# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 21-231

## CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

JAN 29 2001

COMPLETED JAN 29 2001

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

**NDA: 21-231**
ZOMIG-ZMT™ Orally Disintegrating Tablets
Zolmitriptan 2.5 mg, [redacted]

Sponsor: AstraZeneca Pharmaceuticals, LP
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

Reviewer: Carol Noory

Indication: [redacted]
Classification: 1S
Type of Submission: Original NDA
1 BE study; 1PK study, 1 dissolution study

Submission date: April 14, 2000
January 8, 2001
January 9, 2001

**Introduction:**
ZOMIG™ (zolmitriptan) Tablets contain zolmitriptan, which is a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT $_{1B/1D}$) receptor agonist. Zomig™ tablets (NDA #20-768) have been approved since November 1997 for the treatment of migraine headaches. Migraine is characterized by unilateral, throbbing headaches, often associated with nausea, vomiting, gastrointestinal disturbance, phonophobia and photophobia.

The sponsor has developed a new dosage form, which disintegrates rapidly on the tongue and can be swallowed with saliva. These orally disintegrating tablets can be used by patients who are not able to swallow due to nausea or for patients who dislike taking oral tablets. In support of this new dosage form, the sponsor has submitted a bioequivalence study that includes a palatability study, a pharmacokinetic study, and a dissolution study. The sponsor has also conducted a clinical efficacy study. The formulation used in the clinical study, the bioequivalence study and the to-be-marketed formulation are all the same.

**Mechanism of Action:**
Zolmitriptan binds to human recombinant 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors and has a modest affinity for 5-HT$_{1A}$ receptors. The N-desmethyl metabolite also has high affinity for 5-HT$_{1B/1D}$ and modest affinity for 5-HT$_{1A}$ receptors.

**Pharmacokinetics of Zolmitriptan**
The current labeling for Zomig™ conventional tablets indicates that zolmitriptan is well absorbed after oral administration with peak plasma concentrations occurring in 2 hours. Mean absolute bioavailability is approximately 40%. Zolmitriptan displays linear kinetics over the dose range of 2.5 to 50 mg. Zolmitriptan is converted to an active N-desmethyl metabolite which may contribute a substantial portion of the overall effect after zolmitriptan administration. No accumulation occurs on multiple dosing. Food has no significant effect on the bioavailability of zolmitriptan. The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan is 25% over the concentration range of 10 - 1000 ng/mL.

The mean elimination half-life of zolmitriptan and of the active N-desmethyl metabolite is 3 hours with about 95% being recovered in the urine and feces. Mean total plasma clearance is 31.5 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion. During a moderate to severe migraine attack, mean $AUC_{0-4}$ and $C_{max}$ for zolmitriptan were decreased by 40% and 25%, respectively, and mean $T_{max}$ was delayed by one-half hour compared to the same patients during a migraine free period.

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**Studies Submitted:**

- Study #311CIL/0900 is a 2 phase, 2-way crossover study to determine the preferred flavor ( orange) and to compare the pharmacokinetics of the uncoated and rapidly disintegrating tablets formulations of the preferred flavor.
- Study #311CIL/0088 is an open, randomized 3-way crossover, single dose trial to compare the pharmacokinetics of two orally disintegrating formulations to the conventional oral zolmitriptan tablet.
- Dissolution: pH profiling of the final formulation using

**Trial Formulations:**

Since zolmitriptan has a bitter taste, flavoring (orange ) was added to the rapidly disintegrating ( ) tablet. In one formulation, the drug is the flavored ( ) (uncoated or ) and in the other, the taste of the drug has been masked physically by before being incorporated into the flavored or taste-masked).

A summary of the Trial formulations is given in Table 1 below.

| Table 1 | Summary of Trial Formulations | | | |
|---|---|---|---|---|
| **Trial ID** | **Tablet strength (Formulation #)** | **batch #** | **Date of manufacturer** | **Site of manufacturer** |
| **311CIL/0090** | | | | |
| **RDT** | Orange | | | CIMA Laboratories, Eden Prairie, MN |
| | Orange uncoated (F12362) | RK9707 | 11/20/97 | |
| **311CIL/0088** | | | | |

| | | | | |
|---|---|---|---|---|
| **Conventional tablet** | F12092 | JMP207 | 8/11/97 | IPR Pharmaceuticals, Puerto Rico |
| **RDT** | Orange | | | CIMA Laboratories, Eden Prairie, MN |
| | Orange uncoated (F12413) | 980008: TBM | 3/17/98 | |

Trial formulations are similar in composition to the to-be-marketed formulations. A summary of the composition of each of the trial formulations is given Table 2.

