CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-447

MEDICAL REVIEW

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Zanaflex**
Generic Name:	**Tizanidine**
Sponsor:	**Elan Pharmaceuticals, Inc.**
Indication:	**Spasticity**
NDA Number:	**21-447**
Original Receipt Date:	**10/31/01**
Clinical Reviewers:	**Eric Bastings, M.D.**
Review Author:	**Eric Bastings, M.D.**
Review Completed:	**6/13/02**

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Clinical Review for NDA 21-447

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Tizanidine 4 mg tablets was approved for the management of spasticity on November 27, 1996. A supplement for a 2 mg tablet was approved on February 4, 2000. This application concerns a new formulation (capsule), with bioequivalence studies with the tablet dosage form. The sponsor has not modified the indication, so that no new efficacy data are necessary if bioequivalence is established. From a clinical perspective, I recommend approval since no new safety concerns have developed since the drug was approved in the tablet form in 1996.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Elan Pharmaceuticals (Elan) is submitting this New Drug Application for a new formulation of tizanidine hydrochloride: capsules 2 mg, 4 mg, and 6 mg. Elan is referencing to NDA 20-397 for Zanaflex (tizanidine hydrochloride) tablets 2 mg and 4 mg, which was approved on November 27, 1996. The route of administration is oral.

Five studies were performed to evaluate the effect of the capsule formulation. Four studies were designed to evaluate the bioequivalence and bioavailability of the capsule versus the tablet formulation. The fifth study was designed to compare the effects of tizanidine capsules and tablets in fed versus fasted states in a larger population. These 5 studies had a total enrollment of 198 healthy volunteers. All subjects were exposed to the study drug.

B. Efficacy

There were no new efficacy studies with this NDA. Efficacy as a short-acting drug for the treatment of spasticity was established in NDA 20-397.

C. Safety

In NDA 20-397, the safety profile of tizanidine tablets was determined in multiple dose, double-blind, placebo-controlled clinical studies (AN021-001, AN021-003, DS0502) involving 264 patients with spasticity. The most common adverse events associated with tizanidine up to 36 mg/day in patients with spasticity are dry mouth, somnolence, asthenia and dizziness.

The safety data from the Elan Pharmaceuticals postmarket safety surveillance database did not identify any new major safety concern. Tizanidine is currently approved and marketed in 47 countries.

For this NDA, an additional 198 patients were exposed to tizanidine. No serious adverse events occurred in these patients. Adverse events were similar to those reported in NDA 20-397 (tablet form). Overall, 1385 patients have been exposed to tizanidine in clinical studies.

Based upon the findings from reported cases of tizanidine drug interaction in the postmarketing safety surveillance database, I agree with the changes proposed by the sponsor to update the current Zanaflex and proposed tizanidine capsule Package Insert information with information on a risk of increased toxicity when co-administered with rofecoxib (Vioxx).

Additional cases of tizanidine overdosage were identified in the published medical literature post NDA approval and in the postmarket safety surveillance. These cases continue to demonstrate that tizanidine may cause depressed cardiovascular, respiratory, and/or CNS function in case of overdosage. The current Zanaflex and proposed tizanidine capsule Package Insert information regarding tizanidine overdosage need to be updated with information from these cases. In addition, I concur with the clinical pharmacology reviewer recommendation to publish with the sponsor a review article of the presently known overdose cases in collaboration with the sponsor.

D. Dosing

This NDA concerns a new formulation (capsule) for a drug already approved in the tablet form. The sponsor is also adding a new dosage, the 6 mg capsule, but the maximum daily dosage (36 mg) and administration remain the same as for the tablet form. The capsule and tablet are bioequivalent in the fasted state, but bioinequivalent under fed conditions. This presents a switchability issue between capsules and tablets. Description in the labeling with warning regarding switchability should be adequate to manage the risk.

E. Special Populations

No new information about special populations was obtained in this NDA. All information known and summarized here below was obtained in the tizanidine tablet NDA.

Age effects: no specific pharmacokinetic study was conducted to investigate age effect. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine in NDA 20-397 showed that younger subjects cleared the drug four times faster than elderly subjects.

Hepatic impairment: pharmacokinetic differences due to hepatic impairment have not been studied.

Renal impairment: Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatine clearance < 25mL/min) compared to healthy elderly subjects.

Gender/race effects: No specific pharmacokinetic study was conducted to investigate gender or race effects. Retrospective analysis in NDA 20-397 showed that gender had no effect on the pharmacokinetics of tizanidine.

Pregnancy: tizanidine is pregnancy C.

Pediatric use: there is limited information available in the published medical literature and data from postmarket safety surveillance on the use of tizanidine in the pediatric population. Since the mechanism of spasticity is presumably the same in the pediatric and the adult population, further efficacy studies in the pediatric population are not warranted. There is no adequate evidence for the pharmacokinetics and for the safety of tizanidine in the pediatric population. Even tough the types of adverse events reported in children are similar to those seen in adults, the long term safety profile should be better defined, since the side effects of tizanidine may be more severe in the pediatric population, and their functional impact should be evaluated to better define the risk/benefit ratio of tizanidine in that population.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Tizanidine hydrochloride (5-chloro-4-(2-imidazolin-2-ylamino)-2, 1 ,3-benzothiadiazole hydrochloride) is a white to off-white, fine crystalline powder, odorless or with a faint characteristic odor. Molecular formula is C9H8CIN5S-HCI. Molecular weight is 290.20. The active moieity, tizanidine is also referred to as the salt (hydrochloride [HCl]), as well as the marketed forms: Zanaflex (tizanidine HCI tablet for the United States [U.S.]), Sirdalud and Ternelin.

Tizanidine has been shown in clinical studies to have myotonolytic properties and was approved for treatment of spasticity in adult patients in the tablet formulation in 1996. This application concerns a capsule dosage form, with the same recommended total daily dosage, up to 36 mg in 3 divided doses, and the same indication. The drug has not been studied in the pediatric population.

The sponsor believes that less variation in the PK profile (in the presence and absence of food) for the capsule, will have clinical benefit in providing a more consistent pharmacological and safety profile. This has not been established in the present NDA. In addition, the sponsor believes that the ability of the caregiver to be able to dispense the capsule contents with food or fluid may provide advantages in terms of patient compliance and convenience compared to the conventional tablet. The sponsor believes that the capsule form will be preferred by patients with swallowing difficulties.

B. State of Armamentarium for Indication(s)

The armamentarium for the indication of spasticity has not changed much since tizanidine was approved in the tablet formulation in 1996. The main alternative is baclofen, a gaba-ergic agonist with a similar safety and efficacy profile, but which may cause weakness, and cause seizures or confusion in case of abrupt withdrawal. Baclofen may also be used intrathecally using a pump. This is reserved to the most severe cases, and not as a first-line therapy. A second alternative is diazepam (Valium), a benzodiazepine which may induce dependence and cause a withdrawal syndrome in case abrupt withdrawal. Finally, dantrolene, a muscle relaxant, remains available but is rarely used because of possible severe liver side effects.

Neural transmission blocks using botulinum toxin, local anesthetics or other chemical agents can also be used. Botulinum toxin is being studied and used off label for the indication of focal spasticity. Maximum dosage limits applicability in case of spasticity involving multiple muscle groups. There are also non-

pharmacological alternatives, such as muscle stretching, range of motion exercises, and other physical therapy regimens. Finally, surgery for tendon release or posterior rhizotomy can be applied in selected cases.

