

The absolute bioavailability and effect of food on the pharmacokinetics of zolmitriptan in healthy volunteers

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Aims Zolmitriptan (Zomig (formerly 311C90)) is a novel 5-HT_{1B/1D} receptor agonist developed for the acute oral treatment of migraine. A highly sensitive LCMS-MS assay has been developed which allows quantification of plasma concentrations of zolmitriptan and its active metabolite, 183C91, after therapeutic doses. Two studies using this assay method were conducted to investigate the pharmacokinetics, including absolute bioavailability, of 2.5 and 5 mg oral doses of zolmitriptan in men and women, the dose-proportionality of 2.5, 5 and 10 mg doses and the effect of food on the pharmacokinetics of a 5 mg oral dose.

Methods Two randomized, balanced, open-label, 4-period crossover studies were conducted in a total of 32 healthy volunteers. The first study determined the absolute bioavailability of 2.5 and 5 mg doses of zolmitriptan and compared the pharmacokinetics in men and women. The second study examined the dose-proportionality in pharmacokinetics after fasting doses of 2.5, 5 and 10 mg, and the effect of food on a 5 mg dose. Blood pressure, heart rate, ECG, clinical chemistry, haematology and adverse events were also monitored.

Results The mean (s.d.) absolute oral bioavailability was 0.41 (0.14 and 0.40) 0.09 after 2.5 mg and 0.48 ± 0.14 and 0.36 ± 0.07 after 5 mg in women and men, respectively. Without adjustment for bodyweight, plasma concentrations of zolmitriptan, but not 183C91, were higher in women than men. Mean (\pm s.d.) AUC was 32.7 ± 10.1 and 60.2 ± 26.8 ng ml⁻¹ h after 5 mg in men and women, respectively (95% CI for ratio 0.43–0.77). After 2.5 mg mean (\pm s.d.) AUC was 18.4 ± 5.4 and 23.1 ± 9.9 ng ml⁻¹ h in men and women, respectively (95% CI for ratio 0.61–1.09). However, these differences were of no clinical significance. C_{max} and AUC of oral zolmitriptan were dose-proportional and there was a 13 and 16% fall in mean zolmitriptan C_{max} and AUC, respectively, when administered after food. Adverse effects were minor, predominantly mild and transient, and there were no clinically significant effects on ECG, blood pressure, or laboratory parameters.

Conclusions At therapeutic doses zolmitriptan has good oral bioavailability in healthy volunteers and has dose-proportional pharmacokinetics that are not affected by food to any clinically relevant extent.

Keywords: bioavailability, food, pharmacokinetics, zolmitriptan

Introduction

Zolmitriptan (Zomig, formerly 311C90) is a new 5-hydroxytryptamine (5-HT)_{1B/1D} receptor agonist [1] developed for the acute oral treatment of migraine. Clinical studies have shown it to be effective and well tolerated in the acute treatment of migraine at doses of 2.5–25 mg, with a headache response at 2 h in 62–81% of patients [2–4], and 2.5 mg representing the optimal balance between efficacy and adverse effects [5, 6]. Zolmitriptan inhibits the peripheral trigeminovascular system and is able to access central sites in the brainstem involved in processing cranial pain [7, 8].

The pharmacokinetics of single oral doses of zolmitriptan

from 6 to 50 mg in healthy volunteers have already been described [9]. The absolute bioavailability of a single 10 mg dose is 49% [10], compared with 14% reported for sumatriptan 100 mg [11]. Zolmitriptan is rapidly absorbed after oral administration but as plasma profiles show multiple peaks in some subjects, individual *t*_{max} values may vary from 0.5 to 5 h [6]. Zolmitriptan is eliminated mainly by metabolism followed by urinary excretion of the metabolites [9, 10]. There are three major metabolites; the active *N*-desmethyl metabolite, 183C91, which is an agonist at 5-HT_{1B/1D} receptors with at least twice the potency of zolmitriptan, and the *N*-oxide and indole-acetic acid metabolites, both of which are pharmacologically inactive. The half-lives of zolmitriptan and its metabolites are similar at 2.5–3 h. After a single 10 mg oral dose, plasma concentrations of zolmitriptan were higher in women than

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men [10], probably due to lower body weight, lower first-pass metabolism and lower systemic clearance.

