CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-397/S-004

Name:	Zanaflex Tablets (tizanidine hydrochloride)
Sponsor:	Elan Pharmaceuticals
Approval Date:	February 04, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

APPROVAL LETTER

NDA 20-397/S-004

FEB - 4 2000

Elan Pharmaceuticals
Attn: Ms. Louise Johnson
800 Gateway Blvd.
South San Francisco, CA 94080

Dear Ms. Johnson:

Please refer to your supplemental new drug application dated February 24, 1999, received February 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zanaflex (tizanidine hydrochloride) tablets.

We acknowledge receipt of your submissions dated October 4, 1999, December 1, 1999, February 1, 2000 and February 2, 2000. Your submission of October 4, 1999 constituted a complete response to our June 23, 1999 action letter.

Finally, we acknowledge receipt of your Postmarketing Periodic Report submitted March 27, 1998.

This supplemental new drug application provides for the addition of the 2 mg tablet.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revision listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

> The recommended storage conditions should read " Store at 25° C (77° F); excursions permitted to 15° -30° C (59° -86° F) [see USP Controlled Room Temperature]. Dispense in containers with child resistant closure."

Please adopt the following dissolution method and specification for both Zanaflex 2 mg and 4 mg tablets:

Apparatus:	USP Apparatus I (basket) at 100 rpm
Medium:	500 ml 0.1 N HCL at 37° C $\pm$ 0.5° C
Specification:	Not less than [ ]% in 15 minutes

We note that the draft labeling submitted February 1, 2000 includes changes submitted in your Postmarketing Periodic Report dated March 27, 1998. We have reviewed these changes and find them acceptable. In the future, however, labeling changes of this sort should be submitted under 314.70 (b) or (c).

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted February 1, 2000 and February 2, 2000; immediate container and carton labels submitted February 24, 1999). These revisions are terms of the NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-397/S-004." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

2/4/00

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-397
HFD-120/Div. Files
HFD-120/L.Chen 2/4/00
HFD-120/Guzewska/Christodoulou 2/3/00
HFD-120/Katz/Levin RL 2/3/00

HFD-860/Baweja/Zhao RB 2/3/2000; HZ 2/3/00

HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - ONLY for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: lyc/February 2, 2000

final: 2/4/00

filename: C: wpfiles/tizan.nda/s004ap.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

NOT APPROVABLE LETTER

NDA 20-397/S-004

JUN 23 1999

Athena Neurosciences, Inc.
Attn: Ms. Louise Johnson
800 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Johnson:

Please refer to your supplemental new drug application dated February 24, 1999, received February 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zanaflex (tizanidine) 2 mg tablets.

Additionally, we acknowledge receipt of your submission dated March 31, 1999. Finally, we refer to a telephone conversation between Ms. Octavia Norris of your firm and Dr. Mona Zarifa of this division held on June 14, 1999.

This supplement proposes the addition of a 2 mg tablet dosage strength.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Since the excipients in 2 mg and 4 mg formulations are the same on a percentage (w/w) basis, a dissolution profile comparison can be used to show the similarity of the two formulation strengths. However, using the dissolution data for Zanaflex 2 mg tablets, Lot C80002B and 4 mg tablets, Lot D91004, which have multiple time points (5, 10, 15, 20, and 30 min), the calculated f2 metric value is 24. This f2 metric value is below the similarity criteria of 50-100, which suggests that the dissolution profile of the 2 mg tablets is different from that of the 4 mg tablets.

2. You may choose to provide dissolution data to show both the 2 mg and 4 mg Zanaflex tablets dissolve 85% or more of the label amount in $\leq$15 min in the three recommended dissolution media: (1) acidic media, such as 0.1 N HCL or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

3. Failing to show comparability of the two strengths on the basis of dissolution as outlined above, you may use an in vivo bioequivalence assessment to support the addition of the 2 mg tablet strength. You can make the bioequivalence assessment based on the data obtained from the clinical study (Study DS-0008). From the plasma drug concentration-time data, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max},, K_{el}, and $t_{½}$ should be estimated. Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence and treatment effects. The 90% confidence intervals for the estimates of the difference between the

test and reference least squares means for the pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) should be calculated, using the two one-sided t-test procedure.

4. If the clinical study (Study DS0008) fails to show bioequivalence between the 2 mg and 4 mg formulation strengths, a new in vivo bioequivalence study is suggested for supporting the addition of the 2 mg tablet strength.

5. In NDA 20-397, the dissolution specification was set for Zanaflex 4 mg tablets as NLT [redacted]% in 15 minutes. We request you to clarify why a different specification was used for 2 mg tablets (NLT [redacted]% at 30 minutes).