C. Important Milestones in Product Development

Tizanidine HCl was approved on November 27, 1996, as Zanaflex 2 mg and 4 mg tablets. [redacted] The MR form is available in other countries. Elan had developed the capsule formulation overseas, and there was no IND on file at time of the NDA submission. There has been no meeting with the division prior to NDA submission.

D. Other Relevant Information

Tizanidine was first registered by Sandoz Pharma in Europe in December 1983. Its current labeling in Switzerland is as follows: "Sirdalud is well tolerated and effective for the treatment of acute, painful muscle spasms as well as for the treatment of chronic spasticity of spinal or central origin." Tizanidine is marketed in 47 countries in a variety of dosage forms including 2 mg, 4 mg, and 6 mg tablets; 6 mg and 12 mg MR capsules; and 0.2% Sirdalud granules. To the best of Elan's knowledge, tizanidine has not been withdrawn from any country in which marketing authorization had previously been granted.

E. Important Issues with Pharmacologically Related Agents

There are no new known issues with pharmacologically related agents since the drug was approved in the tablet form in 1996. Central adrenergic agonists, such as clonidine, are well known for causing hypotension, which is addressed in the current labeling of tizanidine.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Since the approval of the Zanaflex tablet NDA 20-397, no additional preclinical pharmacology and toxicology studies have been conducted by Elan.

This NDA has been reviewed by Ronald E. Kavanagh and Raman Baweja (team leader), from the Office of Clinical Pharmacology and Biopharmaceutics. OCPB finds this application acceptable.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Tizanidine pharmacokinetics were studied in NDA 20-397 for the tablet formulation. Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. The absolute systemic availability following oral administration is approximately 40%. 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. Tizanidine is widely distributed throughout the body; mean steady state volume of distribution is 2.4L/kg following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins, independent of concentration over the therapeutic range.

Five PK studies were performed to evaluate the tizanidine capsule. Four studies were designed to evaluate the bioequivalence and bioavailability of tizanidine administered as a capsule versus a tablet formulation. The fifth study was designed to examine the effects of tizanidine capsules and tablets in fed versus fasted states in a larger population.

Table 1 summarizes the design of these 5 studies. Studies 0300003, 0400001, and AN021-101 were single dose comparator studies with the highest dose strength of the tablet (4 mg). Protocol 0400001 and AN021-101 were designed to evaluate the impact of food on tizanidine. Protocol 0600002 compared the 6 mg tizanidine capsule to the Zanaflex tablet when administered at 2 + 4 mg. Protocol 0400002 compared the bioequivalence of the 6 mg tizanidine capsule formulation administered intact versus in a sprinkle form.

Table 1: Biopharmaceutics studies

Protocol No.	Route	Dosage Form(s)	Dose	Batch No.	No. Subjects	Conclusions
0300003 Single dose (2-way cross-over) bio-equivalence study	Oral	Capsule Zanaflex Tablet	4 mg 4 mg	PS1066 ZN0162	12 males 16 females	The capsule was shown to be bioequivalent to the Zanaflex tablet in terms of C_{max} and AUC.
0600002 Single dose (2-way cross-over) study	Oral	Capsule Zanaflex Tablet	6 mg 2 mg 4 mg	PS1070 113MFD-0999 ZN0162	11 males PK; 12 males safety 16 females	The 6 mg tizanidine capsule was shown to be bioequivalent to the Zanaflex tablet (4 mg + 2 mg) in terms of C_{max} and AUC.
0400001 Single dose (2-way cross-over) food effect study	Oral	Capsule Zanaflex Tablet	4 mg 4 mg	PS1066 ZN0162	12 males 6 females	The difference in mean C_{max} was >20% between the tizanidine capsule formulation and the Zanaflex tablet in the fed state only and T_{max} was significantly greater for the capsule compared to the tablet.
0400002 Single dose (2-way cross-over) study	Oral	Capsule (intact) Capsule (sprinkle)	6 mg 6 mg	PS1070 PS1070	19 males 9 females	Food has an effect on the absorption of tizanidine.
AN021-101 Single dose (2-way cross-over) food effect study	Oral	Capsule Zanaflex Tablet	8 mg (2x4mg) 8 mg (2x4mg)	PS1056P 197MFD-1299	54 males 42 females	For the tablet formulation, food increases the C_{max}, T_{max}, and AUC_{∞}, for the capsule, food increases the T_{max} and AUC_{∞}, but decreases the C_{max}. The effect of food was greater for the tablet than for the capsule.

A biowaiver was requested for the lowest dose strength (2 mg) on the basis that the formulation is made of beads in a capsule and it is proportionately similar to the higher strengths. In addition, the dissolution of the 2 mg strength has been shown to be similar to the 4 mg and 6 mg strengths across a range of dissolution media.

Below is summary of key findings as evaluated by OCPB:

- 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.

- 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 (Figure 1). [Study 0300003]

- When tizanidine capsules are administered under fed conditions, there is a delay in absorption compared to when the capsule is administered under fasting conditions (Figure 1). 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 of the mean Cmax for the tablet (Figure 1). 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]

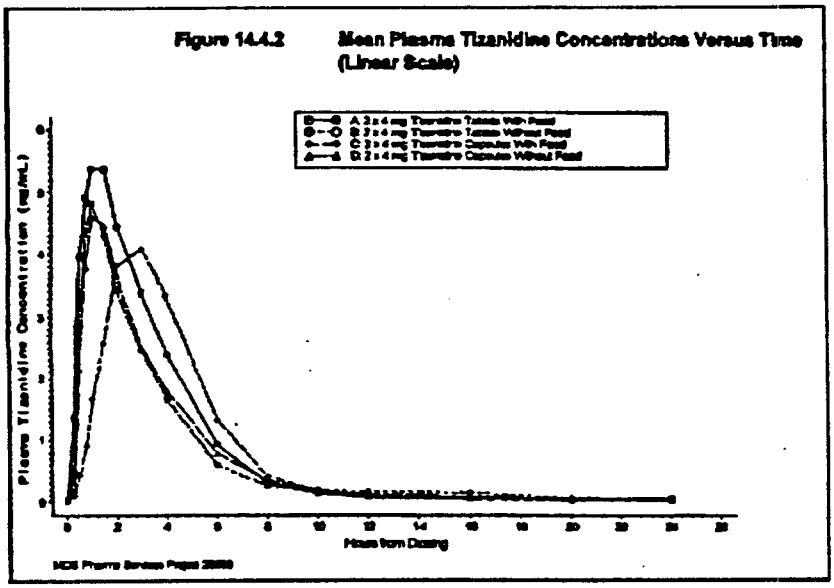
- Sprinkling the capsule contents on applesauce increases the rate of absorption of tizanidine as well as significantly decreases the variability in absorption rate. This is associated with approximately a 15% - 20% increase in Cmax and AUC. The increase in rate of absorption may be secondary to faster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

- A biowaiver is granted for the 2 mg capsule. In assessing this request the following conclusions were made: (a) Tizanidine 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 [redacted]

Figure 1: Comparison of PKs of tablets and capsules in the fed and fasted state

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



B. Pharmacodynamics

Tizanidine is a centrally acting alpha$_2$-adrenergic agonist. The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other alpha$_2$-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have 1/10 to 1/50 of the potency of clonidine in lowering blood pressure.

Tizanidine is thought to produce its effects by reducing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction and has no major effect on monosynaptic spinal reflexes. The greatest effect appears to be on polysynaptic pathways resulting in reduced facilitation of spinal motor neurons.

The reduction of muscle tone that follows the oral administration of a single dose of tizanidine has its peak effect 1 to 2 hours after dosing, and the effect dissipates between 3 and 6 hours.