In the previously reported studies [9, 10, 12], assays of zolmitriptan and its three major metabolites were performed using high performance liquid chromatography with fluorescence detection with a limit of quantification in plasma of 2 ng ml^{-1} [12]. This method was insufficiently sensitive to enable full pharmacokinetic profiling of zolmitriptan at the optimal therapeutic dose of 2.5 mg. Therefore, a more sensitive liquid chromatography-mass spectrometry (LCMS-MS) method was developed to assay zolmitriptan and its active metabolite 183C91. In this paper we report the results of two studies using this assay method investigating the pharmacokinetics, including bioavailability, of 2.5 and 5 mg oral doses of zolmitriptan, the dose-proportionality of 2.5, 5 and 10 mg doses and the effect of food on the pharmacokinetics of a 5 mg oral dose.

Methods

Study design and inclusion criteria

Both studies were conducted at Pharma Bio-Research (PBR), Zuidlaren, The Netherlands. Non-smoking male and female volunteers, aged 18–45 years, of normal build and in good general health with no significant clinical abnormalities were recruited from the volunteer panel of PBR. All volunteers underwent a full medical screen including a 12-lead electrocardiogram. Exclusion criteria included: receipt of any regular medication in the 4 weeks before the study (including over-the-counter preparations, but excluding oral contraceptives), current or past history of drug abuse or excessive alcohol intake, hypertension ($>150/90 \text{ mmHg}$); clinical evidence of cardiovascular disease, Wolff-Parkinson-White syndrome or a family history of premature (<55 years) cardiovascular disease. Female volunteers who were pregnant, breast feeding or not using adequate contraception were excluded.

Ethical approval for both studies was obtained from the Medical Ethics Committee of the Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, Assen, The Netherlands, and written informed consent was obtained from each volunteer.

Volunteers were admitted to the research unit on the afternoon before each study day. Alcoholic beverages and caffeine-containing foods and drinks were not allowed for 48 h before and during each study period and volunteers were also asked to refrain from strenuous exercise for 24 h prior to their arrival and during their stay at the research unit. They rested on their beds for 4 h after each dose but thereafter were unrestricted except for 5 min rest prior to each blood pressure measurement.

Absolute bioavailability study

This was an open, randomized, balanced, four-period crossover study in 10 healthy men (mean (range) age 23 (20–28 years) and weight 77.5 [65.1–90.2] (kg) and 10 healthy women (mean (range) age 23 (19–34 years) and weight 68.9 [52.0–85.0] (kg)). Each volunteer received in random order, single oral 2.5 and 5 mg doses of zolmitriptan

and two intravenous (i.v.) doses which were predicted, based on existing data, to give AUC values similar to those after oral 2.5 and 5 mg doses. It had been observed previously that zolmitriptan bioavailability was higher in women than men after an oral dose of 10 mg [10] so the i.v. doses were calculated using bioavailability estimates of 37% in men and 59% in women. Hence, women received i.v. doses of 1.475 and 2.95 mg and men received 0.925 and 1.85 mg to correspond to 2.5 and 5 mg doses, respectively. The i.v. doses were given by infusion in a volume of 200 ml over 2 h via an IVAC 630-series infusion pump connected to a catheter placed in a suitable forearm vein. The oral doses were given after an overnight fast with 200 ml water. There was a washout period of at least 5 days between doses.

Dose proportionality/food effect study

This was an open, randomized, balanced, four-period crossover study in six healthy men (mean (range) age 21 (20–24 years) and weight 72.1 [64.3–84.6] (kg) and 10 healthy women (mean (range) age 26 (20–43 years) and weight 60.9 [53.0–66.6] (kg)). Each subject received, in random order, single oral doses of zolmitriptan 2.5, 5 and 10 mg after an overnight fast and 5 mg after a standard breakfast. The meal consisted of cornflakes with milk, fried bacon, sausage and egg, toast with butter and marmalade, and orange juice and comprised 967 kcal, 13.1% from protein, 47.3% from fat and 39.6% from carbohydrate. There was a washout period of at least 5 days between doses.

Clinical methods and procedures

Blood samples (5 ml) for assay of plasma concentrations of zolmitriptan and its active metabolite, 183C91, were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 15 h after drug administration in the dose proportionality/food effect study and at the same times but with the addition of a sample at 3.5 h post dose in the absolute bioavailability study. Blood was taken into lithium heparin tubes, centrifuged at 1500 g and 4° C for 10 min to obtain plasma for assay of zolmitriptan and 183C91 which was then frozen at -20° C until analysis.

