CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-447

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
NEW DRUG APPLICATION - REVIEW

NDA:	21-447
Submission Date(s):	October 31, 2001 January 29, 2002 February 12, 2002 Fax (Dissolution Data) February 14, 2002 BL March 13, 2002 Fax (Dissolution Data – Pivotal Batch)
Brand Name	Zanaflex®
Generic Name	Tizanidine
Reviewer	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader	Raman Baweja, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM division	Division of Neuro-psychiatric Drug Products (DNPDP) HFD-120
Sponsor	Elan Pharmaceuticals San Diego, California
Relevant IND(s)	37,891
Relevant NDA(s)	20-397 Tizandine Tablets 20-397 SLR 014
Submission Type; Code	N – New SCF (Supplement – Chemistry – New Formulation)
Formulation(s); Strength(s)	Capsules; 2, 4, 6 mg
Route(s) of Administration	Oral
Indication(s)	Management of Spasticity

1 EXECUTIVE SUMMARY

1.1 BACKGROUND

Tizanidine 4 mg tablets (ZANAFLEX® ELAN), NDA 020-397 was approved Nov 27, 1996 for spasticity and a supplement for a 2 mg tablet was approved Feb 04, 2000. This NDA (21-447) is for approval of 3 capsule strengths, 2 mg, 4 mg, and 6 mg. Dosing is t.i.d. but the schedule is adjusted to time the effect of the drug to when it is needed.

At the time of filing an inspection was requested for the pivotal bioequivalence study (6 mg; study 0600002) and is scheduled to take place in June 2002 in

1.2 RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-447 submitted October 31, 2001.

OCPB finds this application **acceptable**.

Comments should be communicated to the sponsor as appropriate:
(See Section 3.1.2 on page 8).

Labeling comments should also be communicated to the sponsor as appropriate:
(See Section 3.3 Labeling Comments on page 9).

2 CPB FINDINGS

2.1 SCOPE AND QUALITY OF INFORMATION

The scope of information provided is adequate for this new capsule formulation.

Information provided includes:

- Single dose fasting bioequivalence studies with the highest proposed dosage formulation (6 mg capsule) compared to the currently marketed tablet formulation (4 mg + 2 mg)
- Bioequivalence studies in the presence of food (4 mg and 2 x 4 mg)
- Food effect study when sprinkled on applesauce (6 mg capsule – highest strength)
- PK/PD study of tizanidine tablet and capsules in the presence and absence of food (2 x 4 mg)
- Dissolution profiles : ——— tested, 2 mg stability batch, 4mg PK study batch, & 6 mg pivotal clinical batch)
- 2 mg biowaiver request

- The quality of the pivotal pharmacokinetic information is adequate. However, for the PK-PD study the assay did not perform acceptably and the pharmacokinetic metrics generated cannot be considered accurate. In addition, the pharmacodynamic data and analysis from this study was not reviewable as the photocopies provided were not legible. However, the graphs and study report were sufficiently legible to make qualitative inferences. To gain additional insight would require a new study with a different design.

2.2 SUMMARY OF FINDINGS

- Under fasting conditions tizanidine **6 mg capsules** (the highest proposed to-be-marketed strength) are bioequivalent to tizanidine **tablets (4 mg RLD + 2 mg)**. [Study 0600002]

- Under fasting conditions tizanidine 4 mg capsules are bioequivalent to tizanidine 4 mg tablets (the reference labeled drug). [Study 0300003]

- Although tizanidine capsules meet bioequivalence criteria under fasted conditions, there is a delay in tlag and Tmax for the capsules as compared to the tablets that is consistently seen across studies. On average the delay is 6 and 14 minutes respectively.

- When tizanidine capsules are administered under **fed** conditions, there is a delay in absorption compared to when the capsule is administered under fasting conditions. Specifically there is approximately a doubling in tlag from ~25 minutes to ~50 minutes, and in Tmax from ~77 minutes to ~160 minutes. This delay in absorption is associated with a mean decrease in Cmax by 20%. There is also a small increase in the extent of absorption, (10%). [Study AN021-101]

- When bioequivalence of the capsule relative to the tablet is examined under **fed** conditions, There is a delay in absorption and the mean Cmax for the capsule is approximately 2/3's of the mean Cmax for the tablet (90% CI - 50% to 87%). Specifically under fed conditions, the mean tlag and Tmax for the capsule are approximately double the values for the tablet. For the AUC ratio the 90% confidence interval is approximately 70% to 120%. [Study 0400001]

- Sprinkling the capsule contents on applesauce increases the rate of absorption of tizanidine as well as significantly decreases the variability in absorption rate. This is associated with approximately a 15% - 20% increase in Cmax and AUC. The increase in rate of absorption may be secondary to

faster dissolution the tizanidine beads due to removal of the capsule shell and dissolution of the beads beginning in the acidic applesauce even before swallowing the dose of drug. [Study 0400002]

- The PK-PD study indicates that there is a clinically significant difference in cognition and BP between the two formulations under fed conditions. There is clearly a PD difference with the capsules in the fed and fasted conditions, i.e. delayed. There are also likely greater pharmacodynamic effects with the tablet in the fed as compared to under fasted conditions, although this difference may not have reached statistical significance due to drop outs, inter-subject variability and lack of adequate sampling at times when the maximum PK effect might be detected. [Study AN021-101]

- The close relationship between the pharmacokinetic - pharmacodynamic time profile with adverse effects probably also holds for efficacy.

- Based upon biopharmaceutic considerations, the delay in tlag and Tmax with the capsules compared to the tablets are likely due to a pH dependent effect on the excipients that are used in the encapsulated beads.

- Absorption characteristics under fasting conditions are unaffected by dose up to 8 mg. Dissolution is slightly slower at 12 mg, but it is still fast with [redacted] dissolved in [redacted]. Consequently, in spite of this slightly slower dissolution with higher doses, it's still unlikely to cause a clinically significant difference in absorption characteristics with doses up to the maximum recommended dose of 12 mg.

- A biowaiver is requested by the sponsor for the 2 mg capsule strength. In assessing this request the following conclusions were made:

  a) Tizandine exhibits linear kinetics from 1 to 20 mg
  b) The 2 mg, 4 mg, and 6 mg capsules are encapsulated beaded formulations that only differ by the number of beads and are thus compositionally proportional
  c) Dissolution rate is rapid [redacted] in [redacted] for all strengths in all [redacted]

A biowaiver is granted for the 2 mg capsule.

2.3 POTENTIAL RISKS, ASSESSMENTS, AND PROPOSED RISK MANAGEMENT

All risks should be manageable through professional labeling and patient package inserts.

For example for each clinical scenario, i.e. taking a given formulation but changing its administration in the presence or absence of food; switching formulations when administered with food; or switching between intact capsules and sprinkles; the dose of tizanidine must be slowly and carefully retitrated. (See §3.3 Labeling Comments)

Risk 1 Variability in tlag and Tmax resulting in a lower Cmax with the capsule formulation might result in altered therapeutic efficacy.

Assessment

Tizanidine is a narrow therapeutic drug with a short duration of action. Both efficacy and AEs closely follow the concentration time profile. Because of the lack of safety data at higher doses or more frequently than t.i.d., tizanidine is taken in a pseudo as needed manner, with patients taking it at times so that the effect coincides with when they need it.

Although the capsules are bioequivalent to the tablets under fasting conditions, there is a very slight delay under fasting conditions in both tlag and Tmax (average 6 and 14 minutes respectively, although Tmax

may be delayed up to a few hours in some patients). This is associated with a slightly lower Cmax. Because of the narrow therapeutic range, the correlation of time course of effect with concentration, and the greater variability, it might be more difficult for patients to match the time course of effect to when they need it. The differences however in most cases are small and patients are likely to be attuned to the effects on their own bodies especially if they are aware of the possibility.

Proposed Management

Description in the labeling should be sufficient to guide patients in titrating their own dosage regimens.

Risk 2 Diminished and delayed efficacy when administered with food. (initial prescribability)

Assessment

Because tizanidine is taken so as to time the effect to when it is needed, it may not be possible to avoid taking it in close proximity to meals. For example, tizanidine may need to be taken first thing in the morning to allow the patient to move from their bed to their wheelchair. Or at lunch to allow functioning during the afternoon, or at dinner to allow functioning in the evening, or before bed to allow transfer to bed and minimizing discomfort so that a patient can sleep. Unfortunately, we don't know how long before or after meals tizanidine should be taken to minimize the food effect. In addition, the greater variability in absorption when taken with food makes timing administration to desired effect more difficult. However, the lower and/or delay in effects with the capsule with food could be advantageous in some situations when a patient is having difficulty tolerating the tablet. The increased exposure to tizanidine (and associated AEs) due to the effect of food on the tablet are already managed through professional labeling.

Proposed Management

Description in the labeling should be sufficient to guide patients in titrating their own dosage regimens.

Risk 3 Increased side effects when administered sprinkled on applesauce.

Assessment

Sprinkling the capsule contents on applesauce increases the rate of absorption and is associated with approximately a 15% - 20% increase in Cmax and AUC. Therefore there could be an associated increase in AEs. However, a faster and less variable onset, as well as administration in soft food, could be advantageous to some patients. The risks associated with administration on applesauce is low, as there is an even greater risk of AEs when taking the currently approved tablets with food and this is currently managed with labeling.

Proposed Management

Description in the labeling should be sufficient to guide patients in titrating their own dosage regimens.

Risk 4 Lack of switchability of the tablet and capsule under fed conditions. (i.e tablet fed – capsule fed switchability)

Assessment

The extent of absorption is increased for both the tablet and capsule when administered with food relative to the fasting state, but to different extents. In addition, the rate of absorption and Cmax is decreased when the capsule is administered with food relative to fasting conditions. This is opposite to what occurs with the tablet. Consequently, the capsule and tablet are bioinequivalent under fed conditions. This presents a switchability issue when a patient takes the medication with food and changes formulations.

Proposed Management

Description in the labeling with warning regarding switchability should be adequate to manage the risk.

Risk 5 Diminished and delayed efficacy when administered with drugs that alter gastric pH or to patients with conditions with altered gastric pH.

Assessment

Based upon biopharmaceutic considerations, the delay in tlag and Tmax with the capsules compared to the tablets are likely due to a pH dependent effect on the excipients that are used in the encapsulated beads or the drug itself. Consequently, food or any drugs or conditions that raise intragastric pH would be expected to slow absorption, e.g. achlorhydria, antacids, H2 antagonists, or proton pump inhibitors.

Proposed Management

Precautionary statements in labeling regarding conditions or drugs that might effect gastric pH should be sufficient to manage the risks.

Risk 6 Risk of increased toxicity when co-administered with rofecoxib (Vioxx® – Merck)

Assessment

The sponsor reports 8 case reports of interactions with rofecoxib (Vioxx® - Merck).

Most AEs were CNS or cardiovascular in nature. Some of the AEs fit the expected pharmacology of excessive tizanidine administration, and some of the AEs fit the profile expected with abrupt tizanidine withdrawal. Most of the other reported AEs are infrequently associated with tizanidine.

The mechanism and risk from this potential interaction is unclear. However the sponsor is to be commended for proposing labeling changes to raise awareness of the possibility of an interaction.

Proposed Management

Labeling changes should be adequate to address the potential drug interaction with rofecoxib. In addition, the division of Gastrointestinal and Hematologic drug products will be made aware of this potential interaction and will be requested to address this with rofecoxib.

Risk 7 High risk of lethality in suicide attempts (~1 of 3 attempts).

Assessment

Approximately 1 out of 3 suicide attempts resulted in death. Most overdose attempts resulted in respiratory depression typically requiring mechanical ventilation, cardiovascular effects, and CNS depression frequently resulting in coma. Other drugs, that patients on tizanidine may typically require (i.e. benzodiazepines and other muscle relaxants), as well as antidepressants, and possibly the patient's

underlying disease, are likely to have contributed to these deaths. This is because of pharmacodynamic synergy on respiratory, CNS, and cardiovascular depression. Several of the deaths involved only a 1 or 2 week supply of tizanidine. The sponsor's proposed labeling and suggestion to check with a poison control center is inadequate. Review of Poisindex®, the most common information source used by poison control centers, grouped tizanidine with other muscle relaxants and had very generic information. In fact, although clonidine is pharmacologically similar with a wealth of overdose information, there is no cross reference to clonidine. Currently there are 2 published case reports that poison information sources can draw on and neither of these cases resulted in fatality, nor mentions respiratory depression, and only one of the 2 cases mentions CNS depression. In addition, in one case flumazenil (a benzodiazepine antagonist) was used, which is relatively contraindicated with a drug with tizanidine's pharmacologic profile.

Proposed Management

In addition to labeling, this reviewer proposes publication of a review article of the presently known overdose cases in collaboration with the sponsor. This will allow tertiary sources of drug poisoning information, to disseminate more complete information than is possible in the professional labeling.

Risk 8 High risk of drug abuse in combination with narcotics in narcotic addicts.

Assessment

Several overdose cases indicate that tizanidine was being misused by individuals addicted to opioids. This is not surprising as clonidine, which is pharmacologically similar, is commonly misused by addicts to prolong the duration of narcotic effect and minimize opioid withdrawal symptoms. This results in the use of high doses over prolonged periods (e.g. > 50 mg / day of tizanidine and above). Consequently, a withdrawal syndrome can be precipitated due to going cold turkey, lack of awareness during treatment for addiction, lack of supply due to running out or incarceration.

Proposed Management

In addition to labeling changes similar to clonidine regarding slow withdrawal, this reviewer proposes including information in the proposed publication.

Risk 9 Increased risk of withdrawal in children due to the high incidence of gastrointestinal illness and the risk of emesis of tizanidine.

Assessment

Although tizanidine is currently not approved in children, the lack of good treatments for muscle spasms suggests a high likelihood of off-label use in children. Since, young children often have gastrointestinal illness, withdrawal due to emesis similar to that observed with clonidine is expected to occur with tizanidine.