**Table 2 Composition of to-be marketed and trial formulations.**

| **Formulation** | **To-be-marketed** | **F12362** | **F12363** | | **F12365** |
|---|---|---|---|---|---|
| Zolmitriptan | 2.5 | 2.5 | 2.5 | | |
| Mannitol | | | | | |
| Microcrystalline cellulose | | | | | |
| Crospovidone | | | | | |
| Aspartame | | | | | |
| Sodium bicarbonate | | | | | |
| Citric acid anyhdrous | | | | | |
| Collodial silicon dioxide | | | | | |
| Orange flavor SN027512 | | | | | |
| Magnesium stearate | | | | | |

1.

equivalent to 2.5 mg of zolmitriptan .

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**Palatability study #311CIL/0900**

**Objective:**
To compare the taste of four orally disintegrating tablet formulations and to determine the preferred flavor and the pharmacokinetics of the — and uncoated drug formulations of the preferred flavor.

**Principal Investigator:** R. M. Dixon
**Location:** Clinical Pharmacology Unit,
Zeneca Pharmaceuticals,
Mereside, Alderley Park, Macclesfield,
Cheshire, UK SK104TG

**Study Design:**
This was a two-phase, 2-way crossover study. The first phase of the study was to determine the preferred flavor — orange) for the final product. 12 healthy volunteers were enrolled in the study and given four single oral doses of 2.5 mg zolmitriptan rapidly disintegrating tablets. Two flavors — and orange) and two formulations — and uncoated) were tested. On each trial day, two doses were given,

5 hours apart. The flavors were kept constant; however, the order in which the formulations (— or uncoated) were given was randomized. The two trial days were separated by at least 48 hours. The taste preparations were assessed at 1 and 10 minutes after dosing on a 5-point scale: very unpleasant (1), unpleasant (2), acceptable (3), pleasant (4) and very pleasant (5). The median sum score (across all volunteers) for each flavor (regardless of formulation) was calculated using the associated numbers (1-5) to determine the effects of flavor (primary endpoint). This assessment was performed before proceeding with the second phase.

The second phase was designed to compare the pharmacokinetics of the uncoated and — ! rapidly disintegrating tablets formulations of the preferred flavor (orange). Nine subjects from the first phase went on to second phase. The orange-flavored rapidly disintegrating tablet formulation was selected and an additional subject was recruited for a total of 10 subjects for the second phase of the study. Two separate oral doses of 5 mg of zolmitriptan (2 X 2.5 mg) rapidly disintegrating tablets (uncoated or —— ) were given in a single dose after fasting for 12 hours. One dose was given on each trial day, in a randomized order, separated by a minimum of 72 hours. Although the recommended daily dose for Zomig™ is 2.5 mg, twice this dose was given to improve the pharmacokinetic measurements for both the parent and its active metabolite N-desmethyl zolmitriptan (183C191). Plasma samples were taken at predetermined times and analyzed by HPLC.

**Study Results:**
The results of the palatability phase of the study determined that all formulations were palatable with no clear preference for flavor or formulation. The orange flavor was selected to continue the study. The pharmacokinetic results for both the coated and uncoated orange tablets are given in the following table (Table 3).

**Table 3 Pharmacokinetic Parameters of Zomitriptan and its Active Metabolite**

| Zolmitriptan | N= | AUC ng·hr/mL (CV) | Cmax (ng/mL) (CV) | Tmax (hours) (Range) | T ½ (hours) (SD) |
|---|---|---|---|---|---|
| Uncoated | 10 | 46.77 (71.29) | 7.88 (57.53) | 3.0 (0.5-3.0) | 3.2 (0.638) |
| **183C91** | **N=** | **AUC ng·hr/mL** | **Cmax (ng/mL)** | **Tmax (hours)** | **T ½ (hours)** |
| Uncoated | 10 | 24.81 (29.01) | 4.02 (38.22) | 3.5 (2.5-5.0) | 3.3 (0.855) |

Plasma concentrations were slightly higher following dosing with the coated formulation compared to the uncoated formulation. T ½ and Tmax were similar for both formulations.