Routine full blood counts and biochemistry evaluations were performed before and 24 h after each dose. Supine systolic and diastolic blood pressures (SBP and DBP) and pulse rate were recorded 60 and 40 min before drug administration and at the same times as the blood samples until 10 h after each dose. Final readings were taken 24 h after administration. Patients were semirecumbent for the first 4 h and rested supine for 5 min prior to each BP reading thereafter. A 12-lead ECG was recorded just before and 24 h after each drug administration.

Plasma concentrations and pharmacokinetics

Plasma concentrations of zolmitriptan and 183C91 were determined by automated solid phase extraction followed by high performance liquid chromatography mass spectrometry. The solid phase extraction was carried out using 50 mg C18 Porvair Filtronics microlut blocks which were first conditioned using 0.5 ml aliquots of acetonitrile, water and 10 mM

ammonium formate buffer at pH 5. 0.1 ml of a 10 ng ml⁻¹ solution of internal standard (²H₆-zolmitriptan) and 0.4 ml 10 mM ammonium formate buffer were mixed with 0.5 ml aliquots of the plasma samples, which were then transferred to the wells of the microlut blocks. After adsorption of the compounds onto the C18 matrix, the wells were washed with 0.5 ml aliquots of 10 mM ammonium formate buffer, water and acetonitrile. Zolmitriptan, 183C91 and internal standard were eluted from the matrix using 0.3 ml of 50% (v/v) acetonitrile, in 150 mM ammonium formate buffer. An aliquot of the elutant was injected onto a cation exchange chromatography column (Spherisorb[®] SCX 5 µm, 30 (4.6 mm) and the separation was monitored using tandem mass spectrometry (Sciex[®] API-III mass spectrometer) with positive ion atmospheric pressure ionization, using a turbo ionspray interface and multiple reaction monitoring.

The peak areas for zolmitriptan and 183C91 relative to internal standard were calculated and the concentrations of the analytes were determined by reference to the relevant linear calibration curves which were constructed by adding known amounts of zolmitriptan and 183C91 to control plasma and extracting these standards alongside each batch of samples analysed.

The upper and lower limits of quantification were 0.1 ng ml⁻¹ and 15 ng ml⁻¹ for both zolmitriptan and 183C91 in plasma. Quality control samples at three concentrations (0.3, 1.0 and 12 ng ml⁻¹) were used. In the absolute bioavailability study, the accuracy (% bias) for zolmitriptan and 183C91 ranged from -6.6 to -0.8% and -1.1 to -0.7%, respectively. The overall precision (%CV) for zolmitriptan and 183C91 ranged from 6.7 to 12% and 9.3 to -14.3%, respectively. In the dose proportionality/food effect study, the accuracy ranged from -2.5-3.9% and -1.6 to -15.4%, for zolmitriptan and 183C91, respectively. The overall precision (%CV) for zolmitriptan and 183C91 ranged from 5.5 to 12.5% and 7.2-11.4%, respectively.

In both studies, noncompartmental pharmacokinetic parameters were calculated for each set of assay data using PC-SAS version 6.10. For both zolmitriptan and 183C91, the area under the plasma concentration-time curve (AUC) was determined using the trapezoidal rule and extrapolated beyond the last measurable concentration (*C_t*) to infinity (AUC(0,∞)) using the elimination rate constant (*λ_z*). *λ_z* was obtained by log-linear regression of the terminal portion of the plasma concentration *vs* time curve, and the terminal plasma elimination half-life (*t_{1/2}*) was calculated as ln [2]/*λ_z*. Peak plasma concentration (*C_{max}*) and time to reach *C_{max}* (*t_{max}*) were taken directly from the curves of plasma concentration *vs* time. Clearance (CL) and the volume of distribution (*V*) of zolmitriptan after intravenous administration were calculated as Dose/AUC(0,∞) and CL/*λ_z*, respectively. CL and *V* after oral administration were calculated as for i.v. administration and expressed as CL/*F* and *V*/*F* in both studies, where *F* is bioavailability after an oral dose. The absolute oral bioavailability (*F*) was calculated as:

$$F = \frac{\text{AUC}_{\text{p.o.}}}{\text{AUC}_{\text{i.v.}}} \times \frac{\text{Dose}_{\text{i.v.}}}{\text{Dose}_{\text{p.o.}}}$$

The AUC from the lower i.v. dose was used to calculate

the bioavailability of the 2.5 mg oral dose and that from the higher i.v. dose for the 5 mg oral dose.