As discussed in the June 14, 1999 teleconference, your supplemental application refers to the incorrect DMF for manufacturing information on the proposed 2 mg tablets. Please provide the correct DMF reference, or an amendment containing the missing information.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, contact Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

6/23/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CDER User

cc:
Archival NDA 20-397
HFD-120/Div. Files
HFD-120/L.Chen
HFD-120/Levin/Katz e.l 6/22/99
HFD-120/Zarifa/Guzewska MZ 6/24/99 MEL for MG 6/22/99

HFD-860/Zhao/Baweja HZ 6/22/99; RB 6/22/99.

HFD-95/DDMS
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: lyc/June 21, 1999
Initialed by:
final: 6/24/99 LYC
filename: c:\wp6\files\hzan.nda\s004NA.doc

NOT APPROVABLE (NA)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

FINAL PRINTED LABELING

Zanaflex Capsules™
(tizanidine hydrochloride)

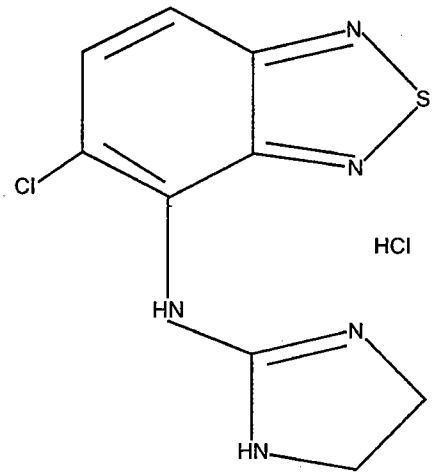
Zanaflex® Tablets
(tizanidine hydrochloride)

PHARMACOKINETIC DIFFERENCES BETWEEN ZANAFLEX CAPSULES™ AND ZANAFLEX® TABLETS:

ZANAFLEX CAPSULES™ ARE NOT BIOEQUIVALENT TO ZANAFLEX® TABLETS IN THE FED STATE. THE PRESCRIBER SHOULD BE THOROUGHLY FAMILIAR WITH THE COMPLEX EFFECTS OF FOOD ON TIZANIDINE PHARMACOKINETICS (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

DESCRIPTION

Zanaflex® (tizanidine hydrochloride) is a centrally acting α_2-adrenergic agonist. Tizanidine HCl (tizanidine) is a white to off-white, fine crystalline powder, which is odorless or with a faint characteristic odor. Tizanidine is slightly soluble in water and methanol; solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride. Tizanidine's molecular formula is $C_9H_8ClN_5S$-HCl, its molecular weight is 290.2 and its structural formula is:



Zanaflex Capsules™ are supplied as 2, 4, and 6 mg capsules and Zanaflex® tablets are supplied as 2 and 4 mg tablets for oral administration. Zanaflex Capsules™ are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base, 4.58 mg equivalent to 4 mg tizanidine base, and 6.87 mg equivalent to 6 mg tizanidine base), and the inactive ingredients, hydroxypropyl methyl cellulose, silicon dioxide, sugar spheres, titanium dioxide, gelatin, and colorants.

Zanaflex® tablets are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base and 4.58 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tizanidine is an agonist at α_2-adrenergic receptor sites 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.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Absorption and Distribution

Following oral administration, tizanidine is essentially completely absorbed. The absolute oral bioavailability of tizanidine is approximately 40% (CV = 24%), due to extensive first-pass hepatic metabolism. Tizanidine is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/kg (CV = 21%) following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins.

Pharmacokinetics, Metabolism and Excretion

Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. Tizanidine has a half-life of approximately 2.5 hours (CV=33%). Approximately 95% of an administered dose is metabolized. The primary cytochrome P450 isoenzyme involved in tizanidine metabolism is CYP1A2. Tizanidine metabolites are not known to be active; their half-lives range from 20 to 40 hours.

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.

Pharmacokinetic differences between Zanaflex Capsules™ and Zanaflex® Tablets

Zanaflex Capsules™ and Zanaflex® tablets are bioequivalent to each other under fasted conditions, but not under fed conditions.

A single dose of either two 4 mg tablets or two 4 mg capsules was administered under fed and fasting conditions in an open label, four period, randomized

crossover study in 96 human volunteers, of whom 81 were eligible for the statistical analysis.

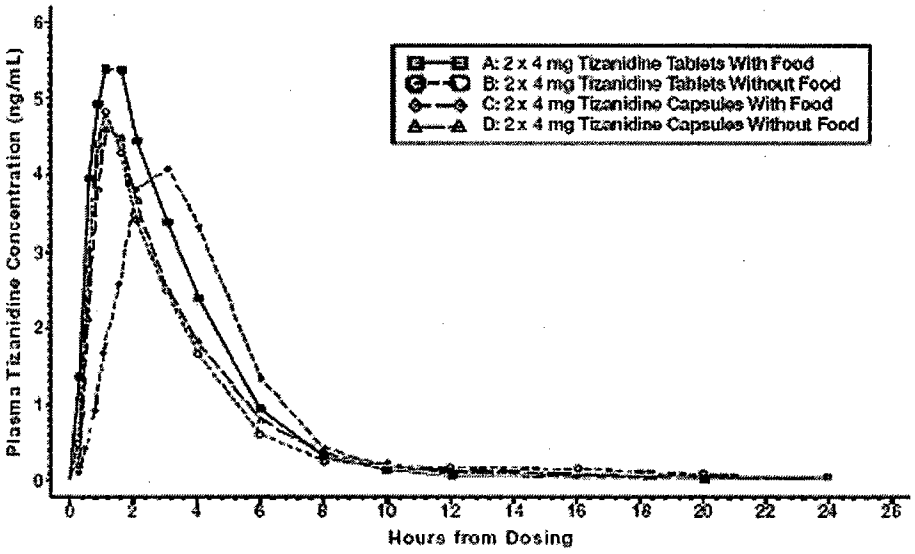
Following oral administration of either the tablet or capsule (in the fasted state), tizanidine has peak plasma concentrations occurring 1.0 hours after dosing with a half-life of approximately 2 hours.

When two 4 mg tablets are administered with food the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

In contrast, when two 4 mg capsules are administered with food the mean maximal plasma concentration is decreased by 20%, the median time to peak plasma concentration is increased by 2 hours to 3 hours. Consequently, the mean Cmax for the capsule when administered with food is approximately 2/3's the Cmax for the tablet when administered with food.

Food also increases the extent of absorption for both the tablets and capsules. The increase with the tablet (~30%) is significantly greater than with the capsule (~10%). Consequently when each is administered with food, the amount absorbed from the capsule is about 80% of the amount absorbed from the tablet (See Figure 1). Administration of the capsule contents sprinkled on applesauce is not bioequivalent to administration of an intact capsule under fasting conditions. Administration of the capsule contents on applesauce results in a 15% - 20% increase in Cmax and AUC of tizanidine compared to administration of an intact capsule while fasting, and a 15 minute decrease in the median lag time and time to peak concentration.

Figure 1: Mean Tizanidine Concentration vs. Time Profiles For Zanaflex Tablets and Capsules (2 × 4 mg) Under Fasted and Fed Conditions



SPECIAL POPULATIONS

Age Effects

No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine showed that younger subjects cleared the drug four times faster than the elderly subjects. Tizanidine has not been evaluated in children (see PRECAUTIONS).

Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of tizanidine has not been evaluated. Because tizanidine is extensively metabolized in the liver, hepatic impairment would be expected to have significant effects on pharmacokinetics of tizanidine. Tizanidine should ordinarily be avoided or used with extreme caution in this patient population (see WARNINGS).

Renal Impairment

Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance < 25 mL/min) compared to healthy elderly

subjects; this would be expected to lead to a longer duration of clinical effect. Tizanidine should be used with caution in renally impaired patients (see PRECAUTIONS).

Gender Effects

No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis of pharmacokinetic data, however, following single and multiple dose administration of 4 mg tizanidine showed that gender had no effect on the pharmacokinetics of tizanidine.

Race Effects

Pharmacokinetic differences due to race have not been studied.

DRUG INTERACTIONS

Fluvoxamine

The effect of fluvoxamine on the pharmacokinetics of tizanidine was studied in 10 healthy subjects. The Cmax, AUC, and half-life of tizanidine increased by 12-fold, 33-fold, and 3-fold, respectively. These changes resulted in significant decreases in blood pressure, increased drowsiness, and psychomotor impairment. (See CONTRAINDICATIONS and WARNINGS).

Ciprofloxacin

The effect of ciprofloxacin on the pharmacokinetics of tizanidine was studied in 10 healthy subjects. The Cmax and AUC of tizanidine increased by 7-fold and 10-fold, respectively. These changes resulted in significant decreases in blood pressure, increased drowsiness, and psychomotor impairment. (See CONTRAINDICATIONS and WARNINGS).

CYP1A2 Inhibitors

The interaction between tizanidine and either fluvoxamine or ciprofloxacin is most likely due to inhibition of CYP1A2 by fluvoxamine or ciprofloxacin. Although there have been no clinical studies evaluating the effects of other CYP1A2 inhibitors on tizanidine, other CYP1A2 inhibitors, such as zileuton, other fluoroquinolones,

antiarrythmics (amiodarone, mexiletine, propafenone and verapamil), cimetidine, famotidine oral contraceptives, acyclovir and ticlopidine, may also lead to substantial increases in tizanidine blood concentrations. (See WARNINGS)

Oral Contraceptives

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine compared to women not on oral contraceptives (see PRECAUTIONS).

CLINICAL STUDIES

Tizanidine's capacity to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal cord injury.

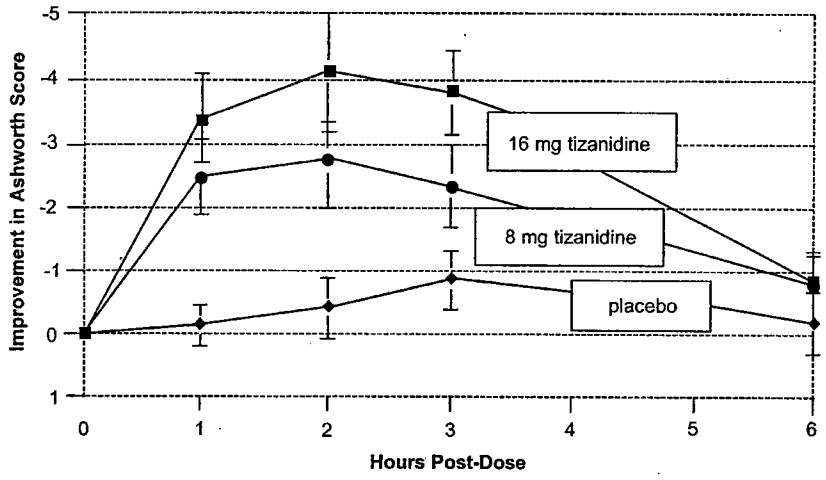
In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo. Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of tizanidine.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Zanaflex compared to placebo was

detected at 1, 2 and 3 hours after treatment. Figure 2 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, 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. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

Figure 2: Single Dose Study—Mean Change in Muscle Tone from Baseline as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



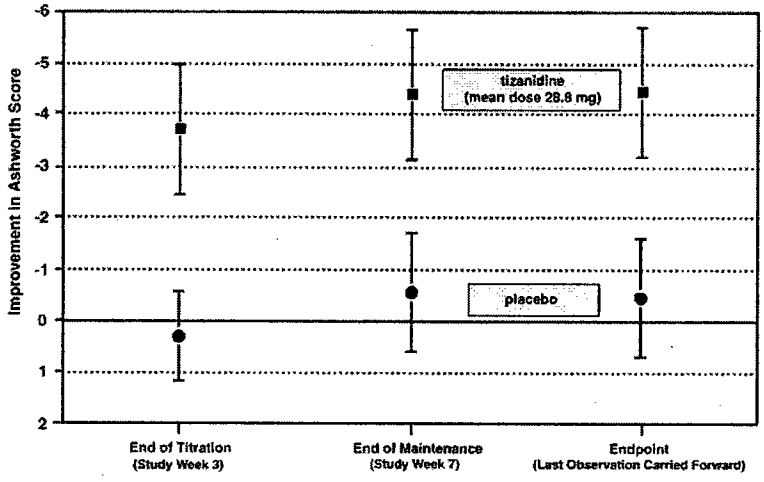
In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or tizanidine. Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and 16 mg given at night). Patients were then maintained on their maximally tolerated

dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose. The number of daytime spasms was recorded daily by patients.

At endpoint (the protocol-specified time of outcome assessment), there was a statistically significant reduction in muscle tone and frequency of spasms in the tizanidine treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of tizanidine treated patients on measures of activities of daily living. Figure 3 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale.

Figure 3: Multiple Dose Study—Mean Change in Muscle Tone 0.5–2.5 Hours After Dosing as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



INDICATIONS AND USAGE

Tizanidine is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important (see DOSING AND ADMINISTRATION).

CONTRAINDICATIONS

Concomitant use of tizanidine with fluvoxamine or with ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine including increased AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant administration of either fluvoxamine or ciprofloxacin. This pharmacokinetic interaction can result in potentially serious adverse events (See WARNINGS and CLINICAL PHARMACOLOGY: Drug Interactions).

Zanaflex is contraindicated in patients with known hypersensitivity to Zanaflex or its ingredients.

WARNINGS

LIMITED DATA BASE FOR CHRONIC USE OF SINGLE DOSES ABOVE 8 MG AND MULTIPLE DOSES ABOVE 24 MG PER DAY

Clinical experience with long-term use of tizanidine at doses of 8 to 16 mg single doses or total daily doses of 24 to 36 mg (see Dosage and Administration) is limited. In safety studies, approximately 75 patients have been exposed to individual doses of 12 mg or more for at least one year or more and approximately 80 patients have been exposed to total daily doses of 30 to 36 mg/day for at least one year or more. There is essentially no long-term experience with single, daytime doses of 16 mg. Because long-term clinical study experience at high doses is limited, only those adverse events with a relatively high incidence are likely to have been identified (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS).

HYPOTENSION

Tizanidine is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two-thirds of patients treated with 8 mg of tizanidine had 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 was 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 ≥ 2 mg.

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to fixed upright position may be at increased risk for hypotension and orthostatic effects.

Caution is advised when tizanidine is to be used in patients receiving concurrent antihypertensive therapy and should not be used with other α_2-adrenergic agonists.

Clinically significant hypotension (decreases in both systolic and diastolic pressure) has been reported with concomitant administration of either fluvoxamine or ciprofloxacin and single doses of 4 mg of tizanidine. Therefore, concomitant use of tizanidine with fluvoxamine or with ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Drug Interactions).

RISK OF LIVER INJURY

Tizanidine occasionally causes liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with tizanidine had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated) compared to 0.4% in the control patients. Most cases resolved rapidly upon drug withdrawal with no reported residual problems. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. Based upon postmarketing experience, death associated with liver failure has been a rare occurrence reported in patients treated with tizanidine.

Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug

should ordinarily be avoided or used with extreme caution in patients with impaired hepatic function.

SEDATION

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of tizanidine reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to < 1% in the placebo treated patients. Sedation may interfere with everyday activity.

The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. 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.

In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

HALLUCINOSIS/PSYCHOTIC-LIKE SYMPTOMS

Tizanidine use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. These 5 cases occurred within the first 6 weeks. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient among these 5 continued to have problems for at least 2 weeks following discontinuation of tizanidine.

USE IN PATIENTS WITH HEPATIC IMPAIRMENT

The influence of hepatic impairment on the pharmacokinetics of tizanidine has not been evaluated. Because tizanidine is extensively metabolized in the liver, hepatic

impairment would be expected to have significant effects on the pharmacokinetics of tizanidine. Tizanidine should ordinarily be avoided or used with extreme caution in patients with hepatic impairment (See also RISK OF LIVER INJURY).

POTENTIAL INTERACTION WITH FLUVOXAMINE OR CIPROFLOXACIN

In a pharmacokinetic study, tizanidine serum concentration was significantly increased (Cmax 12-fold, AUC 33-fold) when the drug was given concomitantly with fluvoxamine. Potentiated hypotensive and sedative effects were observed. Fluvoxamine and tizanidine should not be used together. (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Drug Interactions).

In a pharmacokinetic study, tizanidine serum concentration was significantly increased (Cmax 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin. Potentiated hypotensive and sedative effects were observed. Ciprofloxacin and tizanidine should not be used together (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Drug Interactions).

POSSIBLE INTERACTION WITH OTHER CYP1A2 INHIBITORS

Because of potential drug interactions, concomitant use of tizanidine with other CYP1A2 inhibitors, such as zileuton, other fluoroquinolones, antiarrythmics (amiodarone, mexiletine, propafenone, and verapamil), cimetidine, famotidine, oral contraceptives, acyclovir and ticlopidine (see CLINICAL PHARMACOLOGY: Drug Interactions) should ordinarily be avoided. If their use is clinically necessary, they should be used with caution.

PRECAUTIONS

CARDIOVASCULAR

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m^2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

OPHTHALMIC

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m^2 basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

USE IN RENALLY IMPAIRED PATIENTS

Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance < 25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

Because drug interaction studies of tizanidine with oral contraceptives have shown that concomitant use may reduce the clearance of tizanidine by as much as 50%, concomitant use of tizanidine with oral contraceptives should ordinarily be avoided (see CLINICAL PHARMACOLOGY: Drug Interactions). However, if concomitant use is clinically necessary, the starting dose and subsequent titration rate of tizanidine should be reduced.

DISCONTINUING THERAPY

If therapy needs to be discontinued, particularly in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

INFORMATION FOR PATIENTS

Patients should be advised of the limited clinical experience with tizanidine both in regard to duration of use and the higher doses required to reduce muscle tone (see WARNINGS).

Because of the possibility of tizanidine lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see WARNINGS).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (see WARNINGS). Patients should also be instructed that the sedation may be additive when tizanidine is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (e.g., alcohol) that act as CNS depressants.

Patients should be advised of the change in the absorption profile of tizanidine if taken with food and the potential changes in efficacy and adverse effect profiles that may result (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Patients should be advised not to stop tizanidine suddenly as rebound hypertension and tachycardia may occur (see PRECAUTIONS: Discontinuing Therapy).

Tizanidine should be used with caution where spasticity is utilized to sustain posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

Because of the potential for the increased risk of serious adverse reactions including severe lowering of blood pressure and sedation when tizanidine and either fluvoxamine or ciprofloxacin are used together, tizanidine should not be used with either fluvoxamine or ciprofloxacin. Because of the potential for interaction with other CYP1A2 inhibitors, patients should be instructed to inform their physicians and pharmacists when any medication is added or removed from their regimen.

DRUG INTERACTIONS

In vitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither tizanidine nor the major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes.

Fluvoxamine

The effect of fluvoxamine on the pharmacokinetics of a single 4 mg dose of tizanidine was studied in 10 healthy subjects. The Cmax, AUC, and half-life of tizanidine increased by 12-fold, 33-fold, and 3-fold, respectively. These changes resulted in significantly decreased blood pressure, increased drowsiness, and increased psychomotor impairment. (See CONTRAINDICATIONS and WARNINGS).

Ciprofloxacin

The effect of ciprofloxacin on the pharmacokinetics of a single 4 mg dose of tizanidine was studied in 10 healthy subjects. The Cmax and AUC of tizanidine increased by 7-fold and 10-fold, respectively. These changes resulted in significantly decreased blood pressure, increased drowsiness, and increased psychomotor impairment. (See CONTRAINDICATIONS and WARNINGS).

CYP1A2 inhibitors

The interaction between tizanidine and either fluvoxamine or ciprofloxacin is most likely due to inhibition of CYP1A2 by fluvoxamine or ciprofloxacin. Although there have been no clinical studies evaluating the effects of other CYP1A2 inhibitors on tizanidine, other CYP1A2 inhibitors, including zileuton, other fluroquinolones, antiarrythmics (amiodarone, mexiletine, propafenone, and verapamil), cimetidine and famotidine, oral contraceptives, acyclovir, and ticlopidine may also lead to substantial increases in tizanidine blood concentrations. Concomitant use of tizanidine with CYP1A2 inhibitors should ordinarily be avoided. If their use is clinically necessary, they should be used with caution (see WARNINGS).

Acetaminophen

Tizanidine delayed the T_{max} of acetaminophen by 16 minutes. Acetaminophen did not affect the pharmacokinetics of tizanidine.

Alcohol

Alcohol increased the AUC of tizanidine by approximately 20%, while also increasing its C_{max} by approximately 15%. This was associated with an increase in

side effects of tizanidine. The CNS depressant effects of tizanidine and alcohol are additive.

Oral Contraceptives

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine, but retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine that women not on oral contraceptives.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No evidence for carcinogenicity was seen in two dietary studies in rodents. Tizanidine was administered to mice for 78 weeks at doses up to 16 mg/kg, which is equivalent to 2 times the maximum recommended human dose on a mg/m^2 basis. Tizanidine was also administered to rats for 104 weeks at doses up to 9 mg/kg, which is equivalent to 2.5 times the maximum recommended human dose on a mg/m^2 basis. There was no statistically significant increase in tumors in either species.

Tizanidine was not mutagenic or clastogenic in the following *in vitro* assays: the bacterial Ames test and the mammalian gene mutation test and chromosomal aberration test in Chinese hamster cells. It was also negative in the following *in vivo* assays: the bone marrow micronucleus test in mice, the bone marrow micronucleus and cytogenicity test in Chinese hamsters, the dominant lethal mutagenicity test in mice, and the unscheduled DNA synthesis (UDS) test in mice.

Tizanidine did not affect fertility in male rats at doses of 10 mg/kg, approximately 2.7 times the maximum recommended human dose on a mg/m^2 basis, and in females at doses of 3 mg/kg, approximately equal to the maximum recommended human dose on a mg/m^2 basis; fertility was reduced in males receiving 30 mg/kg (8 times the maximum recommended human dose on a mg/m^2 basis) and in females receiving 10 mg/kg (2.7 times the maximum recommended human dose on a mg/m^2 basis).

At these doses, maternal behavioral effects and clinical signs were observed including marked sedation, weight loss, and ataxia.

PREGNANCY

Pregnancy Category C

Reproduction studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m^2 basis, and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m^2 basis, did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m^2 basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Post-implantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m^2 basis. Tizanidine has not been studied in pregnant women. Tizanidine should be given to pregnant women only if clearly needed.

LABOR AND DELIVERY

The effect of tizanidine on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether tizanidine is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.

GERIATRIC USE

Tizanidine should be used with caution in elderly patients because clearance is decreased four-fold.

PEDIATRIC USE

There are no adequate and well-controlled studies to document the safety and efficacy of tizanidine in children.

ADVERSE REACTIONS

In multiple dose, placebo-controlled clinical studies, 264 patients were treated with tizanidine and 261 with placebo. Adverse events, including severe adverse events, were more frequently reported with tizanidine than with placebo.

COMMON ADVERSE EVENTS LEADING TO DISCONTINUATION

Forty-five of 264 (17%) patients receiving tizanidine and 13 of 261 (5%) of patients receiving placebo in three multiple dose, placebo-controlled clinical studies, discontinued treatment for adverse events. When patients withdrew from the study, they frequently had more than one reason for discontinuing. The adverse events most frequently leading to withdrawal of tizanidine treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%), and dizziness (2%).

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE

In multiple dose, placebo-controlled clinical studies involving 264 patients with spasticity, the most frequent adverse effects were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three-quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

The events cited reflect experience gained under closely monitored conditions of clinical studies in a highly selected patient population. In actual clinical practice or in other clinical studies, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 1 lists treatment emergent signs and symptoms that were reported in greater than 2% of patients in three multiple dose, placebo-controlled studies who received tizanidine where the frequency in the tizanidine group was at least as common as in the placebo group. These events are not necessarily related to tizanidine treatment.

For comparison purposes, the corresponding frequency of the event (per 100 patients) among placebo treated patients is also provided.

Table 1: Multiple Dose, Placebo-Controlled Studies—Frequent (> 2%) Adverse Events Reported for Which Tizanidine Tablets Incidence is Greater than Placebo

Event	Placebo N = 261 %	Tizanidine Tablet N = 264 %
Dry Mouth	10	49
Somnolence	10	48
Asthenia*	16	41
Dizziness	4	16
UTI	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 symptom	2	3
SGPT/ALT increased	<1	3
Dyskinesia	0	3
Nervousness	<1	3
Pharyngitis	1	3
Rhinitis	2	3

* (weakness, fatigue, and/or tiredness)

In the single dose, placebo-controlled study involving 142 patients with spasticity, the patients were specifically asked if they had experienced any of the four most common adverse events: dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness) and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of these adverse effects is summarized in Table 2. Other events were, in general, reported at a rate of 2% or less.

Table 2: Single Dose, Placebo-Controlled Study—Common Adverse Events Reported

Event	Placebo N = 48 %	Tizanidine Tablet, 8 mg, N = 45 %	Tizanidine Tablet, 16 mg, N = 49 %
Somnolence	31	78	92
Dry mouth	35	76	88
Asthenia *	40	67	78
Dizziness	4	22	45
Hypotension	0	16	33
Bradycardia	0	2	10

* (weakness, fatigue and/or tiredness)

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

Tizanidine was administered to 1385 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 1385 patients exposed to tizanidine who experienced an event of the type cited on at least one occasion while receiving tizanidine. All reported events are included except those already listed in Table 1. If the COSTART term for an event was so general as to be uninformative, it was replaced by a more informative term. It is important to emphasize that, although the events reported occurred during treatment with tizanidine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare adverse events are those occurring in fewer than 1/1000 patients.

BODY AS A WHOLE

Frequent: Fever

Infrequent: Allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulites, death, overdose

Rare: Carcinoma, congenital anomaly, suicide attempt

CARDIOVASCULAR SYSTEM

Infrequent: Vasodilatation, postural hypotension, syncope, migraine, arrhythmia

Rare: Angina pectoris, coronary artery disorder, heart failure, myocardial infarct, phlebitis, pulmonary embolus, ventricular extrasystoles, ventricular tachycardia

DIGESTIVE SYSTEM

Frequent: Abdomen pain, diarrhea, dyspepsia

Infrequent: Dysphagia, cholelithiasis, fecal impaction, flatulence, gastrointestinal hemorrhage, hepatitis, melena,

Rare: Gastroenteritis, hematemesis, hepatoma, intestinal obstruction, liver damage

HEMIC AND LYMPHATIC SYSTEM

Infrequent: Ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis

Rare: Petechia, purpura, thrombocythemia, thrombocytopenia

METABOLIC AND NUTRITIONAL SYSTEM

Infrequent: Edema, hypothyroidism, weight loss

Rare: Adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis

MUSCULOSKELETAL SYSTEM

Frequent: Myasthenia, back pain

Infrequent: Pathological fracture, arthralgia, arthritis, bursitis

NERVOUS SYSTEM

Frequent: Depression, anxiety, paresthesia

Infrequent: Tremor, emotional lability, convulsion, paralysis, thinking abnormal, vertigo, abnormal dreams, agitation, depersonalization, euphoria, migraine, stupor, dysautonomia, neuralgia

Rare: Dementia, hemiplegia, neuropathy

RESPIRATORY SYSTEM

Infrequent: Sinusitis, pneumonia, bronchitis

Rare: Asthma

SKIN AND APPENDAGES

Frequent: Rash, sweating, skin ulcer

Infrequent: Pruritus, dry skin, acne, alopecia, urticaria

Rare: Exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma

SPECIAL SENSES

Infrequent: Ear pain, tinnitus, deafness, glaucoma, conjunctivitis, eye pain, optic neuritis, otitis media, retinal hemorrhage, visual field defect