In the present NDA, the sponsor conducted a PK/PD study to evaluate the impact of tizanidine formulation and of the effect of administration with food on cognition and blood pressure. OCPB reviewed PD study AN021-101. OCPB notes that the adverse effects that were monitored included various measures of cognition and blood pressure, and that the quantitative results from this study are problematic. However, OCPB believes that 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 tizanidine concentrations.

OCPB notes that the quantitative results are problematic for the following reasons: (1) there were a large number of problems with the bioanalysis (2) Sampling times were inadequate (3) the data analysis was illegible. Specifically, an extremely small font was used and the photocopies provided were so faint that they could not be read. The apparent qualitative results of the study are described below:

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 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. 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.

OCPB made the following observations at different timepoints:

- At 0.75 hr, cognition was better for the capsule formulation under fed conditions, which is consistent with the delayed absorption and lower concentrations.
- At 1.5 hrs, there was a trend for cognition to be worse for the tablet formulation under fed conditions, which is consistent with the higher concentrations with food for the tablet. The other treatments tended to have similar degrees of cognitive impairment.
- At 2.5 hrs, the effects on cognition were greatest for the capsule formulation under fed conditions, which is consistent with the delayed absorption when administered with food. 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, likely due to the nearly complete elimination of the compound by 6 hours for each and every treatment arm.

I concur with OCPB that it is unfortunate that the sponsor only assessed effects on cognition at limited time points, as this did not adequately cover the differences observed over the early portions of the concentration vs. time profiles. I also reviewed this study (AN021-101) in the Sponsor Postmarket Safety Studies section.

Pharmacodynamic Effects on Blood Pressure

OCPB notes that there is 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. Close inspection reveals that the early BP measurements are initially at hourly intervals, (i.e. 1, 2, 3 and 4 hours post dosing), missing the times when the major differences in concentrations between treatment arms occur, i.e. 1.2 hours.

IV. Description of Clinical Data and Sources

A. Overall Data

Since the approval of the Zanaflex tablet NDA 20-397 on November 27,1996, no additional clinical efficacy studies have been conducted by Elan. The core of this NDA consists of 5 pharmacokinetic studies, in support for the bioequivalence between the capsule and the tablet. No efficacy studies have been performed with the tizanidine capsule. The sponsor also provided in this NDA a summary of pertinent data on tizanidine from published literature since 1994.

B. Tables Listing the Clinical Trials

Clinical trials are listed in Table 2.

Table 2: Listing of clinical trials in support of NDA 21,337

Protocol No.	Route	Dosage Form(s)	Dose	Batch No.	No. Subjects	Conclusions
0300003 Single dose (2-way cross-over) bio-equivalence study	Oral	Capsule Zanaflex Tablet	4 mg 4 mg	PS1066 ZN0162	12 males 16 females	The capsule was shown to be bioequivalent to the Zanaflex tablet in terms of C_{max} and AUC.
0600002 Single dose (2-way cross-over) study	Oral	Capsule Zanaflex Tablet	6 mg 2 mg 4 mg	PS1070 113MFD-0999 ZN0162	11 males PK; 12 males safety 16 females	The 6 mg tizanidine capsule was shown to be bioequivalent to the Zanaflex tablet (4 mg + 2 mg) in terms of C_{max} and AUC.
0400001 Single dose (2-way cross-over) food effect study	Oral	Capsule Zanaflex Tablet	4 mg 4 mg	PS1066 ZN0162	12 males 6 females	The difference in mean C_{max} was >20% between the tizanidine capsule formulation and the Zanaflex tablet in the fed state only and T_{max} was significantly greater for the capsule compared to the tablet.
0400002 Single dose (2-way cross-over) study	Oral	Capsule (intact) Capsule (sprinkle)	6 mg 6 mg	PS1070 PS1070	19 males 9 females	Food has an effect on the absorption of tizanidine.
AN021-101 Single dose (2-way cross-over) food effect study	Oral	Capsule Zanaflex Tablet	8 mg (2x4mg) 8 mg (2x4mg)	PS1066P 197MFD-1299	54 males 42 females	For the tablet formulation, food increases the C_{max}, T_{max} and AUC_{∞}; for the capsule, food increases the T_{max} and AUC_{∞} but decreases the C_{max}. The effect of food was greater for the tablet than for the capsule.

C. Postmarketing Experience

The sponsor summarized in the NDA the postmarketing experience in all countries were tizanidine has been approved and marketed. This covers the experience from the first introduction of tizanidine in 1983.

D. Literature Review

The sponsor conducted a literature search on new information on the efficacy and safety of tizanidine, as well as pediatric experience. I also performed a medline search in order to identify additional pertinent information.

V. Clinical Review Methods

A. How the Review was Conducted

Since no new efficacy study was conducted for NDA 21-447, my review focused on the safety data originating mainly from the postmarketing experience, but also from the literature published after ND 20-397. I also performed a medline search to identify if any important published tizanidine studies were missing from the NDA.

B. Overview of Materials Consulted in Review

I reviewed in detail volumes 1.1, 1.2, 1.39 and 1.40 of NDA 21-447. I also consulted volumes 1.23 to 1.38 (PK studies) to assess clinically relevant safety issues in the PK and PK/PD studies. No electronic material was submitted on clinical data.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audited [redacted] Audit results are pending.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

The sponsor submitted a financial disclosure statement. There was no apparent conflict.

VI. Integrated Review of Efficacy

There was no new efficacy study in this NDA. Evidence demonstrating the effectiveness of tizanidine is derived from a single dose study and from a 7-week multiple dose study conducted in patients with multiple sclerosis and spinal cord injury, respectively. These studies were presented in NDA 20-397.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety data from NDA 21-447 do not change FDA previous assessment of the general safety profile of tizanidine established in NDA 20-397, and presented in the Zanaflex Package Insert. Limited new safety information could be expected from the short-term pharmacokinetic studies with relatively low doses of tizanidine in NDA 21-447. No major new safety signal emerged from the post-marketing safety database.

There is a switchability issue when a patient takes the medication with food and changes formulations between the tablet and the capsule. 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. Description in the labeling with warning regarding switchability should be adequate to manage the risk.

The tizanidine tablet and capsule Package Insert information must be updated regarding a possible drug interaction with rofecoxib (Vioxx). The sponsor reported 8 case reports of possible interaction, mostly in the CNS or cardiovascular systems.

There is very limited information available in the published medical literature and in the postmarket safety surveillance on the safety of tizanidine in the pediatric population. There is no information on dosing regimen in children with an acceptable risk/benefit ratio. I recommend to evaluate tizanidine PK in the pediatric population and to study tizanidine long-term safety in the pediatric population.

The tizanidine overdosage post-marketing experience confirms that tizanidine may cause depressed cardiovascular, respiratory, and/or CNS function.

B. Description of Patient Exposure

In NDA 20-397, the safety profile of tizanidine hydrochloride was determined in multiple dose, double-blind, placebo-controlled clinical studies (AN021-001, AN021-003, DS0502) involving 264 patients with spasticity. In NDA 21-447, an additional 198 patients were exposed to tizanidine. Overall, 1385 patients were exposed to tizanidine in clinical studies.

C. Methods and Specific Findings of Safety Review

For the safety review, I will first briefly summarize the safety information from NDA 20397 (tablet form), then review the new safety information from the post-NDA period.

NDA 20-397

In NDA 20-397, the safety profile of tizanidine hydrochloride was determined in 3 double-blind, placebo-controlled clinical studies (AN021-001, AN021-003, DS0502) involving 264 patients with spasticity. The most common adverse events associated with tizanidine up to 36 mg/day in patients with spasticity were dry mouth, somnolence, asthenia and dizziness.