Statistical analysis

Absolute bioavailability study All pharmacokinetic parameters (except *t_{max}*) were log-transformed and subjected to analysis of variance (ANOVA). A mixed model was used, with factors of subject, sex, dose, period, formulation and interactions. Bioavailability was estimated for each oral dose with 95% confidence intervals (CI) for all subjects and for each gender separately. Pharmacokinetic parameters for zolmitriptan and 183C91 were compared between men and women using ANOVA and the differences between the genders with 95% CI were calculated. *C_{max}* and AUC after intravenous zolmitriptan were dose-normalized for the between-gender comparison. For analyses conducted on a logarithmic scale, point estimates and differences between treatments resulted in geometric means and ratio estimates when back-transformed. *t_{max}* was summarized by descriptive statistics only.

Dose proportionality/food effect study In order to determine dose-proportionality, AUC and *C_{max}* were dose-normalized to a 5 mg dose before analysis. AUC(0,∞), *C_{max}*, *t_{1/2}* and *V*/*F* were log-transformed and subjected to a 4-factor ANOVA (factors of sex, subject, period and treatment). Point estimates and 95% CI were calculated for the comparison of AUC(0,∞), *C_{max}*, *t_{1/2}*, and *V*/*F* between 2.5 and 5 mg, fasted, 10 mg and 5 mg, fasted and between 5 mg fed and 5 mg fasting. *t_{max}* was analysed using the Wilcoxon signed rank test, and differences between medians after 5 mg fed and 5 mg fasting were estimated with 95% CIs.

Based on data from previous studies with zolmitriptan in healthy volunteer it was estimated 12 subjects would give 80% power to detect a 30% change in AUC within a study group.

Results

All subjects completed the study as planned.

Zolmitriptan pharmacokinetics

After intravenous administration, peak zolmitriptan concentrations occurred at or near the end of the infusion followed by a biphasic distribution and elimination phase (Figure 1). In contrast, after oral administration there was a fairly rapid initial absorption of drug, on average reaching 75-80% of eventual *C_{max}* within 1 h; plasma concentrations were then sustained for up to 6 h with multiple peaks in some subjects, followed by the elimination phase. There was considerable variability in zolmitriptan concentrations within each gender group. After oral doses of 2.5 and 5 mg in women, AUC ranged between 13 and 42 ng ml⁻¹ h and 26-100 ng ml⁻¹ h, respectively; in men at the same doses the ranges were 11-26 ng ml⁻¹ h and 13-44 ng ml⁻¹ h, respectively.

After oral dosing, zolmitriptan AUC and *C_{max}*, were higher in women than men although this was only statistically significant after 5 mg (Table 1). There was no