Proposed Management

3 INFORMATION FOR COMMUNICATION TO SPONSOR

3.1 COMMENTS TO SPONSOR

3.1.1 Comments Already Conveyed

Full dissolution profiles for the pivotal clinical and bioequivalence batches are always needed.

3.1.2 Comments to be Conveyed

3.1.2.1 Dissolution Method and Specifications

- Please adopt the following dissolution method and specifications for all strengths of tizanidine capsules.

Table 1 Proposed Regulatory Dissolution Method and Specifications

Procedure:	As per (USP 23) <711>
Apparatus type:	USP Type II Apparatus (Rotating Paddles)
Medium:	
Volume (mL):	
Temperature	
Speed of rotation (r.p.m.):	
Sampling	
Sample time (hours):	
Sample Preparation	
Measurement:	
Acceptance Specification:	

3.1.2.2 General Comments

1) The overdose and drug withdrawal information provided is clinically important. Consequently, we are requesting a collaboration to publish more detailed information on these overdoses than can be provided in the labeling. This will provide poison control centers and tertiary poisoning information sources the best information available regarding overdoses.

3.1.2.2.1 NDA Format

Pivotal sections of study AN021-101 (Single Dose Pharmacokinetic, Pharmacodynamic, and Safety Study of Zanaflex® (Tizanidine Hydrochloride) Tablets 8 mg (2 x 4 mg) and Capsules 8 mg (2 x 4 mg) Administered with and without Food in Healthy Subjects) were illegible due to small font size and poor photocopy quality. This issue has been noted in previous tizanidine submissions. For example the following was communicated to the sponsor in a letter dated March 5, 1995 in regards to the original tablet NDA submission. "The NDA contained several illegible and unreadable figures... in ...all future submissions, please provide legible and readable figures." Legibility will be specifically looked for in future submissions, and per FDA guidances illegible submissions will not be filed.

3.2 PHASE IV COMMITMENTS

3.2.1 Commitments

The sponsor is requested to fulfill the following phase IV commitments.

3.2.2 Rationale(s)

Not applicable.

3.3 LABELING COMMENTS

In addition to labeling for the capsules that the sponsor has proposed in this NDA (#21-447), the sponsor has also submitted a labeling supplement to the tablet NDA, (20-397 SLR-014), that proposes changes to the tablet labeling regarding food effects. The labeling change for the tablet is based upon food effect study AN021-101 that is included in both the capsule NDA and the tablet labeling supplement.

Consequently, there are 2 options with regards to labeling:

a) separate labeling for the tablet and capsule formulations
b) combined labeling for both formulations

In order to assess the two approaches, the proposed tablet labeling was reviewed concurrently with the proposed capsule labeling. Labeling comments for both individual sets of labels follow and are presented side by side for comparison. In addition, a combined label for the tablets and capsules is also presented concurrently for comparison of the alternative approach.

For all three sets of labels, the basis for changes is the currently approved tablet labeling.

The following editorial marks are used in the labeling comments to indicate various changes:

Single underline is sponsor's proposed addition to currently approved tablet labeling
Single ~~strikethrough~~ is sponsor's proposed deletion to currently approved tablet labeling

highlighted text differs between tablet and capsule labeling (i.e. formulation specific labeling)

Double underline is reviewer's proposed addition to sponsor's proposed labeling
Double ~~strikethrough~~ is reviewer's proposed deletion to sponsor's proposed labeling

15 Draft Labeling Page(s) Withheld

4 SIGNATURES

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

Raman Baweja, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

4.1 OCPB BRIEFING MEETING:

Date:	Wednesday, May 15, 2002
Time:	10:00 AM – 11:30 AM
Location:	WOC-2 3rd Floor Conference Room C
Level:	Optional Inter-division
Attendees:	BastingsE, OlivaA, MalinowskiH, SelenA, MarroumP, ParekhA, BawejaR, KavanaghR

4.2 CC LIST:

NDA 21-447 (orig., 1 copy)
HFD-120 (ChenL, BastingsE, OlivaA, Katz, ChristodoulouD)
HFD-860 (Kavanagh, Baweja, Mehta, Marroum)
Central Document Room (Barbara Murphy)

5 TABLE OF CONTENTS

6 REVIEW

6.1 CHEMISTRY

6.1.1 Drug Product

Proposed – Capsules containing immediate release beads in 2 mg, 4 mg and 6 mg strengths

Currently Approved – 2 mg and 4 mg immediate release tablets.
The 4 mg tablet is the referenced labeled drug.

6.1.1.1 Manufacturing Process

[redacted]

6.1.1.2 Qualitative-Quantitative Formula(e)

Table 2 Qualitative-Quantitative Formulation of Tizanidine Capsules

Capsule Strength (TIZANIDINE BASE)	2 mg	4 mg	6 mg	% of Coating (w/w)	Function
Component	Content (mg / capsule)				
Tizanidine HCl	2.29	4.58	6.87		
[redacted]					
Hydroxypropyl Methylcellulose					
[redacted] Silicon Dioxide					
[redacted]					
Total	—	—	—	100.0 %	
HARD GELATIN CAPSULE					
Capsule Size	3	3	2		
Body					
Gelatin					
Cap					
Gelatin					

Proposed content uniformity is

6.1.2 Bioanalysis

Bioanalyses for this submission had numerous problems. However, for the pivotal bioequivalence study, (fasting conditions at the highest dose strength of 6 mg), this reviewer believes that the problems are sufficiently limited so that the sponsor's conclusion of bioequivalence is justified. (See section 6.1.2.2 below for discussion)

Bioanalysis for all studies in NDA 21-447 were conducted using a single method (see Table 3).

Table 3 Bioanalytic Method Used for Tizanidine in NDA 21-447

Analytic Method Number	Implementation Date	Biologic Matrix	Method Type	Title
—	9/27/00	Plasma - Human	—	Test Method for the Detemination of Tizanidine in Plasma by —

For a summary of the validation report findings see Appendix Section 7.2.

6.1.2.1 Bioanalytic Method Issues

The claimed assay range was — and utilized — standards. At the 2 lowest standard concentrations —, the degree of bias and imprecision were exceptionally high. For example, the intra-assay bias at — for the — runs ranged from -21.6% to 19.5%. For these — runs only one intra-assay CV was reported, and it was 17.5 %. Consequently, the Upper 95% CI for the — standard is at least 154%, and is likely higher. Even though these values are within the limits of ± 20% set by the bioanalytic guidance; these recommendations are holdovers from when analytic techniques were not as well developed. Consequently, this reviewer is not comfortable with assay values below — In fact, the sponsor threw out the results from a number of the assay runs in many of the later studies, although the specific reasons were not delineated. In addition, even upon excluding the — standard, many of the assay runs that were accepted, had excessively high errors for the next 2 lowest standards, even according to the sponsor. Thus, this reviewer would have eliminated the data from these runs as well, as the 3 lowest of the — standards were problematic. These standards are also in the concentration range where the patient samples are used to calculate half-life and to extrapolate AUC_∞. Consequently, the AUC_∞ is especially prone to inaccuracies.

Unfortunately, the large size of the symbols used on the semi-log plots and the size of the graphs themselves make it difficult to determine which data sets are the most problematic. Also no error plots are provided, which would have helped.

The consequences of these assay problems are most obvious in the PK-PD study, (AN021-101), where the capsules easily meet the 80 – 125 rule using AUC_{last}, but fail when AUC_∞ is used, due to the excessive variability in the extrapolated area.

6.1.2.2 Acceptability of Bioanalysis of Pivotal Bioequivalence Study

This reviewer accepts the conclusions of the pivotal bioequivalence trial, as the problems mentioned above are at a minimum compared to other studies and should not effect the sponsor's conclusion of bioequivalence.

Specifically:

- The data from both treatment arms are run within the same assay run.
- The values of AUC_{last} and AUC_∞ are very close to each other. So there is minimal extrapolation.
- The concentrations observed tend to be within the mid-range of the assay where there are the least problems, so there shouldn't be as many problems with the extrapolated areas.
- The limits for the 90% CIs for both AUC metrics do not approach the outer range of acceptable values.
- There is only 1 run that this reviewer would exclude based upon the back-calculated standards and/or QC samples. Even if the data from this run was excluded, the mean values of the BE metrics would not change significantly as the values from this subject are relatively close to the mean values. Plus, the 90% CIs would likely get tighter as the true values from this subject, (based upon the bias observed in the QC samples), are probably closer to the mean than reported.

6.2 PHARMACOKINETICS / BIOPHARMACEUTICS / PHARMACODYNAMICS

6.2.1 Biopharmaceutics

6.2.1.1 Bioequivalence –Fasting Studies

6.2.1.1.1 Cmax and AUC

Under fasting conditions, Tizanidine capsules meet the bioequivalence requirement relative to tizanidine tablets at the highest proposed capsule strength, i.e. 6 mg, (See Table 4, and appendix section 7.3.2.1) (Study 0600002).

Tizandine 4 mg capsules also meet the bioequivalence requirement relative to the 4 mg reference labeled formulation of tizanidine tablets under fasting conditions (See appendix section 7.3.2.2) (Study 0300003).

When 2 x 4 mg (8 mg) tizanidine capsules are compared to 2 x 4 mg (8 mg) tizanidine tablets the lower limit of the 90% CI for $AUC_{0-\infty}$ falls just below the acceptance criteria for bioequivalence, (79.2%). However, detailed review of the data indicates bioanalysis and possibly statistical analysis of this study is flawed and that the conclusions from the 6mg and 4 mg fasted bioequivalence studies are valid. Detailed review of this study can be found in appendix section 7.3.2.5 (Study AN021-101).

6.2.1.1.2 Time Metrics

Evaluation of Tlag and Tmax for the capsules as compared to the tablets reveals a slight delay for some subjects.

These delays average of 6 minutes for Tlag and 14 minutes for Tmax. However, the main issue is that the upper range for these values is much higher for the capsules. This is associated with trend toward a lower Cmax.

The magnitude of the clinical significance is difficult to evaluate. However, as tizanidine is a narrow therapeutic compound, albeit with presumed central mechanism for the hypotension and effects on cognition, it could be clinically significant. In addition, the degree and duration of the desired pharmacologic effect might be altered. However, the effect would likely be less than the effect of meals on the tablet formulation, which is currently simply described in the labeling. Consequently, these lags appear to be acceptable risks and may be minimized through appropriate labeling.

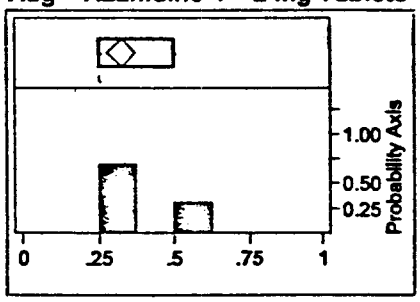
Table 4 Comparative Pharmacokinetic Metrics for Tizanidine 6 mg Capsules and Tizanidine Tablets (4 mg + 2 mg) Under Fasting Conditions (Study 0600002)

Metric	Mean ± SD (CV) Range		Median[a] & Geometric Mean Ratios		Relative Exposure (Test:Reference) Percent 90% CI
	Reference Tablets (4 mg + 2 mg)	Test Capsules 6 mg	Reference Tablets (4 mg + 2 mg)	Test Capsules 6 mg	
Tlag (hours)	0.33 ± 0.12 (36.0) 0.25 - 0.5	0.45 ± 0.12 (28.0) 0.25 - 0.75	0.25	0.5	—
Tmax (hours)	0.95 ± 0.27 (28.2) 0.5 - 1.5	1.16 ± 0.55 (46.6) 0.75 - 3	1.0[b]	1.0	—
Cmax (ng/ml)	5.53 ± 3.96 (71.6)	4.94 ± 2.77 (56.1)	4.53	4.17	92 84.74 - 111.44
AUC_{last} (ng/ml x hr^{-1})	14.13 ± 11.69 (82.7) 2.43 – 53.26	13.85 ± 9.71 (70.2) 1.44 – 48.93	10.87	10.87	100 96.65 - 119.69
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	15.25 ± 11.7 (77.0) 2.9 – 54.0	14.65 ± 9.81 (67.0) 1.77 – 49.4	12.19	11.76	96 94.42 – 113.69
$t_{1/2}$ (hours)	1.50 ± 0.40 (26.4) 0.77 - 2.27	1.41 ± 0.50 (35.8) 0.76 - 3.13	—	—	—
Frel	—	107.55 ± 31.53 (29.3) 65.47 - 201.64	—	—	—

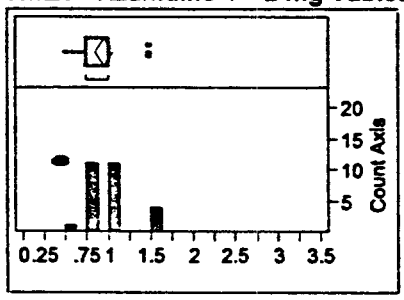
a Medians reported for Tlag and Tmax
b Mode = 0.75 hours

Figure 2 Comparative Time Metric Distributions for Tizanidine 6 mg Capsules and Tizanidine Tablets (4 mg + 2 mg) Under Fasting Conditions (Study 0600002)