**Bioequivalence Study 311CIL/0088:**

**Objective:**

To compare the pharmacokinetics of the two rapidly disintegrating formulations (coated and uncoated) zolmitriptan tablets with the pharmacokinetics of the conventional oral tablet.

**Principal Investigator:** R. M. Dixon

**Location:** Clinical Pharmacology Unit,
Zeneca Pharmceuticals,
Mereside, Alderley Park, Macclesfield,
Cheshire, UK SK104TG

**Treatment:**

A 5 mg dose (2 X 2.5 mg for the RDT and 5 mg for the conventional tablet) was given in three single doses at least 48 hours apart. The rapidly disintegrating [redacted] tablet was placed on the tongue and allowed to dissolve. The conventional tablet was dosed with 200 mL of water.

| Treatment | Formulation | Dosage |
|---|---|---|
| Orange flavored orally disintegrating tablets Uncoated tablets | F12413: TBM | 2 X 2.5 |
| Orange flavored orally disintegrating tablets [redacted] | | 2 X 2.5 |
| Conventional tablet | F12092 | 1 X 5.0 |

**Study Design:**

This was an open, randomized 3-way crossover, single dose trial conducted in 18 healthy subjects (17 white and 1 black) ages 27-54 years. There were 18 healthy volunteers in each treatment group (9 males and 9 females). Food was not allowed until 2 hours post-dose.

**Analysis:**

Blood samples were taken at intervals up to 15 hours after each dose for the determination of plasma concentrations of zolmitriptan and its active metabolite 183C91. Results are summarized in Table 4.

**Table 4: Statistical comparison of the PK properties of the uncoated and coated rapidly dissolving zolmitriptan tablets and the conventional oral tablet (Study 311CIL/0088) N=18**

| | Geometric mean (%CV) | | |
|---|---|---|---|
| **Zolmitriptan** | **AUC ng hr/mL (CV)** | **Cmax (ng/mL) (CV)** | **Tmax (hours) (Range)** |
| F12413 (uncoated) | 51.06 (51.9) | 8.82 (43.6) | 3.00 (0.6- 5.0) |
| F12092 (conventional tablet) | 51.36 (45.9) | 9.65 (32.7) | 1.50 (0.5 – 3.0) |
| **90% CI** | **92-107%** | **82-102%** | |
| [redacted] | | | |
| [redacted] | | | |
| F12092 (conventional tablet) | 51.36 (45.9) | 9.65 (32.7) | 1.50 (0.5 – 3.0) |
| **90% CI** | **93-108%** | **80-99%** | |
| [redacted] | | | |
| **Active Metabolite-183C91** | **AUC ng hr/mL** | **Cmax (ng/mL)** | **Tmax (hours)** |
| F12413(uncoated) | 36.47 (18.1) | 5.83 (20.2) | 3.00 (1.0 - 6.0) |
| F12092 (conventional) | 35.33 (14.7) | 5.58 (20.9) | 3.00 (0.7 – 5.0) |
| **90% CI** | **96-111%** | **94-116%** | |
| [redacted] | | | |

| | | | |
|---|---|---|---|
| F12092 (conventional) | 35.33 (14.7) | 5.58 (20.9) | 3.00 (0.7 – 5.0) |
| **90% CI** | **92-105%** | **87-106%** | |
| [redacted] | | | |
| 90%CI is expressed as a ratio of orally disintegrating tablet/conventional oral tablet. | | | |

Both the uncoated and [redacted] orally disintegrating tablet formulations were bioequivalent to the conventional oral tablet as determined by AUC and Cmax for both zolmitriptan and the active metabolite 183C91. Absorption of zolmitriptan from the rapidly disintegrating tablet was prolonged compared to the conventional oral tablet (Tmax averaged approximately 3.0 hours for both [redacted] formulations and 1.5 hours for the conventional tablet). The Tmax ranged from approximately one-half hour to 5 hours for the uncoated RDT and one-half hour to 3 hours for the conventional tablet. However, plasma concentration of zolmitriptan for the orally disintegrating and conventional tablet formulations are similar up to 45 minutes post dose. Individual Tmax values for zolmitriptan for ten of the eighteen subjects had either earlier Tmax or comparable Tmax for the to-be-marketed RDT compared to the conventional tablet. The Tmax for the active metabolite was comparable for both the RDT (1.5-5 hours) and the conventional tablet (1-5 hours).