Table 3: Adverse events in controlled NDA studies

Event	Placebo N=261	Tizanidine N=264
Dry mouth	10%	49%
Somnolence	10%	48%
Asthenia (weakness, fatigue and/or tiredness)	16%	41%
Dizziness	4%	16%
UTI (Urinary Tract Infection)	7%	10%
Infection	5%	6%
Constipation	1%	4%
Liver function tests abnormal	<1%	3%
Vomiting	0%	3%
Speech disorder	0%	3%
Amblyopia (blurred vision)	<1%	3%
Urinary frequency	2%	3%
Flu syndrome	2%	3%
SGPT/ALT increased	<1%	3%
Dyskinesia	0%	3%
Nervousness	<1%	3%
Pharyngitis	1%	3%
Rhinitis	2%	3%

The rate of discontinuation due to AEs in the 3 multiple dose trials was 14% (38 patients) in the tizanidine group and 5% (12 patients) in the placebo group. The most common AEs that led to discontinuations in the tizanidine group were asthenia, dry mouth, and somnolence. Treatment-related serious adverse events were reported by 9 patients in the tizanidine group (3%) and by 2 patients (1%) in the placebo group. The only death during the 3 studies occurred in a placebo-treated patient.

In the 3 multiple dose trials, the sponsor did not identify clinically meaningful differences in the overall reporting rates of treatment-related adverse events among evaluated subsets of patients treated with tizanidine. Subset analyses were performed by age, sex, duration of disease/condition, geographic region, underlying disease/condition, severity of spasticity at baseline, and pharmacological class of concomitant medications. No substantial differences among the subsets were seen for the four most frequently reported AEs (dry mouth, asthenia, dizziness, and somnolence).

Postmarket Periodic Safety Reports

Following the Zanaflex tablet NDA approval on 27 November 1996, there have been 13 periodic reports presenting adverse drug reactions and adverse drug experiences. No new safety signals have been identified in these safety reports.

Postmarket Safety Studies

The sponsor reviewed the published medical literature post NDA 20-397 approval and data from postmarket safety studies. Four published articles address general safety issues related to the use of tizanidine. [redacted] sponsor postmarket safety studies are completed or ongoing. In a medline search, I did not identify any additional important information concerning the safety of tizanidine.

Published Medical Literature

Three publications concerned open-label safety studies (Table 4).

Table 4: Literature safety studies

Study	N	Indications	Design	Dose
Taittonen	19	Healthy volunteers	Random, double-blind, cross-over	6–12 mg
Wallace	63	Severe chronic spasticity due to SCI	Open, non-comparative	Up to 36 mg/day
Schapiro and Trotter	33	Severe chronic spasticity due to MS or SCI	Open, comparative	28–36 mg/day

Taittonen et al (1995) conducted a pilot study on the metabolic effects of placebo and 6mg and 12mg of oral tizanidine tablets in a double blind, crossover fashion in five healthy volunteers. Subjective assessment of tiredness and dryness of mouth were measured by visual analog scales (VAS). There were no statistically significant differences in tiredness or dryness of mouth between the groups.

Wallace et al (1998) reviewed the long-term (up to 4 years) safety and efficacy of Zanaflex tablets in patients with spasticity from spinal cord injury who successfully completed a prior double-blind study. All patients were titrated to optimal dose (maximum 36 mg/day), administered t.i.d. Examinations were performed weekly during titration, and approximately twice a year thereafter. Fifty-five patients completed a 3-

week titration to optimal dose; 16 patients (23%) completed the 4-year study. Forty-two patients had up to one year of exposure to tizanidine. The most frequent reason for discontinuation was adverse events (34%). Other patients discontinued due to insufficient therapeutic effect (16%), poor compliance (7%), loss to follow-up (14%), or sponsor request (4%). The most frequently reported adverse events were somnolence (43%), asthenia (29%), dry mouth (29%), and dizziness (20%). Urinary tract infection (36%), accidental injury (17%), skin ulcer (16%), infection (14%), and peripheral edema (14%) were also common.

Schapiro and Trotter (2001) reported that high-dose tizanidine treatment produced some cardiovascular and hepatic effects in an open-label study of 176 patients with spasticity from multiple sclerosis or spinal cord injury. Tizanidine was initiated at 2 mg/day and increased 2 mg/day every day until 36 mg/day or optimal doses >28 mg were achieved. Patients intolerant of >28 mg were discontinued; all others continued for up to 6 months. A comparison group receiving antispasticity medications other than tizanidine was evaluated similarly. Orthostatic hypotension occurred in 8% of tizanidine patients versus 11% of the comparison group. 87% tizanidine versus 72% patients of the comparison group reported adverse events. Most were mild to moderate in severity and reversible. More tizanidine patients had transient values above the upper limits of normal for AST (10%) or ALT (12%).

de Graaf et al (1996) presented a case history of a woman who developed serious liver injury while taking 36 mg tizanidine daily. Other causes of hepatic injury were excluded. Symptoms resolved after discontinuation of tizanidine, and the liver enzyme levels were nearly normal 6 weeks after discontinuation of the drug. Rechallenge with 4 mg tizanidine caused a relapse. The temporal relationship between the symptoms and liver enzyme elevations, the absence of other potential causes, and the reaction to rechallenge, strongly implicate tizanidine as the cause of hepatic injury.

Overall, these published studies confirm the known side effects of tizanidine, mostly hypotension, somnolence, and liver toxicity. These are appropriately addressed in the current labeling.

Sponsor Postmarket Safety Studies

Elan Pharmaceuticals has conducted several postmarket safety studies: AN021-002, AN021-004, AN021-227, AN021-301, AN021-402, AN021-450, AN021-455, AN021-456, AN021-101, 0300003, 0400001, 0400002, and 0600002. The sponsor provided a synopsis of these studies, which is summarized in Table 5. As of 30 June 2001, additional postmarket safety studies are currently ongoing: AN021-401, AN021-451, AN021-452, AN021-454, AN021-457, [redacted], AN021-351, and AN021-501 (Table 6).

Table 5: Clinical studies after NDA approval

Study	Form	Population	Open-Label	X2-Blind, Placebo-Controlled	N	Duration	Objective: evaluation of	Safety issue
AN021-002	Tablet	MS	X		262	36 months	• Safety of long-term treatment • Long term benefits	53 discontinuation for AEs: somnolence (16), asthenia (11), postural hypotension, mysathenia, abnormal liver tests,dry months, insomnia (2 each)
AN021-004	Tablet	SCI	X		82	30 months	• Safety of long-term treatment • Long term benefits	Discontination for AEs in 24%; 3 deaths: one possible MI, one heart failure, one cardiac desease and sepsis, all considered unrelated to tizanidine.
AN021-227	MR	Healthy	X		28	Single dose	PK and safety of MR capsules 24mg and 48mg	No deaths or SAEs. 5 withdrawals for dizziness or fainting
AN021-301	MR	MS SCI		X	37	Single dose	PK, efficacy and safety of MR capsules 24mg and 48mg	No death. 2 serious AEs: one decubitus ulcer, and one case of severe hypotension, confusion, dizziness, somnolence,and bradycardia. Possible dose effect leading to a first degree AV block. Dose-related hypotension, greater at 6 hours post-dose.
AN021-402	Tablet	MS SCI	X		43	Single dose	Safety of single doses of 16mg tizanidine in patients on chronic dose of 20-28 or 29-36mg tizanidine	8 cases of hypotension reported as AE (6/8 in the 20-28mg group). No SAEs. Orthostatic hypotension in 41% of patients stabilized on tizanidine tablets.
AN021-450	Tablet	Stroke	X		47	18 weeks	Safety and efficacy of tizanindine with dose-titration schedule up to 36mg daily.	Total modified Ashworth score improved. Somnolence 62%, dizziness 38%, asthenia 30%, accidental injury 23%, hypotension 17%. 15 SAEs , one evnt of anorexia possibly related to study drug.
AN021-455	Tablet	MS	X		30	6 weeks	Safety and efficacy in treatment of [redacted]	Low enrollment. Early study discontinuation. No SAEs or death.
AN021-456	Tablet	[redacted]	X		50	12 weeks	Safety and efficacy [redacted] Titration up to 18 mg.	Some positive efficacy findings. 3 discontinuations for somnolence and dry mouth. One case of elevated liver enzymes. No deaths or SAEs.
AN021-101	Tablet Capsule	Healthy	X		96	Single dose	PK, PD and safety of 8mg tizanidine tablets and capsules with and without food. 4 way crossover study	Power of attention not different from baseline. Orthostatic hypotension in 24-31% subjects, mostly at 1-2 hours post-dose.No deaths or SAEs.
0300003	Tablet Capsule	Healthy	X		28	Single dose	Bioequivalence, safety and tolerability of tizanidine 4mg tablets and capsules	AEs in 54% subjects. No SAEs. No death. No change in vital signs.
0400001	Tablet Capsule	Healthy	X		18	Single dose	Effect of food on bioavailability of tizanidine 4mg tablet and capsule; safety and tolerability of tizanidine 4mg tablets and capsules	AEs in 67% subjects. No SAES. No death. No change in vital signs.
0400002	Capsule	Healthy	X		28	Single dose	Relative bioavailability of tizanidine 6mg caspule versus in sprinkle form. Safety and tolerability of tizanidine 6 mg capsules.	AEs in 61%. No SAEs. Systolic BP 17% decrease for both treatments at the 1-h post dose timepoint.
0600002	Tablet Capsule	Healthy	X		28	Single dose	Bioequivalence, safety and tolerability of tizanidine 4mg+2mg tablets and 6mg capsules	AEs in 71% subjects. No SAEs and no deaths. No difference in vital signs.

Table 6: Ongoing post-marketing studies

Study	Form	Population	Open-Label	X2-Blind, Placebo-Controlled	N	Duration	Objective: evaluation of
AN021-401	Tablet	MS SCI	X		150	6 months	Long-term safety study. 100 patients on Zanaflex 28-36mg/day. 50 patients on other drug.
AN021-451	Tablet	ABI		X		6 weeks X 2 (crossover)	Safety and efficacy crossover study; titration up to 36mg per day.
AN021-452	Tablet	Stroke	X		24	1 year	Long term safety. Maximum dose of 36mg.
AN 021-454	Tablet	[redacted]	X		?	7 days	Efficacy and safety of Zanaflex [redacted]
AN021-457	Tablet	[redacted]	X		23	5 weeks	Safety, dose range and efficacy of tizanidine [redacted] Titration up to 12mg per day.
AN021-351	MR	MS SCI	X		600	1 year	Long term safety.
AN021-501	Tablet	CDH		X	200	12 weeks	Safety and efficacy in [redacted] up to 24mg daily.

Study AN021-002 was a multi-center, open-label, long-term study (up to 36 months) to evaluate the safety of tizanidine tablets in patients suffering from spasticity due to MS (n=262).

Study AN021-004 was a multi-center, open-label, long-term study (up to 30 months) to evaluate the safety of tizanidine tablets in patients suffering from spasticity due to SCI (n=82).

Studies AN021-227 and AN021-301 concerned the MR formulation. [redacted]

Study AN021-402 was requested as a phase IV commitment for NDA 20-397, and was reviewed and found acceptable by the division. Study AN021-402 was a multicenter, open-label, uncontrolled trial in outpatients with spasticity due to MS or SCI who were undergoing chronic therapy with tizanidine tablets. The objective of this study was to evaluate the safety and hypotensive effects of single doses of 16 mg tizanidine tablets in patients maintained on stable doses (20-28 mg or 29-36 mg). Thirty nine patients received completed the study. Following a screening visit, patients returned 7-14 days later for a 6-hour test day during which study medication was administered. Vital signs were assessed at regular intervals following study drug administration and at each time point, pulse and blood pressure were measured after the patient had spent at least 5 minutes in the supine position, after 1 minute upright and after 5 minutes upright. Patients completed a visual analog scale at the end of Visit 2 to assess tolerability. Patients returned 4 to 7 days later for follow-up. A single 16 mg dose of tizanidine tablet produced orthostatic hypotension in 41 % of patients, and was most prominent 0 to 4 hours after dosing. There was some indication that patients who had been maintained on higher doses of tizanidine adjusted to the hypotensive effects of the 16 mg dose more readily than patients maintained at lower doses.

Study AN021-450 was an 18-weeks open-label study in stroke, with up to 36mg tizanidine daily.

Study AN021-456 investigated [redacted] patients, with a maximum daily dose of 18mg for 12 weeks.

The next 5 studies are the pharmacokinetic studies used in support of NDA 20-447.

Study AN021-101 compared the single administration of 8 mg tizanidine tablets or capsules with or without food in healthy subjects (n=96). In addition to evaluate bioavailability of tizanidine tablets, this study was designed to assess the impact of somnolence on cognitive function as measured by the Power of Attention and to assess orthostatic hypotension (as measured by a decrease from the supine to standing position of at least 20 mm Hg in systolic or 10 mm Hg in diastolic blood pressure).

This was a 4-way crossover study, single dose for each treatment period. 80 subjects completed the study. Computerized cognitive function tests were performed predose and at 0.75, 1.5, 2.5 and 6.0 hours postdose in each treatment period. The tests were:

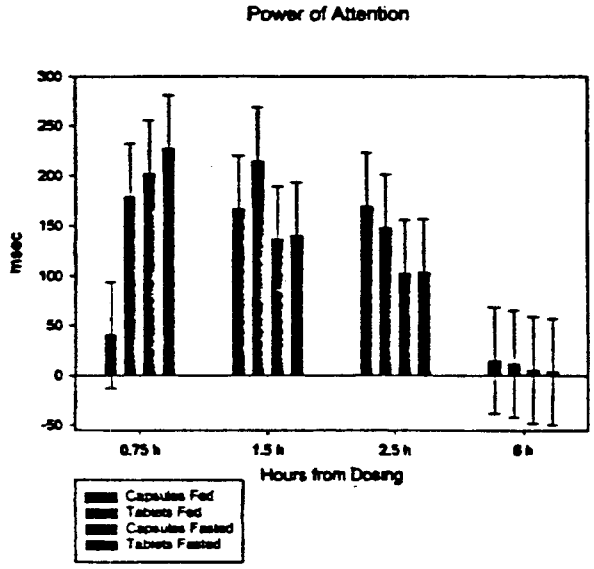
- Simple Reaction Time (SRT- the volunteer was instructed to press the 'yes" response button as quickly as possible every time the word "yes" was presented on the monitor and fifty stimuli were presented with a varying interstimulus interval),
- Digit Vigilance Task (DVT- a target digit was randomly selected and constantly displayed to the right of the monitor screen; a series of digits was then presented in the center of the screen at the rate of 150 per minute and the volunteer was required to press the "yes" button as quickly as possible every time the digit in the series matched the target digit),
- Choice Reaction Time (CRT- either the word "no" or the word "yes" was presented on the monitor and the volunteer was instructed to press the corresponding button as quickly as possible)
- Visual analogue scales of mood and alertness.