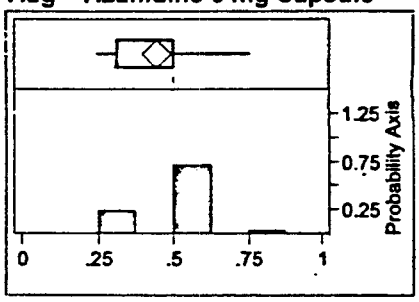
Tlag - Tizanidine 4 + 2 mg Tablets



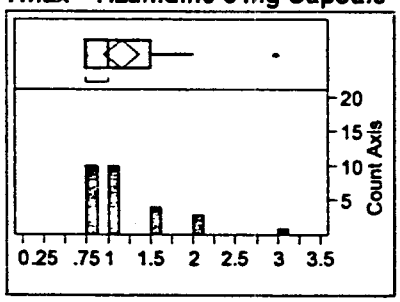
Tmax - Tizanidine 4 + 2 mg Tablets



Tlag - Tizanidine 6 mg Capsule



Tmax - Tizanidine 6 mg Capsule



6.2.2 Effect of Extrinsic Factors

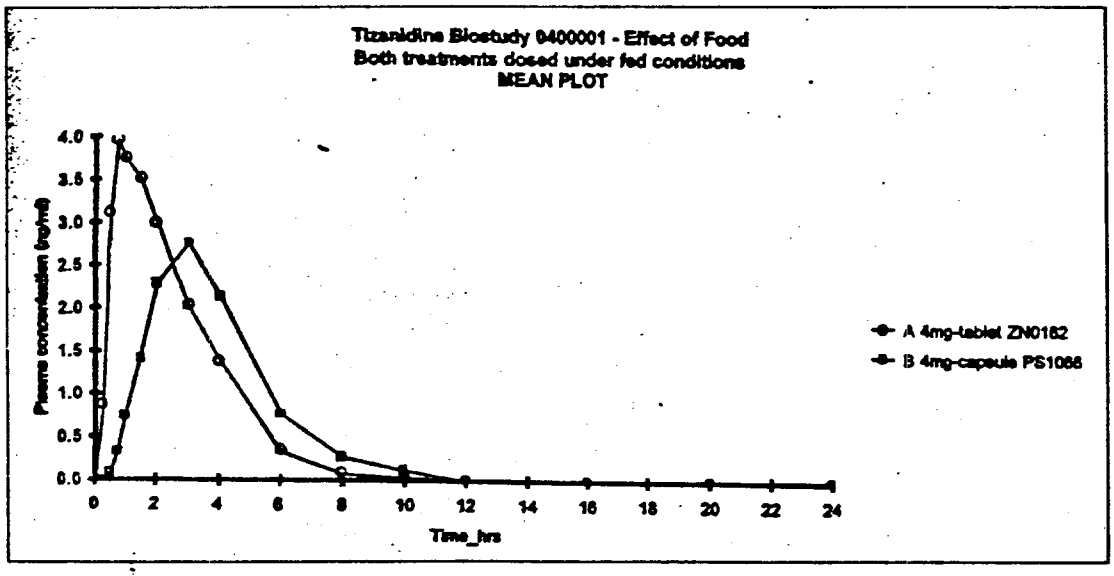
6.2.2.1 Food

6.2.2.1.1 High Fat / High Caloric Meals

When the capsule formulation is administered with food Tlag and Tmax both increase. This is associated with approximately a 20% decrease in Cmax and a 10% increase in AUC (study AN021-101). For the tablet when data from all studies are considered, including those from the tablet NDA. there's approximately a 30% increase in both Cmax and AUC when administered with food (study AN021-101).

Consequently, the Cmax for the capsule in the fed state is approximately 2/3's of the Cmax for the tablet in the fed state (geometric mean ratio of $Cmax^{fed}$ 0.66; 90% CI 50.4 – 87.2) (See Figure 3 and appendix sections 7.3.2.3 and 7.3.2.5). Although the AUC for the capsule increases when administered with food (10%), since the extent of increase is less than with the tablet (30%) the mean relative extent of absorption is only slightly less (geometric mean ratio 0.93). However, there's also an increase in the variability in the extent of absorption (AUC) when administered with a high fat meal (90% CI 0.71 – 1.22). Consequently the net effect on the relative extents of absorption for the 2 formulations when administered with food are difficult to tell. (See appendix sections 7.3.2.3 and 7.3.2.5) (study 0400001).

Figure 3 Comparative Effects of Food on Tizanidine Pharmacokinetics by Formulation



6.2.2.1.1.1 Clinical Scenarios for Switching Tizanidine Administration

As a consequence, the following clinical scenarios upon switching formulations are possible:

- Situation 1 - switching taking one formulation for the other in the absence of food.

  This should not have any clinical ramifications.

- Situation 2 - Change from taking a dose of either formulation in the presence or absence of food to the opposite situation.

  Since the drug is taken 3 times daily this may occur fairly frequently as it might be unavoidable at times. Consequently, appropriate labeling would be the most appropriate way to deal with the food effect rather than simply labeling to consistently take the medication with or without food.

- Situation 3 – Consistently taking tizanidine with food but changing the formulation.

  This would likely have the greatest clinical impact.

6.2.2.1.2 Sprinkled on Applesauce

Based on the sponsor's reported data for study 0400002, there's approximately a 20% increase in Cmax due to faster absorption of tizanidine when the contents of the capsule are sprinkled on applesauce. There's also a similar degree of increase in AUC (14%), (see Table 5 and Figure 4).

Again addressing this in the labeling is the most appropriate way to address this issue.

The bioanalysis for this study is discussed in appendix section 7.3.2.4.

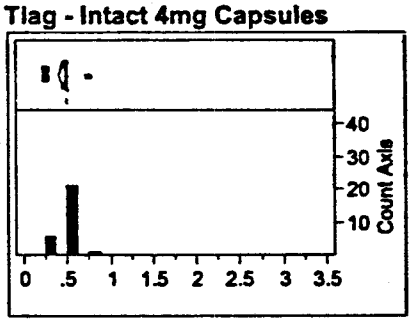
Table 5 Comparative Pharmacokinetic Metrics for Tizanidine 6 mg Capsules Administered Intact and Sprinkled on Applesauce Under Fasting Conditions (Study 0400002)

Metric	Mean ± SD (CV) Range		Median[a] & Geometric Mean Ratios		Relative Exposure (Test:Reference) Percent 90% CI
	Reference Intact 6 mg Capsules	Test Sprinkled 6 mg Capsules	Reference Intact 6 mg Capsules	Test Sprinkled 6 mg Capsules	
Tlag (hours)	0.46 ± 0.12 (26.1) 0.25 - 0.75	0.30 ± 0.1 (33.1) 0.25 - 0.5	0.5	0.25	—
Tmax (hours)	1.04 ± 0.54 (51.7) 0.5 - 3	0.84 ± 0.29 (34.3) 0.38 – 1.5	1.0	0.75	—
Cmax (ng/ml)	5.91 ± 3.78 (64.1)	7.1 ± 5.6 (79.7)	4.88	5.7	117 103.95 - 133.66
AUC_{last} (ng/ml x hr^{-1})	16.1 ± 11.9 (74.3) 1.35 - 53.1	18.3 ± 14.5[b] (79.4) 2.5 - 67.7	12.02	13.97	116 106.8 - 130.53
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	16.9 ± 12.0 (70.7) 2.7 - 54.4	19.2 ± 14.5[b] (75.5) 3.2 – 68.2	13.27	15.16	114 105.47 - 127.01
$t_{1/2}$ (hours)	1.32 ± 0.27 (20.2) 0.82 – 1.84	1.33 ± 0.21 (16.2) 0.84 – 1.70	—	—	—
Frel		120.05 ± 34.4 (28.7) 65.0 - 199.8	—	—	—

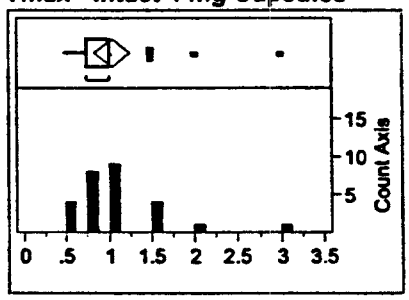
a Medians reported for Tlag and Tmax
b $p > 0.05$

Figure 4 Comparative Time Metric Distributions for Tizanidine 4 mg Capsules Administered Intact and Sprinkled on Applesauce Under Fasting Conditions (Study 0400002)

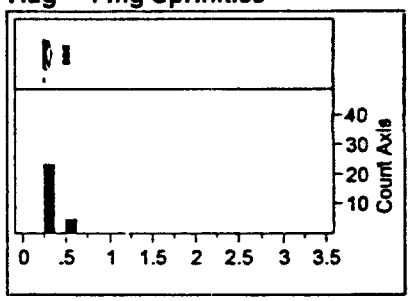
Tlag - Intact 4mg Capsules



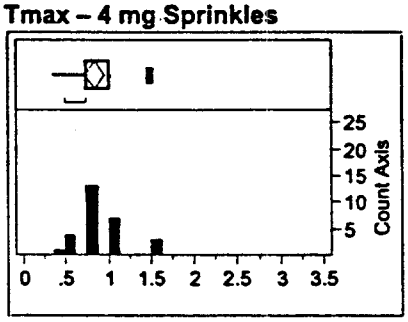
Tmax - Intact 4 mg Capsules



Tlag – 4 mg Sprinkles



Tmax – 4 mg Sprinkles



APPEARS THIS WAY
ON ORIGINAL

6.2.3 Drug Interactions

6.2.3.1 Gastrointestinal pH Alteration

Review of dissolution data, product formulation, and food effects indicate that drug release and absorption rate is likely pH dependent and clinically significant. Drugs that raise pH would also be expected to slow absorption. These include antacids, H2 antagonists, proton pump inhibitors, and some laxatives.

6.2.3.2 Rofecoxib

The sponsor reports 8 case reports of interactions with rofecoxib (Vioxx® - Merck).

Most AEs were CNS or cardiovascular in nature. Some of the AEs fit the expected pharmacology of excessive tizanidine administration, and some of the AEs fit the profile expected with abrupt tizanidine withdrawal. Most of the other reported AEs are infrequently associated with tizanidine.

All AEs resolved on discontinuation of one or both drugs. In the one case where the patient was rechallenged with tizanidine alone, no AEs occurred.

Since tizanidine is metabolized by microsomal P450s, whereas rofecoxib is metabolized by reduction by cytosolic enzymes, competitive *inhibition* is unlikely, but other forms of metabolic interactions are possible.

The sponsor proposes to include this potential interaction in the labeling, and in this reviewer's opinion based on the information presented, additional work on this potential AE is not warranted at this time.

6.2.3.3 Other Drugs

According to the sponsor: "one case each was reported of potential tizanidine drug interaction with warfarin, baclofen, 4-aminopyridine, Ticlid (ticlopidine), Avonex (interferon beta--1A), ciprofloxacin, Propulsid (cisapride), and Xanax (benzodiazepine). Some of these cases involved bradycardia and/or hypotension; however, the majority of AEs reported were varied and disparate from case to case. All AEs resolved, often without therapy."

More detailed case reports should be submitted for review.

6.2.4 Pharmacodynamics

Adverse effects (AEs) related to tizanidine concentrations and the effect of the formulation used and administration with food on these AEs were assessed in study AN021-101. The adverse effects that were monitored included various measures of cognition and blood pressure. The **quantitative results** from this study are problematic. However, the **qualitative conclusions** from this study are useful and indicate the potential for clinically significant differences in cognition and blood pressure under fed conditions for both the tablet and capsule, and these differences appear to follow the differences in plasma tizandine concentrations.

The quantitative results are problematic for the following reasons:

- There were a large number of problems with the bioanalysis.
- Sampling times were inadequate
- The data analysis was illegible. Specifically, an extremely small font was used and the photocopies provided were so faint that they couldn't be read.

It's noteworthy that the following biopharmaceutic deficiency dealing with the original Tizanidine tablet NDA was communicated to the sponsor in a letter dated March 5, 1995. "The NDA contained several illegible and unreadable figures... in ...all future submissions, please provide legible and readable figures."

In addition, even when mean data is presented graphically the type of error bars used is not defined.

The apparent **qualitative results** of the study are described below:

6.2.4.1 Pharmacodynamics of Cognition

Cognition was assessed at 0.75, 1.5, 2.5, and 6 hours post dosing.

The differences in cognitive adverse effects with food and formulation appear to follow the same patterns as the changes in the concentration profiles associated with the effects of food and formulation.

For tizanidine capsules there was a delay in the effect on cognition when tizanidine was administered with food. This is consistent with the effect of food on absorption (see Figure 5 and Figure 6).

For tizanidine tablets there was a trend for greater effects on cognition when the tablets were administered with food. This is also consistent with the effect of food increasing the absorption from tizanidine tablets (see Figure 5 and Figure 6).

Figure 5 Effect of Formulation and Food on Tizanidine Mean Concentration vs. Time Profiles (Study AN021-101)

Figure 14.4.2 Mean Plasma Tizanidine Concentrations Versus Time (Linear Scale)