The clinical effect of the difference in Tmax was addressed in an efficacy study conducted by the sponsor (efficacy study # 311CUK.0107). This was a randomized, placebo-controlled, double-blind trial, parallel group, multicenter comparative trial of patients treating a single migraine attack. The to-be-marketed formulation was dosed at 2 X 2.5 mg, for a total dose of 5 mg. The active metabolite, N-desmethyl zolmitriptan (183C91) was measure along with zolmitriptan. Zolmitriptan (2.5 mg orally disintegrating tablets) showed significantly greater efficacy than the placebo. 63% of the patients randomized to zolmitriptan experienced a headache response at 2 hours versus 22% of patients randomized to the placebo. According to the Medical Officer, the safety and tolerability profile of zolmitriptan was consistent with that previously described for the conventional oral tablets

**Dissolution Study:**

The sponsor conducted a solubility study on zolmitriptan as a preliminary to dissolution testing. The results are given in Table 5.

[redacted] Table 5: Solubility of zolmitriptan

| Media | Solubility at 25°C (mg/mL) |
|---|---|
| Water | 1.3 |
| 0.1M HCl | 33 |
| 0.1M NaOH | 1.5 |
| pH 7.0 buffer | 8 |
| pH 9.0 buffer | 3.3 |
| Octan-1-ol | 3.4 |

The dissolution studies were conducted using the paddle method at 50 rpm and 500 mL [redacted] Dissolution of [redacted] over this pH range. The firm chose to use the same dissolution procedure for the *in vitro* dissolution testing of the rapidly disintegrating oral tablets as they use for the conventional tablet. The dissolution procedure used was:

| | |
|---|---|
| Apparatus: | USP Paddle Method (Apparatus II) |
| RPMs: | 50 rpm |
| Medium: | [redacted] |
| Sampling time: | 15 minutes |
| Specification: | [redacted] |

Dissolution aliquots were analyzed by [redacted] The summary results for the bio-batches are given in the following table (Table 6). Lot 980008 represents the to-be-marketed uncoated, orange [redacted] formulation.

**Table 6: Dissolution results using the NDA 20-768 approved method.**

| Date of test | Mgs/ tab | Batch number | Collection times (minutes) | % claim (range) |
|---|---|---|---|---|
| May 1998 | 5.0 | JMP207 (conventional) | 15 | [redacted] |
| Apr 1998 | 2.5 | 980008 (orange, uncoated) | 15 | [redacted] |
| Apr 1998 | 2.5 | 980012 (orange, coated) | 15 | |

The firm's selection of the same procedure and specification used for the conventional tablets is acceptable

**General Comments**

1. All formulations were palatable with no clear preference for flavor or formulation.
2. The orange uncoated and [redacted] orally disintegrating tablet formulations were bioequivalent to the conventional oral tablet as determined by AUC and Cmax for zolmitriptan and its active N-desmethyl metabolite (183C91).
3. Absorption of zolmitriptan from the RDT was prolonged compared to the conventional oral tablet (average Tmax was approximately 3.0 hours for the [redacted] formulations compared to 1.5 hours for the conventional tablet). It is expected that [redacted] be taken as a single dose [redacted]. The Medical Officer may want to evaluate the clinical relevance of this increase in Tmax.
4. The firm's selection of the same dissolution procedure and specification used for the conventional tablets is acceptable. The approved dissolution procedure uses the USP Paddle Method (Apparatus II) at 50 rpm and [redacted] dissolution medium. The specification is [redacted] 15 minutes.
5. OCPB accepts the following labeling proposed by the sponsor in the Clinical Pharmacology section for Absorption:

*ZOMIG-ZMT™ Orally Disintegrating Tablets*

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

**Recommendation:**
NDA 21-231 has been reviewed and has been found acceptable by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). This submission meets the OCPB requirements for approval. Comment number 3 should be brought to the attention of the Medical Officer. Comment number 4 should be forwarded to the sponsor.

ClinPharm Briefing: January 25, 2001
Attendees: Mehul Mehta, Chandra Sahjawalla, Armando Oliva, Ray Baweja, Carol Noory

Carol Noory: _____

FT: initialed by Ray Baweja, Ph.D. _____

Cc: NDA 21-231 ( [redacted] ), HFD-120, HFD-860 (Noory, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

APPEARS THIS WAY
ON ORIGINAL

/s/
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Carol Noory
1/29/01 09:41:40 AM
UNKNOWN

Raman Baweja
1/29/01 10:16:31 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL