

Rev. December 95