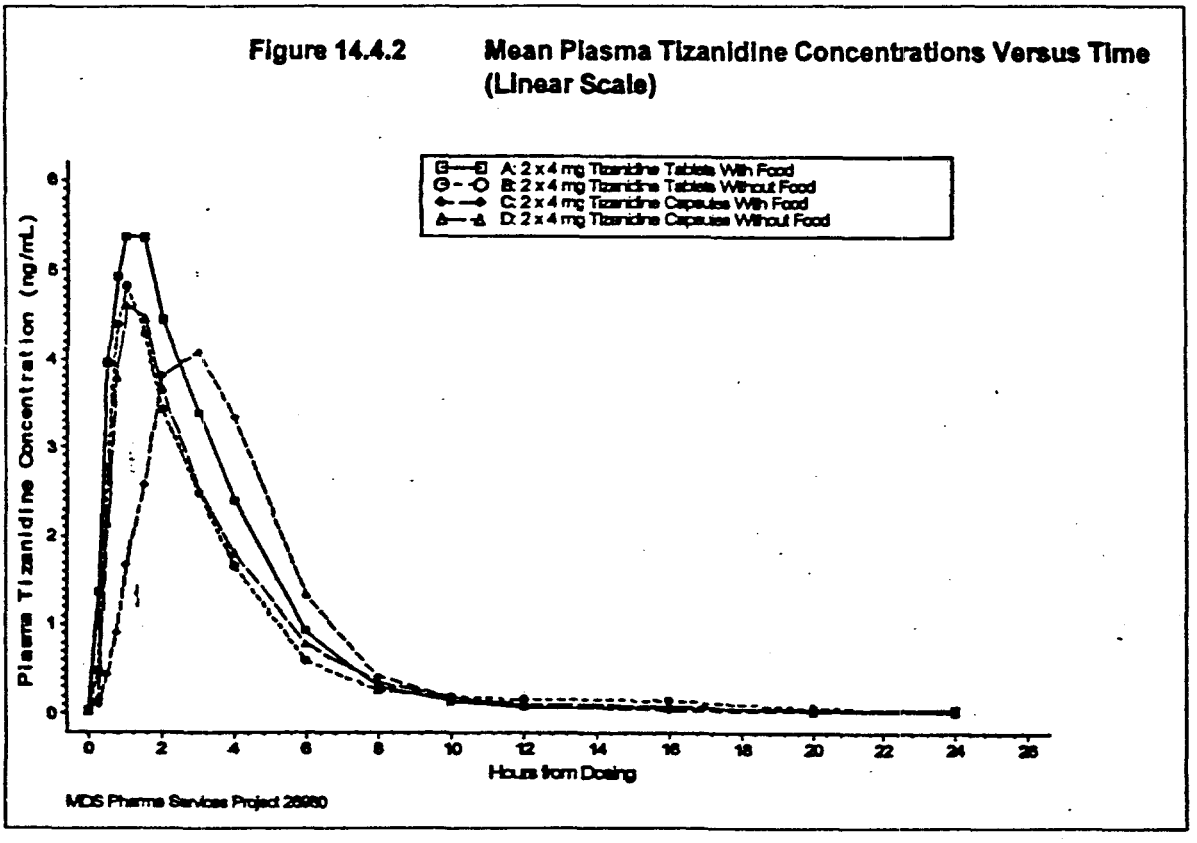
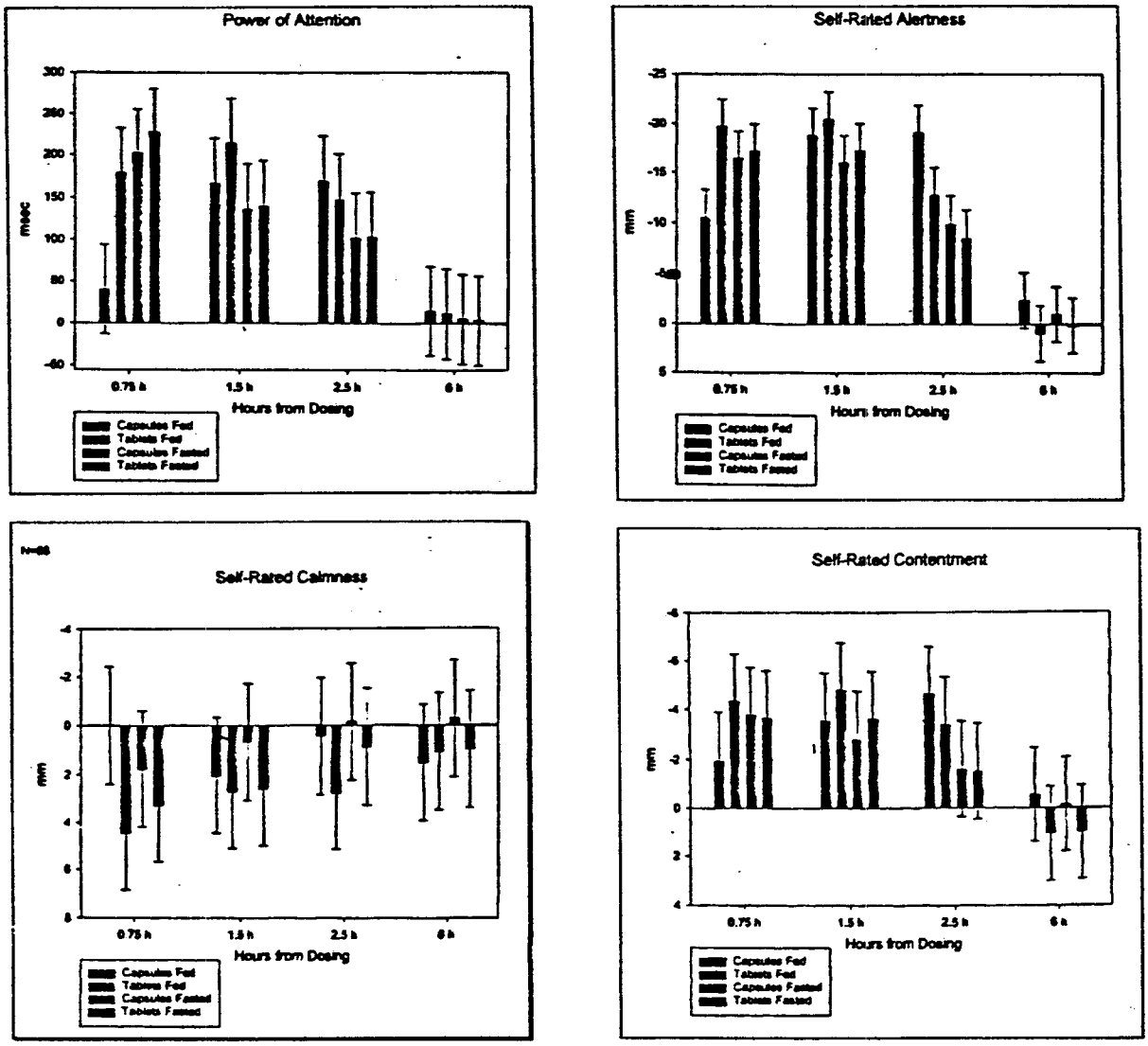


Figure 6 Pharmacodynamic Metrics Over Time by Formulation (Study AN021-101)



In summary the following is observed in the above figures:

At 0.75 hrs cognition was better for the capsule formulation under fed conditions. This is consistent with the delayed absorption and lower concentrations.

At 1.5 hrs there was a trend (although not statistically significant) for cognition to be worse for the tablet formulation under fed conditions. This is consistent with the higher concentrations with food. The other treatments tended to have similar degrees of impairment of cognition. This is consistent with the relative mean concentrations of the treatments.

At 2.5 hrs the effects on cognition were greatest for the capsule formulation under fed conditions. This is consistent with the delayed absorption when administered with food. The effect due to the tablet under fed conditions also tended to be slightly higher. The fasted treatment arms had similar degrees of impairment of cognition relative to each other. Again, the overall pattern observed is consistent with the relative mean concentrations of the treatments.

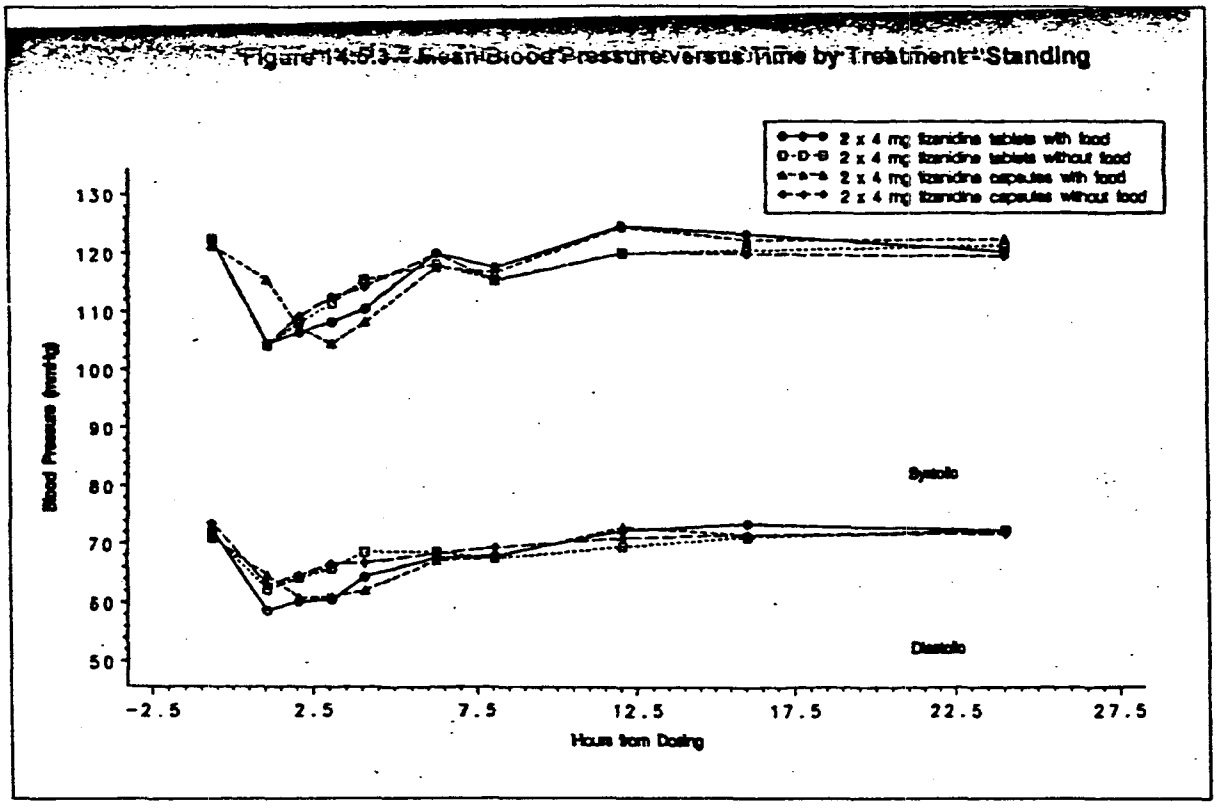
At 6.0 hrs the effects on cognition had effectively disappeared for all four treatment arms, and is likely due to the nearly complete elimination of the compound by 6 hours for each and every treatment arm.

It's unfortunate however that the sponsor only assessed effects on cognition at limited time points. As this didn't adequately cover the differences observed over the early portions of the concentration vs. time profiles. However, we're fortunate that measurements were taken at least at one time point, i.e. 0.75 hours, when there were significant differences between the concentration vs. time profiles.

6.2.4.2 Pharmacodynamic Effects on Blood Pressure

As shown in Figure 7 there's a significant drop in both systolic and diastolic blood pressure that tends to follow the concentration time profile. Consequently, the drop in BP occurs later with the capsule formulation when administered with food.

Figure 7 Blood Pressure vs. Time Upon Standing by Tizandine Treatment Arm - (Study AN021-101)



Although it appears that Emax is achieved, close inspection reveals that the early BP measurements are initially at hourly intervals, (i.e. 1, 2, 3 and 4 hours post dosing). Thus they miss the times when the major differences in concentrations between treatment arms occur, i.e. 1.2 hours.

Since this is presumably a centrally mediated effect we need to consider whether there might be a diffusional dysequilibrium, and if so by how important is it. If there is a significant diffusional dysequilibrium the maximum drops in BP may significantly lag behind the maximum concentration difference. However, visual examination of the PK-PD plots for cognition suggests that the lag may be neglible. Consequently, the lack of an adequate number of sampling times likely results in missing the maximum effect.

We also need to consider the effect on individuals with spasticity. However, as this study was conducted in normal volunteers, whether the degree and consequences of the effect on BP is greater or less in patients is pure conjecture.

For example assuming the same degree of hypotension, patients taking tizandine may go from a supine to standing position more slowly than healthy volunteers, thus there's less chance of syncope. Alternatively, patients may take tizanidine with a meal. Then when they get up after the meal when the degree of spasticity is lessened, they go to a standing position more rapidly and thus have a greater degree of syncope. Alternatively, both scenarios could occur. In addition, we don't know if the effect on BP, heart rate and consequently incidence of syncope is different for patients with different causes of spasticity.

Consequently, this reviewer believes the best way to handle this issue is to describe it in the labeling

6.3 APPLIED CLINICAL PHARMACOLOGY

6.3.1 Overdosage

6.3.1.1 Suicide Attempts

The sponsor provided information on 16 suicide attempts (see Appendix 7.5). Approximately 1 out of 3 attempts resulted in death. Most overdose attempts resulted in respiratory depression typically requiring mechanical ventilation, cardiovascular effects, and CNS depression frequently resulting in coma. Other drugs, that patients on tizanidine may typically require (i.e. benzodiazepines and other muscle relaxants), as well as antidepressants, and possibly the patient's underlying disease, are likely to have contributed to these deaths. This is because of pharmacodynamic synergy on respiratory, CNS, and cardiovascular depression. Several of the deaths involved only a 1 or 2 week supply of tizanidine. The sponsor's proposed labeling and suggestion to check with a poison control center is inadequate. Review of the most common information source used by poison control centers grouped tizanidine with other muscle relaxants and had very generic information. In fact, although clonidine is pharmacologically similar with a wealth of overdose information, there is no cross reference to clonidine. Currently there are 2 published case reports that poison information sources can draw on and neither of these cases resulted in fatality, nor mentions respiratory depression, and only one of the 2 cases mentions CNS depression. In addition, in one case flumazenil (a benzodiazepine antagonist) was used, which is relatively contraindicated with a drug with tizanidine's pharmacologic profile.

6.3.1.2 Drug Abuse / Addicition / Withdrawal

Several overdose cases indicate that tizanidine was being misused by individuals addicted to opioids. This is not surprising as clonidine, which is pharmacologically similar, is commonly misused by addicts to prolong the duration of narcotic effect and minimize opioid withdrawal symptoms. This results in the use of high doses over prolonged periods (e.g. > 50 mg /day of tizanidine and above). Consequently, a withdrawal syndrome can be precipitated due to going cold turkey, lack of awareness during treatment for addiction, lack of supply due to running out or incarceration (see Appendix 7.5).

6.3.2 Pediatrics

Although tizanidine is currently not approved in children, the lack of good treatments for muscle spasms suggests a high likelihood of off-label use in children. Since, young children often have gastrointestinal illness, withdrawal due to emesis similar to observed with clonidine is expected to occur with tizanidine. Consequently, there may be a different risk benefit ratio in children compared with adults.

6.4 PRODUCT PERFORMANCE

6.4.1 Dissolution

The sponsor's proposed dissolution method is acceptable provided that changes are made to the acceptance criteria specifications. Acceptance criteria specifications should be changed to

The sponsor's proposed method and specifications, and a comparison to the approved method for tizandine tablets, appears in Table 22.

Review of the dissolution method and comparison to the method for the tablets can be found in appendix section 7.6 Dissolution.