The primary outcome variable in this study was Power of Attention, calculated as the sum of the scores of the SRT, CRT and DVT. The sponsor claims that Power of Attention has been widely used and closely reflects the ability to focus attention on everyday tasks. However, the references given by the sponsor concern the Cognitive Drug Research (CDR) integrated computerized test battery, which is more comprehensive than the measures used to calculate the "Power of Attention". It is unclear how the validation of the CDR computerized test applies to the "Power of Attention". For this reason, I consider that outcome measure as exploratory.

The administration of the tizanidine capsule in the fed state resulted in a delay of the onset of impairment in Power of Attention compared with tablets and capsules taken under fasted conditions and the tablets under fed conditions (**Figure 2**). There was no significant impairment from baseline in the Power of Attention score at 0.75 hours with the capsule in the fed state, but performance with all 3 other conditions was highly significantly impaired. At 1.5 hours and 2.5 hours, performance was impaired for all four dosing groups and this effect resolved completely by 6 hours. The capsules taken under fed conditions produced significantly lower impairment compared to tablets under fed conditions at 0.75 hour, but impairment was not different at 1.5 and 2.5 hours. At 1.5 hours there was some tendency for performance following tablets taken under fed conditions to be poorer than that under fasted conditions, but besides that there were no further differences between the dosing groups. The overall cognitive impairment (change in Power of Attention from baseline) produced by each treatment, irrespective of time, was not significantly different between the four treatments. There was no difference in impairment between capsules and tablets under fasted conditions at any time point. The scores of Power of Attention were comparable between all four treatments at 1.5 and 2.5 hours following dosing, but it is interesting to note that capsule under fed condition had the worst score at the 2.5h timepoint, which can be explained by PKs of the capsule, with delayed Tmax compared to the 3 other conditions. Therefore, it is unclear if the capsule

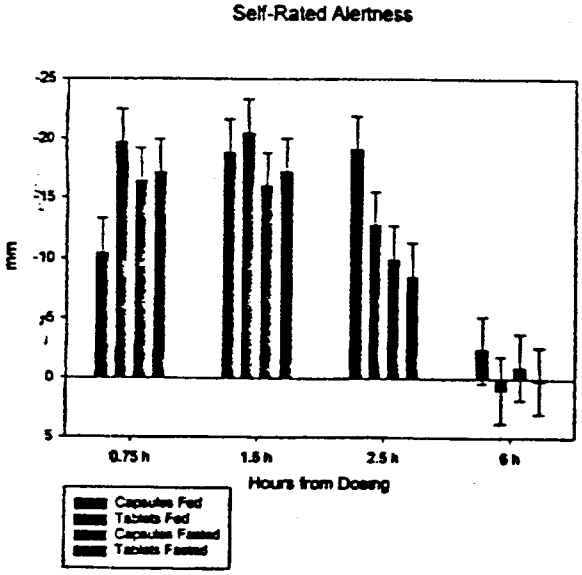
provides any clinical benefit over the tablet – it seems instead to have only delayed side effects – and possibly efficacy –under fed condition.

Figure 2 : Power of attention



The self-rated alertness showed the same pattern of change as for Power of Attention. With the capsule under fed condition, the self-rated alertness was better than the other conditions at 0.75h, and worse at 2.5h (Figure 3).

Figure 3: Self-rated Alertness



The magnitude of the impairments was sufficient to put the subjects at risk of injury if they performed dangerous tasks. The impairments were generally twice as large as impairments which would be produced by a dose of alcohol which makes it illegal to drive in most European countries.

There were 386 adverse events reported by 96% of subjects. The majority of the events were mild in severity and no serious adverse events occurred. Study drug was discontinued for two subjects due to AEs; one due accidental injury (verbatim term "mouth injury") and one due to periodontal infection.

Asthenia and somnolence were the most common treatment-related AEs following all treatments. Mild asthenia reported in 82% of subjects. Somnolence was reported by 61%, mild headache by 24%, mild dizziness by 15%, and mild dry mouth by 14% of subjects. The remaining events were each reported by 5 or fewer subjects (5%); the following were considered drug related: abdominal pain; hypotension; palpitation; diarrhea; nausea; vomiting; dehydration; thirst; myalgia; confusion; euphoria; incoordination; thinking abnormal; laryngismus; and eye pain..

Mean blood pressure followed a similar pattern for all treatments. There was a slight decrease for supine systolic pressure of approximately 10 mm Hg near the 2 hour postdose time point for all treatments. By 6 hours postdose, supine pressures returned to near predose values (Figure 4, Figure 5).

There were 2 subjects with AEs of hypotension documented during the trial. One subject exhibited a supine pressure of 89/45 mm Hg and a standing pressure of 77/47 mm Hg at approximately 3 hours following dosing with tizanidine capsule in the fed state. This episode of hypotension lasted 3 hours. One subject exhibited a supine pressure of 72/36 mm Hg and standing pressure of 55/42 mm Hg approximately 3 hours following dosing with tizanidine capsule in the fed state with tizanidine capsule in the fed state. This episode lasted approximately 5 hours. The Investigator considered both events related to study drug.

Orthostatic hypotension (supine to standing systolic pressure decrease of 20 mm Hg or diastolic decrease of 10 mm Hg) was experienced by 24% to 31% of subjects of the 4 groups, mostly between 1 and 2 hours postdosing. Greater frequency of subjects in the tablet (fasted and fed) and capsule (fasted) treatment experienced orthostatic hypotension at 1 hour compared to capsule fed treatment, which may be due to higher plasma levels of drug observed in these groups at 1 hour relative to the capsule (fed) treatments (Figure 1). Likekewise, an increase in frequency is seen at a later time of 2 hours in capsule (fed) compared to the other three treatments, again possibly due to delayed time for maximum concentration seen in the capsule fed treatment. This is very similar to the pattern of cognitive and somnolence side effects, and again suggests that the capsule in the fed state induces a delay in Tmax – and side effects - , but with a similar magnitude of side effects, so that the clinical benefit is not obvious.

The proportion of subjects with orthostatic hypotension was not significantly different between the 4 groups, based on McNemars test.

Figure 4: Mean blood pressure versus time: Supine

Figure 14.5.1 – Mean Blood Pressure versus Time by Treatment - Supine

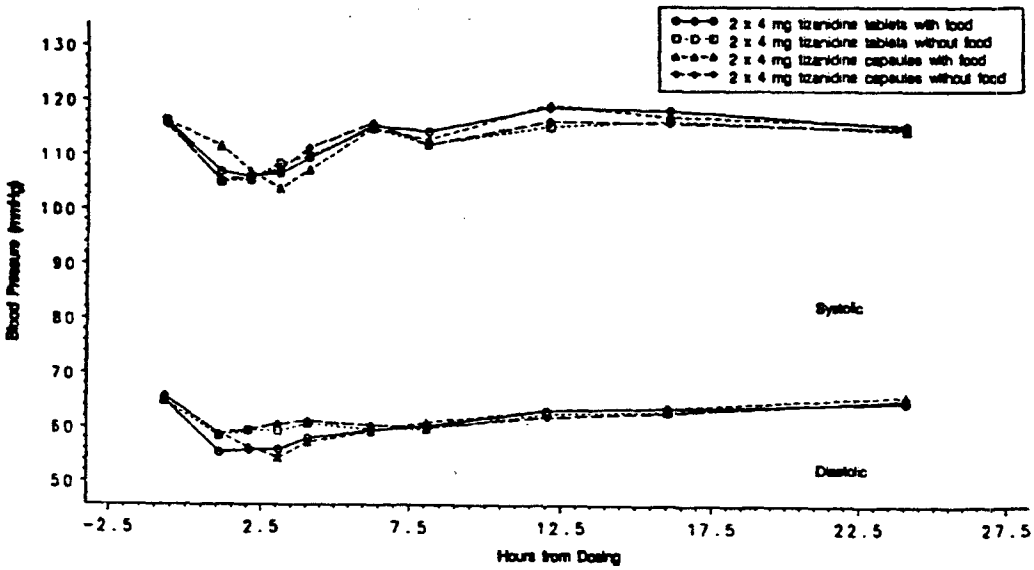
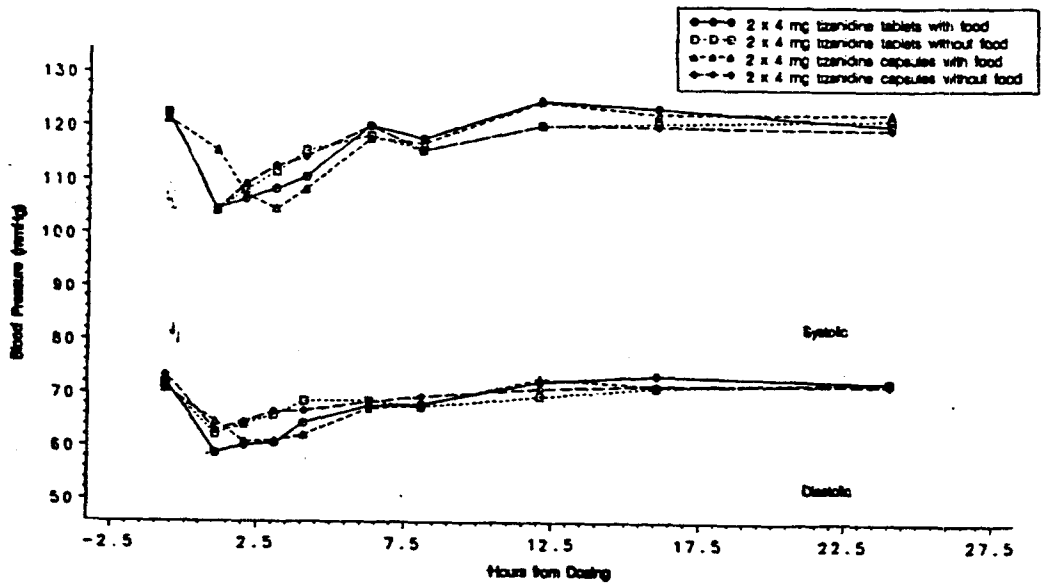


Figure 5: Mean blood pressure versus time: Standing

Figure 14.5.3 – Mean Blood Pressure versus Time by Treatment - Standing



Study 0300003 was a single dose study in healthy subjects to evaluate the bioequivalence of a tizanidine 4 mg capsule formulation relative to the 4 mg tablet. This was an open-label, 2-treatment, 2-period study in 28 subjects.

Study 0400001 was a study in healthy volunteers to assess the effect of food on the bioavailability of tizanidine 4 mg capsules relative to 4 mg tablets. This was an open-labeled, single-dose, 2-treatment, 2-period study in 18 subjects.

Study 0400002 was a single dose, open-label, 2-treatment, crossover trial in 28 subjects with tizanidine 6 mg capsule administered intact versus in a sprinkle form.

Study 0600002 was intended to demonstrate bioequivalence of the 6 mg capsule formulation relative to the tablet (administered as 4 and 2 mg tablets) in 28 healthy subjects.

I. Deaths across post NDA 20-397 studies

Across post-marketing studies, 3 deaths occurred in one single study: AN021-004 (Table 7). Study AN021-004 was a 30-month study evaluating the safety and benefits of long term treatment with Zanaflex capsule. One patient (36 year-old male) was found without respiration or pulse. The patient had a history of coronary artery disease and the coroner's preliminary conclusion was that the patient had died of cardiac causes unrelated to tizanidine tablets. The second patient, a 55 year old male, had a history of coronary artery disease and cardiac failure. A prior cardiac catheterization had measured an ejection fraction of 17%. The patient died as a result of cardiac failure, that the investigator considered being unrelated to tizanidine. The third patient died due to cardiac disease and sepsis, which were considered to be sequelae of a gunshot wound to the chest.

II. Serious Adverse Events across post NDA 20-397 studies

Across all post marketing clinical trials, SAEs were reported for 19 patients (Table 7). There was no SAEs in any of the PK studies (AN021-101, 0300003, 0400001, 0400002, 0600002) used in support for NDA 21-447.

In study AN021-002, 2 SAEs were thought unrelated to tizanidine (urosepsis and concussion). In study AN021-301 (MR), one patient experienced a constellation of symptoms, with hypotension, confusion, dizziness, somnolence and moderate bradycardia. All of these events were considered drug related. However, this occurrence is probably related to the specific PKs of the slow release formulation, and does not clearly apply to the safety of the capsule and tablet formulations. A second patient experienced a severe decubitus ulcer, considered unrelated.

Most SAEs (n=15) occurred in study AN021-450 (18 weeks study in stroke). 14/15 events were considered unrelated to tizanidine. One event of anorexia was considered possibly related to tizanidine.

Table 7: Deaths, SAEs and Adverse dropouts in Zanaflex postmarketing studies

Study	N	Duration	Deaths?	SAEs?	Adverse dropouts?
Studies involving the capsule formulation					
AN021-002	262	36 months	N=0	N=2	20%
AN021-004	82	30 months	N=3	?	24%
AN021-455	30	6 weeks	N=0	N=0	3%
AN021-456	50	12 weeks	N=0	N=0	6%
AN021-402	43	Single dose	N=0	N=0	0%
AN021-450	47	18 weeks	N=0	N=15	?
Studies involving the MR formulation					
AN021-227	28	Single dose	N=0	N=0	18%
AN021-301	37	Single dose	N=0	N=2	0%
Studies involving the capsule formulation					
AN021-101	96	Single dose	N=0	N=0	1%
0300003	28	Single dose	N=0	N=0	0%
0400001	18	Single dose	N=0	N=0	0%
0400002	28	Single dose	N=0	N=0	0%
0600002	28	Single dose	N=0	N=0	0%

III. Adverse Dropouts across post NDA 20-397 studies

The rate of adverse dropouts ranged from 3-24% in multi-dose studies, and 0-1% in single dose studies (Table 7). This is similar to the rate of adverse dropouts in the active treatment arms of the 3 efficacy studies of NDA 20-397. Studies AN021-002 and AN021-004 were long term studies, of total duration respectively of 36 and 30 months, so that the ADO rates of 20 and 24% are not surprisingly higher than the rates observed in the shorter efficacy studies of NDA 20-397. There was only one ADO across the 5 PK studies used in support for NDA 21-447 (anorexia secondary to injury to the mouth). which was). Causes for adverse dropout in study AN021-002, the largest long term safety study (MS population), are summarized in Table 8. These ADOs again are related mostly to the well known side effects of tizanidine: somnolence, asthenia, and hypotension.