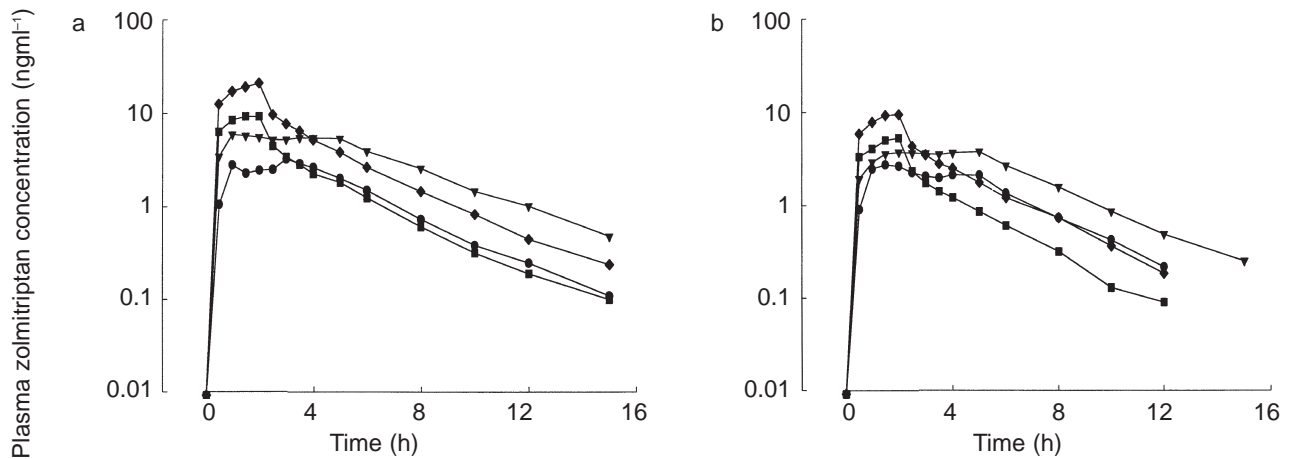


Figure 1 Median plasma zolmitriptan concentrations in a) women and b) men after oral doses of 2.5 mg (●) and 5 mg (▼) and intravenous doses of 1.475 mg (women) or 0.925 mg (men) (■) and 2.95 mg (women) or 1.85 mg (men) (◆).

Table 1 Geometric mean zolmitriptan and 183C91 pharmacokinetic parameters in men (*n*=10) and women (*n*=10) after oral dosing.

	2.5 mg			5 mg		
	Male	Female	Ratio (95% CI)	Male	Female	Ratio (95% CI)
Zolmitriptan						
AUC(0,∞) (ng ml ⁻¹ h)	17.7	21.3	0.82 (0.61, 1.09)	30.9	54.8	0.57 (0.43, 0.77)
C _{max} (ng ml ⁻¹)	3.3	3.8	0.87 (0.66, 1.16)	5.6	9.0	0.64 (0.48, 0.84)
t _½ (h)	2.29	2.56	0.90 (0.74, 1.09)	2.60	2.82	0.92 (0.75, 1.12)
F*	0.39	0.39	1.00 (0.80, 1.26)	0.35	0.45	0.78 (0.62, 0.98)
183C91						
AUC(0,∞) (ng ml ⁻¹ h)	11.6	10.7	1.08 (0.83, 1.40)	20.9	22.8	0.95 (0.73, 1.23)
C _{max} (ng ml ⁻¹)	2.16	1.87	1.16 (0.85, 1.56)	3.7	3.4	1.10 (0.81, 1.49)
t _½ (h)	2.17	2.48	0.87 (0.70, 1.08)	2.53	2.83	0.89 (0.72, 1.11)
Ratio AUC 183C91: AUC zolmitriptan (%)*	0.67	0.55		0.70	0.46	

*Arithmetic mean.

Table 2 Geometric mean zolmitriptan and 183C91 pharmacokinetic parameters in men (*n*=10) and women (*n*=10) after intravenous dosing.

	0.925 mg	1.475 mg	Ratio (95% CI)	1.85 mg	2.95 mg	Ratio (95% CI)
	Male	Female		Male	Female	
Zolmitriptan						
AUC(0,∞) (ng ml ⁻¹ h)	16.8	32.4	0.81 (0.61, 1.09)**	32.5	71.2	0.74 (0.55, 0.99)**
C _{max} (ng ml ⁻¹)	5.8	10.0	0.91 (0.69, 1.21)**	10.6	22.2	0.78 (0.59, 1.03)**
t _½ (h)	2.10	2.50	0.84 (0.69, 1.21)	2.32	2.66	0.87 (0.71, 1.06)
CL (ml min ⁻¹ kg ⁻¹)	11.8	11.2	1.09 (0.79, 1.49)	12.3	10.2	1.20 (0.87, 1.64)
V _z (l kg ⁻¹)	2.16	2.40	0.92 (0.72, 1.17)	2.48	2.33	1.04 (0.81, 1.34)
183C91						
AUC(0,∞) (ng ml ⁻¹ h)	3.9	6.6	0.93 (0.72, 1.21)**	8.1	13.5	0.96 (0.74, 1.25)**
C _{max} (ng ml ⁻¹)	0.9	1.4	0.96 (0.71, 1.31)**	1.8	3.0	0.96 (0.71, 1.30)**
t _½ (h)	2.40	2.51	0.96 (0.77, 1.19)	2.28	2.86	0.80 (0.64, 0.99)
Ratio AUC 183C91: AUC zolmitriptan (%)*	0.23	0.21		0.25	0.20	

*Arithmetic mean. **Parameters dose-adjusted before comparison.

gender difference in oral bioavailability after 2.5 mg but the bioavailability of the 5 mg dose was higher in women (Table 1). After intravenous dosing, especially at the higher dose, plasma zolmitriptan concentrations were again higher in women than men even after correction for the difference in doses (Table 2). However, there were no gender differences

in weight adjusted clearance. In general, elimination half-life was slightly shorter in men, but none of the differences between men and women was statistically significant (Tables 1 and 2).

Half-life was slightly shorter after i.v. compared with oral administration. Combining data from all subjects and both

favourably with the 0.14 reported for 100 mg sumatriptan [11]. The relatively low bioavailability of sumatriptan is due predominantly to presystemic metabolism and incomplete oral absorption [13]. Comparison of the plasma concentration profiles for zolmitriptan and 183C91 after oral and i.v. administration (and the higher 183C91/zolmitriptan AUC ratio after oral dosing) suggests that first-pass metabolism also plays a part in determining the oral bioavailability of zolmitriptan. Incomplete absorption contributes to the oral bioavailability as about 20% of an oral dose of zolmitriptan is recovered in faeces, presumably representing unabsorbed drug [10]. In contrast to i.v. administration, the occurrence of multiple peaks in the plasma profile after oral administration suggests that absorption may occur over a considerable length of the gastrointestinal tract or may reflect delayed or partial gastric emptying after administration of 5-HT_{1B/D} agonists [14]. The single peak after i.v. administration suggests that enterohepatic recirculation does not occur.

The gender differences in bioavailability of zolmitriptan after 5 mg in this study were smaller than reported previously after a 10 mg dose with no apparent gender differences after the 2.5 mg dose [10]. This could suggest dose-related bioavailability, but this is unlikely given the good dose-proportionality between 2.5 and 10 mg reported here and from 5 to 15 mg [15] and 6–50 mg [9] reported in previous studies. The between-study differences probably reflect the small number of subjects in each study. Plasma concentrations after oral administration in women were higher than in men with relatively more metabolism in men, as indicated by higher concentrations of the active metabolite 183C91 relative to those of parent zolmitriptan. The concentration differences between men and women cannot be explained by differences in CL or *V*. The gender differences in concentrations are thus chiefly due to the small gender difference in bioavailability. This, in turn, is most likely explained by a difference in first-pass metabolism [9]. Combining data from all healthy volunteers studied after doses of 2.5–10 mg inclusive, the gender differences in plasma concentrations are found to be consistent across the dose range with AUC(0,∞) and C_{max} 44% and 27% higher in women, respectively, after a 2.5 mg dose and 40% and 30% higher after a 10 mg dose (Layton G. Overview analysis of zolmitriptan volunteer studies—personal communication). This suggests there are no dose-related changes in bioavailability. Furthermore, at the therapeutic dose of 2.5 mg, the magnitude of the gender difference in concentrations is of no clinical consequence. The mean effect is small relative to the variability in concentrations within each gender group, both within and between studies, and there are no gender-related differences in efficacy or adverse effects in clinical trials [16].

Zolmitriptan was well tolerated in both studies. The most frequently reported adverse events, headache and sensations of tightness and/or pain (usually in the jaw and neck) are characteristic of 5-HT_{1B/D} agonists, and have been reported previously with both sumatriptan and zolmitriptan [9, 10, 12, 13, 17, 18]. The tolerability profile of zolmitriptan concurs with safety data from 255 healthy volunteers and ≈2500 patients with migraine in the international zolmitriptan clinical development program [16] which show that adverse events associated with zolmitriptan are generally

dose-related. In the absence of a placebo control the small blood pressure changes observed in these studies must be interpreted with caution. Dose-related, but clinically insignificant, increases in BP have been reported previously after administration of zolmitriptan to healthy volunteers in double-blind, placebo-controlled studies [12, 15].

In conclusion, 2.5 and 5 mg doses of zolmitriptan were well tolerated. Mean bioavailability was ≈40%. A gender difference was observed after 5 mg doses with higher bioavailability in women than men, but this is not of clinical relevance. Plasma concentrations were proportional to dose and there was no significant effect of food on the pharmacokinetics of zolmitriptan or its active metabolite.

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