6.4.1.1 Sponsor's Proposed Method

Table 6 Proposed Dissolution Method

Dosage form:	Capsule, hard gelatin – Encapsulated Beads
Strength(s):	2, 4, 6 mg
Apparatus type:	USP Apparatus II (rotating paddles)
Medium:	
Volume (ml):	
Temperature (°C):	
Speed of rotation (r.p.m.):	
Sample times (h):	
Analysis	

6.4.1.2 Proposed Specification & Acceptance Criteria

Table 7 Proposed Specification & Acceptance Criteria[a]

	Sample Time	Acceptance Criteria
Sponsor Proposal		Q =
OCPB Proposal		Q =

a acceptance criteria as per USP

6.4.2 Biowaiver for 2 mg Strength

A biowaiver is requested by the sponsor for the 2 mg capsule strength.

In assessing this request the following conclusions were made:

a) Tizandine exhibits linear kinetics from 1 to 20 mg
b) The 2 mg, 4 mg, and 6 mg capsules are encapsulated beaded formulations that only differ by the number of beads and are thus compositionally proportional
c) Dissolution rate is rapid in for all strengths in (see § 7.6)

Therefore a biowaiver is granted.

7 APPENDICES

7.1 BACKGROUND

n.b. much of the following introduction and background is taken directly from the currently approved labeling for tizanidine tablets with some additional information gleaned from prior FDA reviews of these products.

7.1.1 Regulatory Status

Tizanidine is currently approved and marketed in the United States by the sponsor (Elan) ZANAFLEX® (tizanidine hydrochloride) 2 and 4 mg tablets.

7.1.2 Indication

Tizanidine is indicated for the management of spasticity. However, because of the short duration of effect, treatment should be reserved for those daily activities and times when relief of spasticity is most important.

Efficacy trials were conducted on patients with spasticity due to multiple sclerosis or spinal cord injury.

7.1.3 Rationale for Development Program

The present supplement is for an additional drug formulation, specifically beaded capsules in the two currently approved strengths (2 mg and 4 mg), and an additional higher strength 6 mg. The beaded capsule formulation is intended to provide additional flexability in administration, (e.g. sprinkled on applesauce). Plus, the 6 mg dose will result in administration of fewer dosage units for patients requiring 6 mg, 10 mg, or $\geq$12 mg per day.

7.1.4 Pharmacology

7.1.4.1 Mechanism of Action

Tizanidine is an (alpha)$_2$-adrenergic agonist and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

7.1.4.2 Assessments of Efficacy

Currently, no measures of spasticity have been validated as surrogate measures for clinical efficacy, in spite of their use in clinical trials and for approval of tizanidine tablets.

In clinical trials for the tablets the following types of pharmacodynamic assessments of efficacy were conducted:

- Ashworth Scale of Muscle Tone
- Measurement of Limb Pendulum Swing
- Patient Diary Counts of Number of Daily Spasms (clonus)

A fuller description of these and other pharmacodynamic measures for spasticity may be found at http://www.wemove.org/

In one pivotal efficacy study for tizanidine tablets, patients with multiple sclerosis received single oral doses of placebo, 8 mg or 16 mg of tizanidine. Response was assessed by physical examination; (Ashworth score), at 1, 2, 3 and 6 hours post-dosing.

Mean reductions in muscle tone roughly follow the concentration time profiles, with the greatest reduction in muscle tone 1 to 2 hours after drug administration. By 6 hours muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration, however inter-subject variability in plasma concentrations was high.

Reductions in muscle tone are not associated with a reduction in muscle strength, (as measured by the British National Research Councils Scale (BNRC), which is a desirable feature.

The problem with the Ashworth scale is that it allows only a limited number of repetitive measurements over a dosage interval, and is also dependent upon some subjective evaluation by the clinician. Consequently, there's a risk of bias. In addition, it's not a good measure for a drug like tizanidine that has an effect profile that closely follows the concentration vs. time profile. Thus a better measure for tizanidine would be near continuous measurements, such as electrophysiologic and biomechanical measurements using an electrogoniometer and tachometer attached to a computerized recorder.

7.1.4.3 Adverse Pharmacologic Effects Related to Exposure

Dose related side effects are shown in Table 8. Three-quarters of the patients rated these events as mild to moderate and one-quarter of the patients rated the events as being severe.

Table 8 Common Adverse Events Reported in a Single Dose, Placebo-Controlled Study

Event	Placebo	Zanaflex	
		8 mg	16 mg
	N = 48 %	N = 45 %	N = 49 %
Somnolence	31	78	92
Dry mouth	35	76	88
Asthenia (weakness, fatigue and/or tiredness)	40	67	78
Dizziness	4	22	45
Hypotension	0	16	33
Bradycardia	0	2	10

Several of these AEs may be attributable to either hypotension or sedation, or both. The time course of both approximately follows the mean concentration vs. time profile. The dose response of these AEs is discussed in more detail below.

7.1.4.3.1 Hypotension

Tizanidine has found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure. However, tizanidine, like clonidine, can produce hypotension.

Two-thirds of patients treated with a single dose of tizanidine 8 mg experienced a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and is associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of $\geq$ 2 mg.

There is a correlation of BP to plasma concentration that's stronger with systolic BP, however the correlation is very weak and is based on naïve pooled data. No formal PK/PD analyses have been performed of this relationship.

7.1.4.3.2 Sedation

Sedation appears to be dose related. 92% of the patients receiving a single dose of 16 mg reported drowsiness when asked. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of tizanidine. The prevalence peaks following the first week of titration and then remains stable.

Muscle strength as measured by the Modified British National Research Council (BNRC) Scale is not effected by tizanidine, which is a desirable trait.

7.1.5 Risk / Benefit

After input was obtained, the assessment was that in spite of the risk of hypotension and inadequate measures of efficacy, that tizandine did provide a significant benefit even if the benefit was short-lived as it might allow patients the ability to move more easily from bed to wheelchair.

7.1.6 Pharmacokinetics

- Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg.
- The absolute systemic availability following oral administration is approximately 40%, (CV = 24%).
- It is essentially completely absorbed and the low systemic availability is due to first-pass metabolism.
- Approximately 95% of an administered dose is metabolized. and following single and multiple oral dosing of ^{14}C-tizanidine, an average of 60% and 20% of total radioactivity was recovered in the urine and feces, respectively.
- Metabolites are not known to be active. However, the activity of the M-10 metabolite has not been determined. Half-lives ranged from 20 to 40 hours.
- Tizanidine has a half-life of approximately 2.5 hours (coefficient of variation CV = 33%).
- Peak plasma concentrations occurred at 1.5 hours (CV = 40%) after dosing of the tablet.
- Administration of the tablet with food increases C_{max} by approximately one-third and shortens time to peak concentration by approximately 40 minutes, but the extent of tizanidine absorption is not affected.
- Tizanidine is widely distributed throughout the body; mean steady state volume of distribution is 2.4 L/kg (CV = 21%) following intravenous administration in healthy adult volunteers.
- Tizanidine is approximately 30% bound to plasma proteins, independent of concentration over the therapeutic range.

7.1.7 Dosage and Administration

A single oral dose of 8 mg of tizanidine reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1 to 2 hours and dissipates between 3 to 6 hours.

Doses of less than 8 mg have not been demonstrated to be effective however, due to the dose-related nature of tizanidine's common adverse events it is prudent to begin treatment with single oral doses of 4 mg, and increase the dose gradually (2 to 4 mg steps) to optimum effect. The dose can then be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours.

Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg.

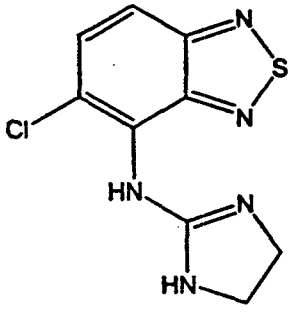
7.1.8 Chemistry

7.1.8.1 Drug Substance

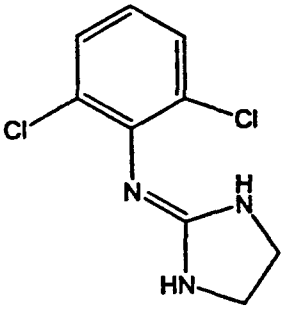
7.1.8.1.1 Structure

Tizanidine is an imidazoline structurally related the anti-hypertensive drug clonidine and other (alpha) $_2$-adrenergic agonists (See Figure 8)

Figure 8 Structures of Tizanidine and Clonidine



Tizanidine



Clonidine

7.1.8.1.2 Nomenclature

5-chloro-4-(2-imidazolin-2-ylamino)-2,1, 3-benzothiodiazole hydrochloride

7.1.8.1.3 Physical-Chemical Properties

7.1.8.1.3.1 Molecular Formula

$C_9H_8ClN_5S \cdot HCl$

7.1.8.1.3.2 Molecular Weight

290.2

7.1.8.1.3.3 pKa

7.46 ± 0.05

7.1.8.1.3.4 Solubility

7.2 ASSAY VALIDATION

Table 9 Assay Validation – Tizanidine HCl - LC/MS/MS – Assay Method TM-130

Laboratory	Bioanalytic Services Elan Pharmaceutical Technologies Monksland, Athlone, Ireland
Method Validation Report Title	Validation of the Method for the Quantitation of Tizanidine in Human Plasma by LC-MS.MS
Method Validation Report #	VTM130
Date	05 December 2000
Analyst(s)	*Barbara Kelly*
Method Description	
Method Number	TM-130
Method Protocol Title	Test Method for the Quantitation of Tizanidine in Human Plasma by LC-MS.MS
Matrix	
Analyte	
Internal Standard	
Sample Volume	
Sample Storage Method	
Structural Model	
Error Model	
Software	MS Excel
Software Validation	Not mentioned
Range **	Claimed by sponsor Standards – Acceptable to reviewer.: The validation report showed an excessive degree of variability at concentrations for standards below
LLOQ	In process QC samples suggest that may achieve the usual acceptance criteria for LLOQ. However, since LLOQ must be limited to a standard in the standard curve, the LLOQ for tizanidine cannot be lower than
Bias - Intra assay	range of mean biases -21.65% to 19.5%)
Bias - Inter assay	Acceptable at all concentrations –9.5% at
Overall Precision	*Not Reported.*
Intra assay Precision	CV 17.54% at Range -2% to 52.2%) CV 5.95% at
Inter (Between) assay Precision	CV 4.1% at
Matrix Effects	*Not Tested.*
Selectivity **Endogenous Substances** **Internal Standard**	
OTC Drugs **Dietary – e.g. Caffeine** **Drugs – Rx**	*Not Reported* *Not Reported* *Not Reported*
Stability - Blood	**Not Reported**
Stability - Plasma **RT** **Refrigerated** **Long Term (-20 °C)** **Stability Freeze/Thaw**	*Not Reported.*
Stability - Extracted **RT** **Refrigerated** **On Machine**	*Not Reported.*
Sample Dilution	

7.3 CLINICAL STUDIES

7.3.1 Study Designs

Study designs for the bioequivalence studies utilized standard 2-way crossover designs. Except for the PK-PD study which was a 4-way crossover study. Pharmacokinetic sampling was identical for each study and was adequate. The measurement times for the PD component of the PK-PD component was inadequate and is discussed in detail under the individual study review (see section 7.3.2.5).
Single dose 2-way crossover study.

Table 10 Study Demographics and Formulation Batches

Study	Males	Females	Formulation	Dose	Batch No.
0600002	11	16	Capsule	6 mg	PS1070
			Tablet	2 mg	113MFD0999
			Tablet	4 mg	ZN0162
0300003	12	16	Capsule	4 mg	PS1066
			Tablet	4 mg	ZN0162
0400001	12	6	Capsule	4 mg	PS1066
			Tablet	4 mg	ZN0162
0400002	19	9	Capsule	6 mg	PS1070
AN021-101	54	42	Capsule	4 mg	PS1066P
			Tablet	4 mg	197MFD1299

7.3.2 Individual Study Reviews

7.3.2.1 Pivotal Fasted Bioequivalence Study of Highest Proposed Capsule Strength (6 mg) to Tablets (4 mg + 2 mg) – Study 0600002

7.3.2.1.1 Results

Table 11 Comparative Pharmacokinetic Metrics for Tizanidine 6 mg Capsules and Tizanidine Tablets (4 mg + 2 mg) Under Fasting Conditions (Study 0600002)

Metric	Mean ± SD (CV) Range		Median[a] & Geometric Mean Ratios		Relative Exposure (Test:Reference) Percent 90% CI
	Reference Tablets (4 mg + 2 mg)	Test Capsules 6 mg	Reference Tablets (4 mg + 2 mg)	Test Capsules 6 mg	
Tlag (hours)	0.33 ± 0.12 (36.0) 0.25 - 0.5	0.45 ± 0.12 (28.0) 0.25 - 0.75	0.25	0.5	—
Tmax (hours)	0.95 ± 0.27 (28.2) 0.5 - 1.5	1.16 ± 0.55 (46.6) 0.75 - 3	1.0[b]	1.0	—
Cmax (ng/ml)	5.53 ± 3.96 (71.6)	4.94 ± 2.77 (56.1)	4.53	4.17	92 84.74 - 111.44
AUC_{last} (ng/ml x hr^{-1})	14.13 ± 11.69 (82.7) 2.43 – 53.26	13.85 ± 9.71 (70.2) 1.44 – 48.93	10.87	10.87	100 96.65 - 119.69
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	15.25 ± 11.7 (77.0) 2.9 – 54.0	14.65 ± 9.81 (67.0) 1.77 – 49.4	12.19	11.76	96 94.42 – 113.69
$t_{1/2}$ (hours)	1.50 ± 0.40 (26.4) 0.77 - 2.27	1.41 ± 0.50 (35.8) 0.76 - 3.13	—	—	—
Frel	—	107.55 ± 31.53 (29.3) 65.47 - 201.64	—	—	—

a Medians reported for Tlag and Tmax
b Mode = 0.75 hours

7.3.2.1.2 Statistical Analysis

The statistical analysis for bioequivalence should have used SAS type III sum of squares. Instead types I and II were reported. In addition, there are some minor differences in the square error terms between the different types of sum of squares used. Whereas there usually isn't any between the 3 types. However the differences are minor, and as the confidence intervals aren't close to the rejection limits for bioequivalence, this reviewer does not believe that reanalysis using type III sum of squares would alter the conclusions of bioequivalence.

7.3.2.1.3 Formulation Effect on Absorption Delay

The delay observed in absorption with the capsule as compared to the tablet formulation might be due to some of the beads being injected into the duodenum where they might dissolve slower at the higher pH. This has been shown for structurally similar imidazole proton pump inhibitors with pKas in the 6's although for tizanidine it's more likely due to the excipients, (See section 7.6).

7.3.2.2 Fasted Bioequivalence Study of 4 mg Capsule to Reference Labeled Drug (4mg Tablets) – Study 0300003

Time metric distributions are shown in Figure 9. The sponsor's metrics excluding subject 5, who only had a single measurable concentration, are shown in Table 12.

The bioanalysis was again variable, with the sponsor having to exclude the data from several subjects due to excessive assay variability. This is mainly a problem with pushing the limits of the assay and should not really effect AUClast or Cmax as much. Without excluding subject 5 we need to pause before concluding bioequivalence, as AUClast and AUC∞ are significantly different from each other. However, excluding subject 5, who had only a single measurable concentration and only completed 1 arm of the study, brings the AUC metrics much closer. Indicating that subject 5 should be disregarded.

Consequently, even with the same issues with the statistical analysis as with study 0600002, this reviewer again reaches a conclusion of bioequivalence.

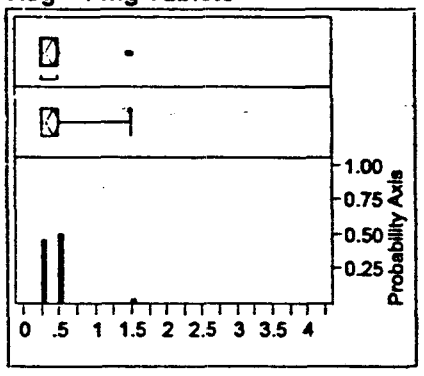
Table 12 Comparative Pharmacokinetic Metrics for Tizanidine 4 mg Tablets and Capsules Under Fasting Conditions – Excluding Subject 05 (Study 0300003)

Metric	Mean ± SD (CV) Range		Median[a] & Geometric Mean Ratios		Relative Exposure (Test:Reference) Percent 90% CI
	Reference 4 mg Tablets[b]	Test 4 mg Capsules	Reference 4 mg Tablets	Test 4 mg Capsules	
Tlag (hours)	*0.43 ± 0.25* *(58.3)* *0.25 – 1.5*	0.52 ± 0.12 (22.9) 0.25 - 0.75	*0.5*	0.5	—
Tmax (hours)	*0.95 ± 0.33* *(34.7)* *0.5 – 2.0*	1.09 ± 0.38 (34.9) 0.5 – 2.07	*1.0*	1.0	—
Cmax (ng/ml)	*3.41 ± 1.92* *(56.3)*	3.35 ± 1.9 (56.7)	*2.91*	2.9	100 89.8 - 110.8
AUC_{last} (ng/ml x hr^{-1})	*7.97 ± 5.49* *(68.9)* *1.46 - 21.65*	8.16 ± 5.86 (71.8) 1.35 - 24.11	*6.3*	6.52	103 92.4 - 115.3
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	*8.75 ± 5.5* *(62.9)* *1.96 - 22.78*	9.28 ± 5.82 (62.7) 3.23 – 24.59	*7.29*	7.90	108 94.8 - 116.2
$t_{1/2}$ (hours)	*1.34 ± 0.29* *(21.4)* *0.92 - 2.19*	1.37 ± 0.27 (19.91) 0.88 – 2.05	—	—	—
Frel	—	110.62 ± 43.1 (38.97) 65.21 - 295.33	—	—	—

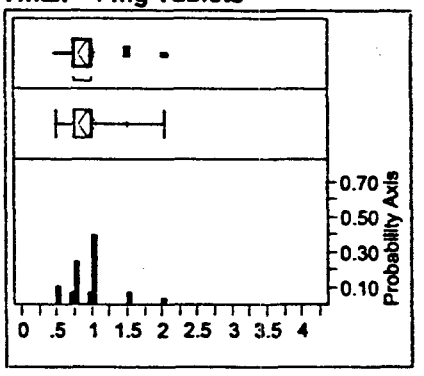
a Medians reported for Tlag and Tmax
b Data from subject 05 excluded

Figure 9 Comparative Time Metric Distributions for Tizanidine 4 mg Tablets and Capsules Under Fasting Conditions (Study 0300003)

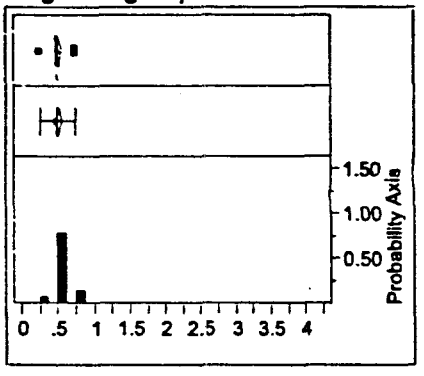
Tlag - 4 mg Tablets



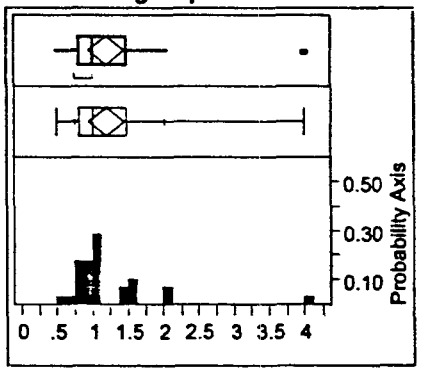
Tmax - 4 mg Tablets



Tlag - 4 mg Capsules



Tmax - 4 mg Capsules



APPEARS THIS WAY
ON ORIGINAL

7.3.2.3 Bioequivalence Study Under Fed Conditions - Study 0400001

A bioequivalence study under fed conditions was also performed. Under fed conditions the two formulations were not bioequivalent.

Results showed that under fed conditions the Cmax for the capsule was approximately 2/3's of the Cmax with the tablet, (See Table 13). However, the variability in extent of absorption was too great to determine if there is a consistent pattern for any difference in extent of absorption with the 2 formulations.

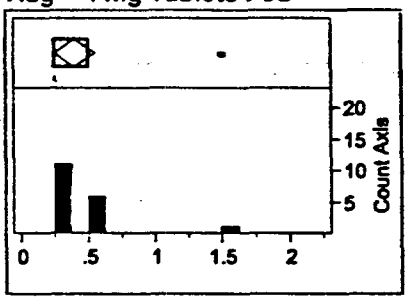
Table 13 Comparative Pharmacokinetic Metrics for Tizanidine 4 mg Tablets and Capsules Under Fed Conditions (Study 0400001)

Metric	Mean ± SD (CV) Range		Median[a] & Geometric Mean Ratios		Relative Exposure (Test:Reference)
	Reference 4 mg Tablets Fed	Test 4 mg Capsules Fed	Reference 4 mg Tablets Fed	Test 4 mg Capsules Fed	Percent 90% CI
Tlag (hours)	0.40 ± 0.30 (74.2) 0.25 – 1.5	1.07 ± 0.51 (48.0) 0.5 – 2	0.25	1.0	—
Tmax (hours)	1.17 ± 0.65 (55.3) 0.5 - 3.0	2.56 ± 0.69[b] (27.0) 1.5 - 4.0	1.0	3.0	—
Cmax (ng/ml)	4.7 ± 2.72 (57.9)	3.06 ± 1.66[b] (54.0)	4.01	2.66	66 50.4 - 87.2
AUC_{last} (ng/ml x hr^{-1})	11.66 ± 8.03 (68.9) 2.87 – 28.16	10.60 ± 7.0 (66.2) 2.21 – 25.9	9.2	8.53	93 70.6 - 121.9
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	12.82 ± 7.73 (60.3) 3.4 - 27.58	11.93 ± 6.83 (57.3) 4.5 – 26.4	10.76	10.3	96 70.1 - 118.8
$t_{1/2}$ (hours)	1.41 ± 0.39 (27.7) 0.91 - 2.34	1.57 ± 0.40 (25.4) 0.97 - 2.36	—	—	—
Frel	—	122.8 ± 169.4 (138.0) 46.2 - 776.2	—	—	91.26

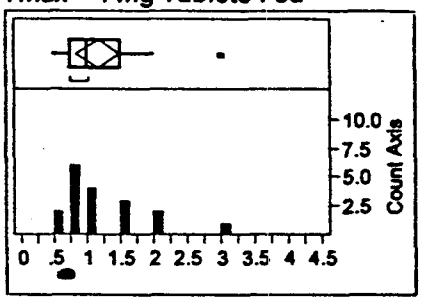
a Medians reported for Tlag and Tmax
b $p < 0.05$

Figure 10 Comparative Time Metric Distributions for for Tizanidine 4 mg Tablets and Capsules Under Fed Conditions (Study 0400001)

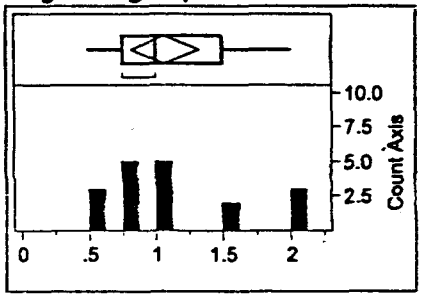
Tlag – 4 mg Tablets Fed



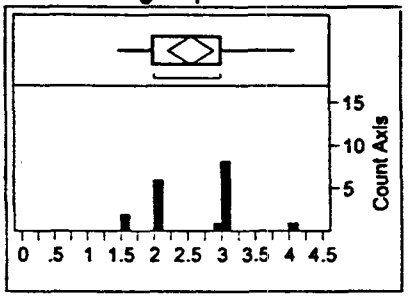
Tmax – 4 mg Tablets Fed



Tlag – 4 mg Capsules Fed



Tmax – 4 mg Capsules Fed



APPEARS THIS WAY
ON ORIGINAL

7.3.2.4 Effect of Sprinkling on Applesauce on Bioavailability (Study 0400002)

The bioanalytic data used by the sponsor for estimation of pharmacokinetic metrics is acceptable. However, the sponsor did have to disregard data from several subjects due to problems with assay performance (i.e. excessive variability in standards or quality control samples).

Table 14 Comparative Pharmacokinetic Metrics for Tizanidine 6 mg Capsules Administered Intact and Sprinkled on Applesauce Under Fasting Conditions (Study 0400002)

Metric	Mean ± SD (CV) Range		Median[a] & Geometric Mean Ratios		Relative Exposure (Test:Reference) Percent 90% CI
	Reference Intact 6 mg Capsules	Test Sprinkled 6 mg Capsules	Reference Intact 6 mg Capsules	Test Sprinkled 6 mg Capsules	
Tlag (hours)	0.46 ± 0.12 (26.1) 0.25 - 0.75	0.30 ± 0.1 (33.1) 0.25 - 0.5	0.5	0.25	—
Tmax (hours)	1.04 ± 0.54 (51.7) 0.5 - 3	0.84 ± 0.29 (34.3) 0.38 – 1.5	1.0	0.75	—
Cmax (ng/ml)	5.91 ± 3.78 (64.1)	7.1 ± 5.6 (79.7)	4.88	5.7	117 103.95 - 133.66
AUC_{last} (ng/ml x hr^{-1})	16.1 ± 11.9 (74.3) 1.35 - 53.1	18.3 ± 14.5[b] (79.4) 2.5 - 67.7	12.02	13.97	116 106.8 - 130.53
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	16.9 ± 12.0 (70.7) 2.7 - 54.4	19.2 ± 14.5[b] (75.5) 3.2 – 68.2	13.27	15.16	114 105.47 - 127.01
$t_{1/2}$ (hours)	1.32 ± 0.27 (20.2) 0.82 – 1.84	1.33 ± 0.21 (16.2) 0.84 – 1.70	—	—	—
Frel		120.05 ± 34.4 (28.7) 65.0 - 199.8	—	—	—

a Medians reported for Tlag and Tmax
b $p > 0.05$

APPEARS THIS WAY
ON ORIGINAL

7.3.2.5 Comparative PK / PD & Food Effect Study - Study AN021-101

7.3.2.5.1 Study Design

This was a 4 way crossover study in 96 healthy subjects. Treatment arms included both fed and fasted conditions for both the capsule and tablet formulations. Doses used in each arm were 8 mg (2 x 4 mg). In addition to pharmacokinetics, pharmacodynamic effects on cognition and blood pressure were also assessed and are discussed in sections 7.3.2.5.3 and 7.3.2.5.4.

7.3.2.5.2 Bioanalysis

Evaluation of the data presented indicates that the assay performance was not acceptable (See section 6.1.2 for details).

The poor assay performance, especially at low concentrations, results in excessive variability in estimation of terminal half-life (CV of 97% - 105% under fasted conditions) compared with approximately 20% - 35% in the other fasted bioequivalence studies. This results in excessive variability in estimation of $AUC_{0-\infty}$, as indicated by mean AUC_{last}'s under fasted conditions of 75% of mean $AUC_{0-\infty}$'s. Whereas mean AUC_{last}'s under fasted conditions are ~93% of mean $AUC_{0-\infty}$'s in the 6 mg bioequivalence study.

Specifically, the lower quality control sample of [redacted] had an excessive CV of 27%.for the [redacted] assay runs that were presented out a total of [redacted] runs. Inspection of these [redacted] runs indicates that they probably are representative. As based upon the standard curves, this reviewer would probably have disregarded [redacted] of the [redacted] assay runs ([redacted] due to excessive variability in the lowest 2 standards. Whereas for the [redacted] representative runs presented, this reviewer would have disregarded [redacted] of the [redacted] ([redacted] Also 4 of the 5 runs with the largest positive biases for the low QC sample, (≥37%), also had large positive biases in both of the two lowest standards. (n.b. these statements ignore the lowest standard concentration of [redacted] as this reviewer does not believe the original assay validation data supports a range this low.

However, the mid-range of the assay is the most reliable and this is the range where Cmax is measured.

7.3.2.5.3 Pharmacokinetics

Pharmacokinetic metrics for this study are presented in Table 15 through Table 19.

Inspection of the data reveals a large number of missing subjects. In addition, the statistical analysis may not have been performed correctly.

Even though a dose of 2 x 4 mg fails bioequivalence under fasting conditions in this study, (see Table 19), this reviewer believes there are significant assay and statistical problems and these results should be disregarded.

A food effect by formulation was also detected in this study, and the degree of the effect is of similar magnitude as previously described. However, due to the problems with the study the quantification of the effect cannot be considered reliable.

Table 15 Comparative Pharmacokinetic Metrics for 8 mg (2 x 4 mg) Doses of Tizanidine Tablets and Capsules Under Various Meal Conditions (Study AN021-101)

Metric	Mean ± SD (CV) Range			
	Tizanidine 4 mg Tablets		Tizanidine 4 mg Capsules	
	Fed A	Fasted B	Fed C	Fasted D
Tlag (hours)	0.42 ± 0.36 (86.1) 0 – 2.0	0.38 ± 0.2 (53.1) 0 – 1.5	0.86 ± 0.72 (83.4) 0 – 3.0	0.46 ± 0.25 (54.8) 0 – 2.0
Tmax (hours)	1.64 ± 2.7 (164.0) 0.28 – 24.1	1.28 ± 1.8 (140.0) 0.49 – 16.0	2.65 ± 0.92 (34.9) 0.996-4.08	1.28 ± 0.95 (74.2) 0.5 - 8.04
Cmax (ng/ml)	6.8 ± 5.6 (83.0)	5.5 ± 4.3 (78.4)	4.6 ± 3.7 (80.8)	5.4 ± 4.2 (77.8)
AUC_{last} (ng/ml x hr^{-1})	20.36 ± 18.83 (92.5) 0.18 – 128.6	15.96 ± 19.3 (121.1) 0 – 135.3	17.6 ± 15.6 (88.5) 0.54 - 73.5	15.99 ± 16.4 (102.6) 0.18 – 88.2
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	20.75 ± 14.1 (68.0) 4.04 – 56.26	22.7 ± 23.7 (104.4) 2.26 – 136.0	27.53 ± 16.03 (58.2) 4.24 – 71.6	20.1 ± 19.6 (97.3) 2.6 – 90.1
$t_{1/2}$ (hours)	1.78 ± 1.7 (95.4) 0.61 – 11.9	2.66 ± 3.72 (140.0) 0.645 – 20.0	2.47 ± 2.93 (119.0) 0.834 - 13.0	1.77 ± 1.48 (83.5) 0.76 - 8.2

APPEARS THIS WAY
ON ORIGINAL

Table 16 Comparative Metrics for Tizanidine 4 mg Tablets Fed /4mg Tablets Fasted[a]

	Tablets Fed	Tablets Fasted		
Tlag (hours)	0.25	0.25		
Tmax (hours)	1.41	1.0		
	Geometric Means		Geometric Mean Ratio	90% CI
Cmax (ng/ml)	1.58	1.37	122.6	111.5 - 134.7
AUC_{last} (ng/ml x hr^{-1})	2.58	2.25	145.2	129.8 - 162.3
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	2.76	2.52	118.6	101.3 - 138.8

a Median reported for time metrics

Table 17 Comparative Metrics for Tizanidine 4 mg Capsules Fed / 4 mg Capsules Fasted[a]

	Capsules Fed	Capsules Fasted		
Tlag (hours)	0.75	0.5		
Tmax (hours)	3.0	1.0[b]		
	Geometric Means		Geometric Mean Ratio	90% CI
Cmax (ng/ml)	1.16	1.37	81.4	74.1 - 89.5
AUC_{last} (ng/ml x hr^{-1})	2.42	2.25	117.6	105.2 – 131.4
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	2.84	2.52	138.2	115.4 - 165.6

a Median reported for time metrics
b $p < 0.0001$ by Wilcoxon Sign Rank Test

Table 18 Comparative Metrics for Tizanidine 4 mg Capsules Fed / 4 mg Tablets Fed[a]

	Capsules Fed	Tablets Fed		
Tlag (hours)	0.75	0.25		
Tmax (hours)	3.0	1.41[b]		
	Geometric Means		Geometric Mean Ratio	90% CI
Cmax (ng/ml)	1.16	1.58	66.2	60.3 - 72.7
AUC_{last} (ng/ml x hr^{-1})	2.42	2.58	84.6	75.7 - 94.5
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	2.84	2.76	108.5	90.8 – 129.7

a Median reported for time metrics
b $p < 0.0001$ by Wilcoxon Sign Rank Test

Table 19 Comparative Metrics for Tizanidine 4 mg Capsules Fasted / 4 mg Tablets Fasted[a]

	Capsules Fasted	Tablets Fasted		
Tlag (hours)	0.5	0.25		
Tmax (hours)	1.0	1.0		
	Geometric Means		Geometric Mean Ratio	90% CI
Cmax (ng/ml)	1.37	1.37	99.6	90.6 – 109.5
AUC_{last} (ng/ml x hr^{-1})	2.25	2.21	104.5	93.4 – 116.8
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	*2.52*	*2.59*	*93.1*	*79.2 - 109.5*

a Median reported for time metrics

7.3.2.5.4 Pharmacodynamics

7.3.2.5.4.1 Effects on Cognition

Cognition was assessed at 0.75, 1.5, 2.5 and 6.0 hours post-dosing. According to the sponsor only the difference in effect on cognition at 0.75 hours reached statistical significance. However, this could not be confirmed, as the data was illegible[1].

However, this conclusion appears reasonable based upon the graphs provided, even though the variability appears extremely large (see § 6.2.4 Pharmacodynamics). In addition, the sponsor's statistical analysis of comparison of means by ANOVA is the only possible approach, as there were so few sampling times for pharmacodynamic effects that a formal PK/PD analysis would be impossible. There was a sufficient difference in concentrations at 0.75 hours so that a difference in pharmacodynamics was detected. With regards to the other sampling times there may not have been sufficient concentration differences to detect a difference in pharmacodynamics.

Thus, we can conclude that there appears to be differences in cognition that are attributable to the differences in the observed concentration vs. time profiles of the various tizanidine treatment arms.

Cognitive Assessments

Cognitive assessments were conducted 1 hour prior to dosing (baseline), 0.75, 1.5, 2.5 and 6 hours post-dosing.

Assessments included computerized cognitive assessments and Bond-Lader Visual Analog Scale (VAS) assessments.

Computerized Cognitive Assessments are reported as 'Power of Attention'. Power of Attention is computed as the sum of 3 primary computerized cognitive measurements that includes simple reaction time, digit vigilance time, and choice reaction time. See Table 20 for a description of these primary measurements.

Table 20 Primary Computerized Cognitive Measurements

Task	Description	Primary Measure	Secondary Measures
Simple Reaction Time (SRT)	Press 'Yes' button when the word 'Yes' appears on the computer monitor	Speed (mSec)	
Digit Vigilance Time (DVT)	150 digits displayed per minute. Subject presses 'Yes' button whenever display digit matches a target digit displayed to the side. There are 45 target digits displayed over 3 minutes.	Speed (mSec)	• % of Targets Detected • False Alarms
Choice Reaction Time (CRT)	Press the 'Yes' or 'No button when the word 'Yes' or 'No' appears on the computer monitor	Speed (mSec)	• Accuracy (%)

Computerized Cognitive Assessments are reported as 'Power of Attention'. Simple Reaction Time Digit Vigilance Time Choice Reaction Time

[1] The sponsor had been warned of illegibility of future submissions in the original tablet NDA review.

Bond-Lader Visual Analog Scale (VAS) Assessments include the following 3 secondary measures:

Self-rated Alertness
Self-rated Contentment
Self-rated Calmness

Descriptions of these measures can be found at www.wemove.org.

There were no clearly obvious differences in adverse event profiles between arms.

7.4 CONSULTS

7.4.1 Pharmacometrics

A pharmacometric consult for the PK-PD data was performed by the primary reviewer and is incorporated in the review.

7.5 SUMMARY OF CASE REPORTS OF OVERDOSE AND WITHDRAWAL

Table 21 Summary of Case Reports of Overdose and Withdrawal

Case #	Demographics Age/ Sex/ Wt / Race	Dx	Situation	Tizanidine Dose	Concomitant Medications	Date	CV	CNS	Resp/Pulm	Musculo-skeletal	Metabolic	Other	Rx	Outcome	Comment
Luc ani et. al. 1995	27 F	Depression	Suicide Attempt	tizanidine 120 mg	lorazepam 30 mg										
						ER Arrival 1:00 PM	hypotensive (80/50) EKG - sinus bradycardia (34 bpm) 1st degree AV block (PQ 240 mSec) Wenckeback 2nd degree AV block 4:3, 3:2 block ratio	drowsy			hematological tests normal'		Flumazenil 2 mg		Flumazenil is a BDP antagonist. However it should have been contraindicated because of the tizanidine and because of the observed arrhythmia.
								woke up post Rx with flumazenil					Transfer to another hospital		
						Hospital Admission 3:30 PM	hypotensive (80/60) EKG - sinus bradycardia (40 bpm) 1st degree AV block (PQ 200 mSec)	drowsiness					Flumazenil 0.5 mg IV Bolus then CIVI 1 mg/hr x 6 hrs. Saline hydration. Furosemide		
						next few hours	BP rose gradually Sinus node dysfunction 37- 65 bpm with P wave morphology	consciousness improved							
						9:00 AM	BP 112/70 HR 46-50 BPM AV conduction time 160 mSec								
						48 hours later	RSR							Recovered	
Inoue et al 199	41 F 58 kg		(Suicide Attempt?)	23 mg											
						3 hours post ingestion	bradycardia, hypotension	Semi-comatose; deep tendon reflexes hyporeflexive in all extremities; No pathological reflexes. EEG α waves with some low amplitude fast waves				Hypothermia Serum Tizanidine 27.1 ng/ml	Tizanidine D/C'ed		Peak could have occurred at 1 hour or later. So concentrations could have been still going up, or already declining. Assuming peak occurred at 1 hour, Cmax could have been up to ~ 60 ng/ml
						7 hours (post-admission?)						Serum Tizanidine 1.8 ng/ml			Based on concentrations at 3 and "10 hours"(when timed from is unknown). Tizanidine was likely maximally absorbed at presentation, and was being eliminated with linear kinetics. (4 x t/12's would give and estimated conc. of 1.7 ng/ml at 10 hours based on a mean half-life of 1.75 hrs)
						20 hours (post-admission?)						Serum Tizanidine <0.3 ng/ml			

Case #	Demographics Age/ Sex/ Wt / Race	Dx	Situation	Tizanidine Dose	Concomitant Medications	Date	CV	CNS	Resp/Pulm	Musculo-skeletal	Metabolic	Other	Rx	Outcome	Comment
						day after ingestion	hypotensive					otherwise recovered		Recovering	
656	1 mo. N/A		Medicinal Error	0.7 mg/kg/day x ?	diphenoxylate atropine pipenzolate			Drowsiness		Hypotonia			Supportive	Recovered	
149	46 F	MS	Suicide Attempt	240 mg	Tramadol? (μ-Opioid & NE/5HT reuptake inhibitor)		Hypotension	Comatose reflexes absent	Respiratory Depression		Anion Gap Acidosis; elevated WBC w left shift, felt due to emesis; mild elevation of LFTs		Intubation Levophed O_2 Activated Charcoal Gastric Lavage Sorbitol		
							SVT, P wave abnormal	hyperreflexive			Diarrhea		Dopamine Imodium AD		
														Discharged	
189	57 F		Suicide Attempt	80 pills	Ambien Trazodone		Hypotension	Somnolence	Ragged heaves'		Hypothermia			[redacted]	
									Respiratory arrest					[redacted]	
263	13 F		Suicide Attempt	40 mg			Bradycardia, Prolonged QT						Atropine for bradycardia		
						2 weeks	QT normalized							Recovered	
377	33 M		Suicide Attempt	90 x 4 mg = 360 mg	Thorazine until 1-2 days prior to admission	ER - 6 hrs post ingestion	Stable	Comatose	Breathing on own	Hypertonia			Gastric Lavage; intubated as a precaution; Fluids; 'Diuresed with Mannitol and Furosemide'	Resolution within 72 hours	Unknown if "hepatic dysfunction" was pre-existing
						4-May		light coma - responsive		choreaform, athetosis-like movements			Benadryl IV		
						72 hours								Resolution within 72 hr	
391	Unknown age M	Muscle Spasms and motor ataxia secondary to Friedreich's ataxia	Suicide Attempt	16 mg - 120 mg		between		Stupor	Respiratory Depression			Renal Failure	Mechanical Ventilation Dialysis	Recovering	
400	38 M	Parapiegic	Suicide	Unknown	Others (unknown)									[redacted]	
420	30 M	Quadrapiegic	Suicide	40 x 4 mg = 160 mg (?)	Oxycodone & 4 others									[redacted]	
442	45 F		Suicide Attempt	90 x 4 mg = 360 mg			Bradycardia, hypotension	Somnolence	Cyanotic, Cold			Aspiration Pneumonitis	IV Fluids Intubation		
443	51 F Assume patient is Japanese	Machado-Joseph Dz	Suicide Attempt	284 x Tizanidine 1 mg (Termalin)	58 x Eperison (Myonal)		ST elevation and QT prolongation	Disturbed Consciousness	Respiratory Depression			Vomited portion of OD; Hypothermia	Mechanical Ventilation and Gastric Lavage		
													extubated	Recovered	
545	45 F	MS	Suicide		Diazepam Codeine Multiple Others Labs - "Non-lethal levels"							Subject found dead		[redacted]	

Case #	Demographics Age/ Sex/ Wt / Race	Dx	Situation	Tizanidine Dose	Concomitant Medications	Date	CV	CNS	Resp/Pulm	Musculo-skeletal	Metabolic	Other	Rx	Outcome	Comment
775	30 M	Quadraplegic	Suicide	20 x 4 mg = 80 mg	drug screen negative		Bradycardia	mild sedation	Respiratory depression				O2 Activated Charcoal		
						Several hrs. post admission	Hypotension		Respiratory Distress - CXR - Bilateral diffuse alveolar infiltrate consistent with pulmonary edema & ARDS				Mechanical Ventilation, Dialysis		
						March ?							Transferred Hospitals		
													Transferred Hospitals		
									Pneumonia - methicillin sensitive S. Aureus				Vancomycin Nafcillin Tracheostomy		
									Acute Respiratory Arrest due to pneumonia with sepsis					[redacted]	
823	49 F	Migraine Pain Drug Dependence	Drug [redacted] Misuse? OD? & Withdrawal	14 /x 4 = 56 mg /day x 4 yrs	Opioids benzodiazepines;										
						tizanidine									
								Presents to ER with Cravings Shaking Trembling					ER Vicodin Valium		
								jitteriness, anxiety				BDP WD	Transferred to Chemical Dependency Unit Clonidine 0.1 q 6h, Depakote, Phenobarbital		
							hypertensive 152/96, HR 92 bpm								
													Clonidine Dose tapered to 0.05 qid		
							Malig? HTN 170/108, Tachycardic 113 bpm					Lightheaded & fell	Clonidine increased to 0.1 mg tid		
													Atenolol Added		
							BP Stabilized 130/89								
														Discharged	
835	44 F	Suspected Overdose	Suspected Overdose (Suicide Attempt?)					Delirium Confusion						Unknown	
853	Age Unknown F	Drug Dependence	Drug Abuse OD & Withdrawal	17 x ?mg = 34 - 68 mg/day			Hypertensive on WD					Addiction	Clonidine	Unknown	

Case #	Demographics Age/ Sex/ Wt / Race	Dx	Situation	Tizanidine Dose	Concomitant Medications	Date	CV	CNS	Resp/Pulm	Musculo-skeletal	Metabolic	Other	Rx	Outcome	Comment
327	40 F		Drug Misuse OD & Withdrawal	Started increasing dose (up to 8 mg q 2 hr)	Neurontin 300 mg tid Duragesic		On WD hypertension, tachycardia,	On WD tremor hallucinations			hypochloremia				
				30 - 45 x 4 mg per day				somnolence (helping insomnia) tremor & hallucinations							
				Supply Depleted											
							ER - On WD hypertension, tachycardia,	On WD hallucinations				Vomiting		Psychiatric FU	
638	Age Unknown F		OD	OD amount unknown			Bradycardia x 18 hours						Pacemaker	Unknown	

Table 23 [redacted] Dissolution for Tizanidine Capsules in [redacted]

Strength (mg)	2	4	6	
Batch Use	Stability	BE & PK Studies (not pivotal BE with 6 mg) & Stability	Stability	**Pivotal BE & PK Study**
Comment	From Report: RPT RS:2001/238	RPT RS:2001/238	Summary Statistics with and without outlier. 2 capsules less than [redacted] 1 outlier [redacted] & the other [redacted] RPT RS:2001/238	From Report: RPT RD: 2002/062
Capsule Batch	PS1063p	PS1066p	PS1071p	PS1070p
Bead Batch	PS1042	PS1041	PS1040	PS1042
[redacted] **Batch**	PS1039	PS1038	PS1037	PS1039
Count	[redacted]			
% Labeled Content[a]				
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]			

a Mean ± SD (CV); Range

APPEARS THIS WAY
ON ORIGINAL

As shown in Table 23, mean dissolution for all strengths is approximately [redacted] at [redacted]

At [redacted] mean dissolution is around [redacted], although a number of individual capsules are always less than [redacted]. Thus [redacted] is too strict for a single point dissolution specification.

At [redacted], dissolution is essentially complete for all strengths, although there appears to be slightly slower dissolution as the amount of drug increases. Consequently, the minimum amount dissolved falls below [redacted], for the stability batch for the 6 mg capsule (but not for the pivotal clinical batch). However, when the 6 mg stability batch is examined more closely; for the statistical outlier, (> -3 s.d.), this particular vessel had [redacted] dissolution at [redacted], thus this [redacted] value is probably spurious. When this outlier is discarded only one out of [redacted] samples is below [redacted] which is the level that would necessitate level 2 testing. This corresponds to ~1 of 10 batches tested and is acceptable, especially as analysis of the effect of pH suggests that acceptance criteria should be kept strict (See section 7.6.4).

7.6.3 Adjustment for Capsule Interference

According to RPT RD: 2000/205 I. 4 V. 012 P. 199 the degree of interference is 3 - 5%. This is less than the 25% limit allowed by the USP and is acceptable.

7.6.4 Effect of pH

Even though tizanidine has pH dependent solubility with a pKa of [redacted] the [redacted] solubility in water indicates that tizanidine should still be highly soluble at pH [redacted]

Since tizanidine is highly soluble it should thus have an acceptance criteria of NLT [redacted], (Q = [redacted], at [redacted] in [redacted]

However, mean dissolution profiles also show slower dissolution as pH increases, as well as a pattern of slower dissolution as the dose increases (See Figure 11).

In addition to tizanidine [redacted] w/w), the 2 major components of the capsule bead coating are hydroxypropyl-methyl-cellulose (HPMC) [redacted] w/w) and [redacted] silicon dioxide [redacted] w/w). Both of these excipients form viscous colloids on exposure to water and the degree of viscosity is pH dependent.

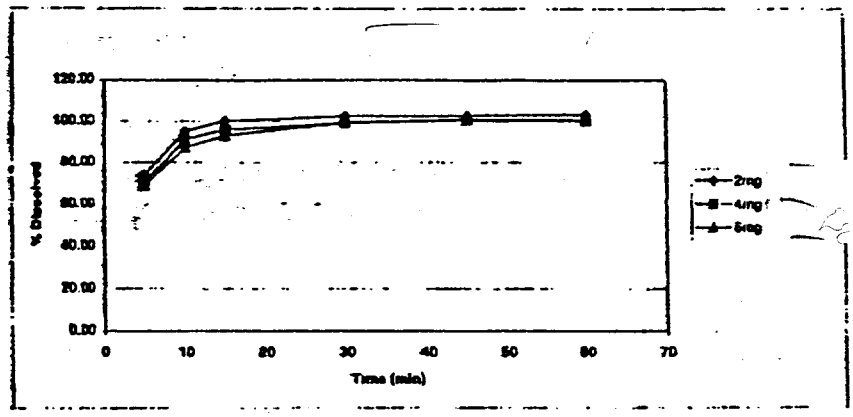
Thus it appears that there's a mechanistic basis for slower dissolution and slower absorption *in vivo* with the capsules beads as compared to the tablets. Which might occur if some beads get into the duodenum before dissolution in the stomach is complete.

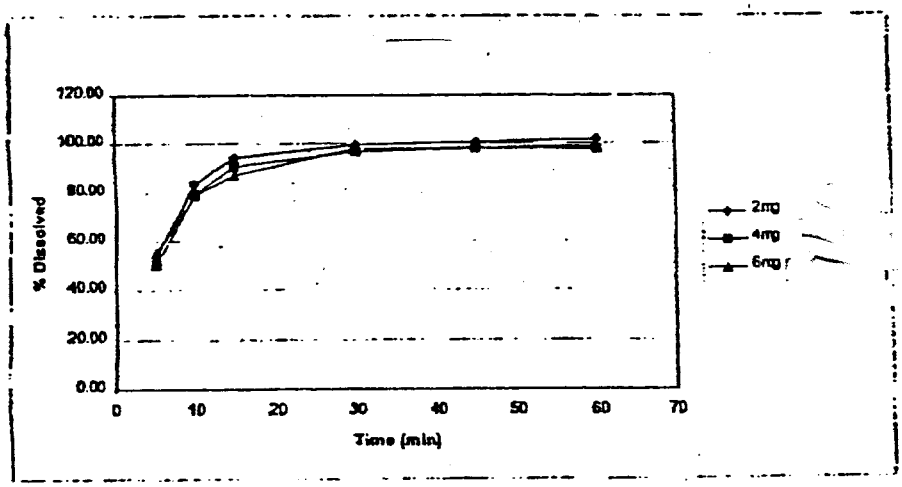
Consequently, the dissolution specification should be either in high pH buffer, or the acceptance criteria in acidic media should be stricter than proposed by the sponsor.

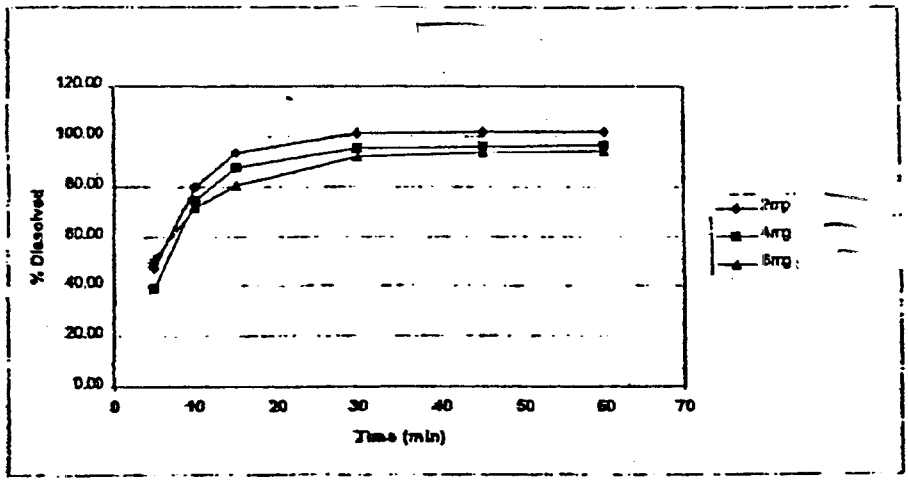
Since, the 6 mg capsule has the slowest dissolution in acidic media and yet still meets bioequivalence, acceptance criteria may be based upon it for the 2 mg and 4 mg strengths.

In addition, food, antacids, H2 antagonists, and proton pump inhibitors can alter pH and therefore might alter absorption characteristics.

Figure 11 Mean Dissolution Profiles of Tizanidine IR Capsules (2mg, 4mg, 6 mg) in '







7.7 BCS CLASSIFICATION

OCPB cannot classify tizanidine according to the BCS classification system at the present time, as there is insufficient information to determine the degree of permeability.

7.8 OCPB FILING MEMO

7.8.1 Issues and Comments

7.8.1.1 Comments to be sent to firm:

- Please provide new electronic and hard copies of the proposed labeling that indicates all changes from the current approved text with strikeouts and insertion marks. Additional electronic and hardcopies with editing marks (insertions & deletions) in a side-by-side 3-column format, (Current, Proposed, Annotations), would also be appreciated as it tends to speed review.
- For study AN021-101 please provide or adequately cross-reference, as appropriate, the missing sections of the analytic report (Vol. 1.33). The submitted information begins with Appendix F.
- For the Cognitive Drug Research Report (Vol. 1.32 pg 151 and Vol. 1.37 pg 331) please provide legible copies of the literature articles cited.
- Please provide the raw data & computer code for the Cognitive Drug Research Report (Vol. 1.37 pg 331) in electronic format (single precision for numeric data).

7.8.1.2 QBR questions (key issues to be considered)

- Is the 4 mg capsule formulation bioequivalent to the highest approved strength of the tablet (4 mg)?
- Is the 6 mg capsule bioequivalent to a similar dose of the tablet formulation (4 mg & 2 mg tablets)?
- Is a biowaiver acceptable for the 2 mg capsule?
- Is there a food by formulation effect?
- Is the food by formulation effect clinically significant?
- Are the dissolution method and acceptance criteria acceptable?

7.8.1.3 Other comments or information not included above

AE of hypotension could be of additional clinical importance in patients with spasticity. Differences in food effect by formulation could result in differences in incidence or severity of first dose effect. Interest is in both prescribability and switchability. Differences would only be seen if dose is on ascending portion of concentration effect curve. In addition, the maximum difference would only be seen if dose is on the upper portion of the ascending portion of the curve. Consequently, must determine if dose used is on that portion of C vs. E curve for PK/PD study to show maximum potential clinical difference due to food?

7.8.2 Table of Studies

Table 24 List of Studies Included in NDA 21-447

Protocol #	Protocol Title
Bioequivalence Studies - Fasted	
0300003	A Single-Dose Study in Healthy Subjects to Evaluate the Bioequivalence of a Tizanidine 4 mg IR Capsule Formulation Relative to Zanaflex® 4 mg IR Tablet
0600002	A Study in Healthy Volunteers to Evaluate the Bioequivalence of a Tizanidine 6 mg IR Capsule Formulation Relative to Zanaflex® 6 mg (Administered as 4 mg and 2 mg IR Tablets)
Bioequivalence when Administered by Sprinkling on Applesauce	
0400002	A Study in Healthy Volunteers to Evaluate the Relative Bioavailability of a Tizanidine IR Formulation when Administered in a Capsule and a Sprinkle Form
Bioequivalence - Food Effect Studies	
0400001	A Study in Healthy Volunteers to Assess the Effect of Food on the Bioavailability of a Tizanidine 4 mg IR Capsule Relative to Zanaflex® 4 mg IR Tablet
AN021-101	Single Dose Pharmacokinetic, Pharmacodynamic, and Safety Study of Zanaflex® (Tizanidine Hydrochloride) Tablets 8 mg (2 x 4 mg) and Capsules 8 mg (2 x 4 mg) Administered with and without Food in Healthy Subjects.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
5/30/02 11:55:35 AM
BIOPHARMACEUTICS

Raman Baweja
5/30/02 02:37:18 PM
BIOPHARMACEUTICS