Table 8: Adverse Dropouts in study AN021-002

	ADO	N =
AN021-002 (n=262)	Somnolence	16
	Asthenia	11
	Postural hypotension	2
	Myasthenia	3
	Abnormal LFT	2
	Dry mouth	2
	Insomnia	2
	Accidental injury	1
	Anxiety	1
	Ataxia	1
	Carcinoma	1
	Chest pain	1
	Dementia	1
	Dizziness	1
	Flu syndrome	1
	Myocardial infarction	1
	Nausea/tremor	1
	Rhinitis	1
	Sweating/tinnitus	1
	Vasodilatation	1
	Viral hepatitis	1

IV. Adverse Events across post NDA 20-397 studies

Adverse events in long term study AN021-002 (MS), were similar to those observed in short-term efficacy studies of NDA 20-397. In study AN021-002, the most frequently reported adverse events were somnolence, asthenia, and dry mouth. The sponsor did not identify any new safety issue in long term study AN021-004 (SCI), but did not provide much detail about that study.

In studies AN021-227 and AN021-301 (MR formulation), beside the serious hypotensive side effect described above, symptomatic hypotension was the most important factor related to safety and tolerability of tizanidine. Given the difference in pharmacokinetics, these data do not directly apply to the safety of tizanidine tablets or capsules immediate release.

In study AN021-402 (phase IV commitment), the most frequently reported treatment-related AEs were somnolence, dry mouth, and hypotension. 6/8 patients who had treatment-related hypotension were in the 20-28 mg/day group. There were no SAEs and no patient discontinued treatment due to an AE.

In study AN021-450 (18-weeks open-label study in stroke), adverse events were similar to those reported in NDA 20-397. The incidence of somnolence (62%) and asthenia (30%) was similar to that reported in NDA 20-397, but the incidence of dizziness was higher (38% versus 16%), and the incidence of dry mouth lower (21% versus 49%). Hypotension was reported in 17% of patients.

In study AN021-456 ([redacted] ,, AEs reported in more than 10% patients were somnolence, asthenia and dry mouth, again similar to NDA 20-397 database.

In study AN021-101 (a 4-way crossover study, single dose 8mg tizanidine tablets or capsules with or without food), orthostatic hypotension was experienced in 24% to 31% of subjects with the majority of the episodes occurring between 1 and 2 hours post dose. Asthenia and somnolence were the most common treatment-related AEs following all treatments.

In study 0300003 (single dose study in healthy subjects to evaluate the bioequivalence of a tizanidine 4 mg capsule formulation relative to the 4 mg tablet), a total of 36 AEs were reported by 15 (54%) subjects. The majority of the events were mild in severity, with only one event considered moderate in severity.

In study 0400001 (effect of food on the bioavailability of a tizanidine 4 mg capsule relative to the 4 mg tablet), 26 AEs were reported by 12 (67%) subjects. Asthenia was the most common event reported in both treatments. All of the events were mild in severity.

In study 0400002 (single dose, open-label, 2-treatment, crossover trial in 28 subjects with tizanidine 6 mg capsule administered intact versus in a sprinkle form), there were 31 AEs reported by 17 (61%) subjects. Asthenia was the most common event. All events were mild.

In study 0600002 (single dose, open-label, 2-treatment, crossover trial of 6 mg capsule and tablet, administered as 4 and 2 mg tablets in 28 healthy subjects), there were 61 AEs reported by 20 (71%) subjects. Asthenia and dizziness were the most commonly reported. The majority of events were mild in severity with two events considered moderate. One subject dropped his systolic BP approximately 17 mm Hg for both treatments at the 1-hour postdate time point, returning to predose values at the 6-hour time point.

V. Laboratory Findings, ECG across post NDA 20-397 studies

In all 5 pharmacokinetic studies in support of this NDA, there were no treatment-related trends regarding clinical laboratory tests, ECGs, or physical examinations. This is not unexpected since these were studies with single doses of tizanidine, and dosage did not

exceed 8 mg per administration. The experience obtained with tizanidine tablet in NDA 20-397 is largely relevant to cover this information. Also, the sponsor did not look at QT changes at Cmax in either NDA.

VI. Vital Signs across post NDA 20-397 studies

The potential for hypotensive side effects after administration of tizanidine were confirmed in several studies. This is a well known side effect; object of a warning in the current labeling for doses ≥2 mg.

Study ANO21-402 (see above for further details) evaluated the safety and hypotensive effects of single doses of 16 mg tizanidine HCl tablets in patients maintained on stable doses of tizanidine HCl tablets (20-28 mg or 29-36 mg) in 39 patients. A single 16 mg dose of tizanidine HCl tablet produced orthostatic hypotension in 41 % of patients, and was most prominent 0 to 4 hours after dosing. There was some indication that patients who had been maintained on higher doses of tizanidine tablets adjusted to the hypotensive effects of the 16 mg dose of tizanidine tablets more readily than patients maintained at lower doses.

Study AN021-101 assessed orthostatic hypotension as measured by a decrease from the supine to standing position of at least 20 mm Hg in systolic or 10 mm Hg in diastolic blood pressure after administration of tizanidine 8 mg capsule or tablet in 80 subjects. Orthostatic hypotension was experienced after administration of the capsule or tablet in the fed or fasted state in 24% to 31% of subjects, with the majority of the episodes occurring between 1 and 2 hours post dose.

Special Populations

Pediatric use

See C. Evaluation of Pediatric Program.

Drug Interactions

In vitro studies of cytochrome P450 isoenzymes using human liver microsomes in NDA 20-397 indicated that neither tizanidine nor the major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes. The following conclusions were drawn with respect to tizanidine drug interactions:

- Acetaminophen: Tizanidine delayed acetaminophen Tmax by 16 minutes. Acetaminophen did not affect tizanidine PK.
- Alcohol: Alcohol increased tizanidine AUC by approximately 20%, and increased tizanidine Cmax by approximately 15%. This was associated with an increase in tizanidine side effects.
- Oral Contraceptives: No specific PK study was conducted to investigate interaction between oral contraceptives and tizanidine, but retrospective analysis of population PK data following single and multiple dose administration of 4 mg tizanidine showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine than women not on oral contraceptives.

Drug Interaction Cases from Postmarket Safety Surveillance

The sponsor examined postmarket safety surveillance data for cases of tizanidine drug interaction reported post NDA 20-397 approval. There were 16 cases involving potential tizanidine drug interaction (Table 9). All AEs resolved, often without therapy.

Table 9: Drug interaction cases

Drug	Reported term	N
Warfarin	Drug interaction	1
Baclofen	Hypotension	1
	Bradycardia	1
	Drug interaction	1
4-aminopyridine	Increased spasticity	1
	Dry heaves	1
	Nausea	1
	Drug interaction	1
Ticlopidine	Drug interaction	1
	Ecchymosis	1
Interferon beta-1A	Thrombocytopenia	1
	Chest pain	1
Ciprofloxacin	Drug interaction	1
	Sedation	1
	Malaise	1
Cisapride	Prolonged QT	1
	Bradycardia	1
	CHF worsening	1
Vioxx	Drug interaction	8
	Hallucinations	4
	Dizziness	2
	Nausea	2
	Bradycardia	2
	Decrease in muscle tone	1
	Pale	1
	Insomnia	1
	Lower extremity edema	1
	Asthenia	1
	Intoxicated feeling	1
	Tachycardia	1
	Hypotension	1
	Psychosis	1
	Swallowing difficulties	1
	Marked sedation	1
	Nightmares	1
Xanax	Drug interaction	1
	Hallucinations	1
	Memory loss	1

There was no clear trend for the reported interactions for most drugs, except for Vioxx. There were 23 events reported for 8 cases involving a potential tizanidine drug interaction with Vioxx (rofecoxib). 12/23 event terms involved the CNS: hallucinations, psychosis, abnormal dreams, somnolence, insomnia, dizziness, stupor, and hypotonia. 6/23 events involved the cardiovascular system: hypotension, bradycardia, tachycardia,