Rare: Iritis, keratitis, optic atrophy

UROGENITAL SYSTEM

Infrequent: Urinary urgency, cystitis, menorrhagia, pyelonephritis, urinary retention, kidney calculus, uterine fibroids enlarged, vaginal moniliasis, vaginitis

Rare: Albuminuria, glycosuria, hematuria, metrorrhagia

DRUG ABUSE AND DEPENDENCE

Abuse potential was not evaluated in human studies. Rats were able to distinguish tizanidine from saline in a standard discrimination paradigm, after training, but failed to generalize the effects of morphine, cocaine, diazepam, or phenobarbital to tizanidine. Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m^2 basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behavior toward the observer) were not reversed by naloxone administration.

Tizanidine is closely related to clonidine, which is often abused in combination with narcotics and is known to cause symptoms of rebound upon abrupt withdrawal. Three cases of rebound symptoms on sudden withdrawal of tizanidine have been reported. The case reports suggest that these patients were also misusing narcotics. Withdrawal symptoms included hypertension, tachycardia, hypertonia, tremor, and anxiety. As with clonidine, withdrawal is expected to be more likely in cases where high doses are used, especially for prolonged periods.

OVERDOSAGE

A review of the safety surveillance database revealed cases of intentional and accidental tizanidine overdose. Some of the cases resulted in fatality and many of the intentional overdoses were with multiple drugs including CNS depressants. The clinical manifestations of tizanidine overdose were consistent with its known pharmacology. In the majority of cases a decrease in sensorium was observed including lethargy, somnolence, confusion and coma. Depressed cardiac function are also observed including most often bradycardia and hypotension. Respiratory depression is another common feature of tizanidine overdose.

Should overdose occur, basic steps to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems should be undertaken. In general, symptoms resolve within one to three days following discontinuation of tizanidine and administration of appropriate therapy. Due to the similar mechanism of action, symptoms and management of tizanidine overdose are similar to those following clonidine overdose. For the most recent information concerning the management of overdose, contact a poison control center.

DOSAGE AND ADMINISTRATION

A single 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. Effects are dose-related.

Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of tizanidine's common adverse events make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose).

The dose can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours. The total daily dose should not exceed 36 mg.

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 (see WARNINGS).

Food has complex effects on tizanidine pharmacokinetics, which differ with the different formulations. These pharmacokinetic differences may result in clinically significant differences when [1] switching administration of the tablet between the fed or fasted state, [2] switching administration of the capsule between the fed or fasted state, [3] switching between the tablet and capsule in the fed state, or [4] switching between the intact capsule and sprinkling the contents of the capsule on applesauce. These changes may result in increased adverse events or delayed/more rapid onset of activity, depending upon the nature of the switch. For this reason, the prescriber should be thoroughly familiar with the changes in kinetics associated with these different conditions (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

HOW SUPPLIED

Zanaflex Capsules™

Zanaflex Capsules™ (tizanidine hydrochloride) are available in three strengths as two-piece hard gelatin capsules containing tizanidine hydrochloride 2 mg, 4 mg or 6 mg. The 2 mg capsules have a standard blue opaque body with a standard blue opaque cap with "2 MG" printed on the cap. The 4 mg capsules have a white opaque body with a standard blue opaque cap with "4 MG" printed on the cap. The 6 mg capsules have a light blue opaque body with a white stripe and light blue opaque cap with "6 MG" printed on the capsules. The capsules are provided as follows:

Zanaflex Capsules™ (tizanidine hydrochloride), 2 mg, bottles of 150 capsules (NDC 10144-602-15)

Zanaflex Capsules™ (tizanidine hydrochloride), 4 mg, bottles of 150 capsules (NDC 10144-604-15)

Zanaflex Capsules™ (tizanidine hydrochloride), 6 mg, bottles of 150 capsules (NDC 10144-606-15)

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Dispense in containers with child resistant closure

Zanaflex® tablets

Zanaflex® (tizanidine hydrochloride) tablets are available in two strengths as white, uncoated tablets containing tizanidine hydrochloride 2 mg or 4 mg. The 2 mg tablets have a bisecting score on one side and debossed with "A592" on the other side. The 4 mg tablets have a quadrisecting score on one side and are debossed with "A594" on the other side. Tablets are provided as follows:

Zanaflex® (tizanidine hydrochloride) tablets, 2 mg, bottles of 150 tablets (NDC 10144-592-15)

Zanaflex® (tizanidine hydrochloride) tablets, 4 mg, bottles of 150 tablets (NDC 10144-594-15)

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Dispense in containers with child resistant closure

Rx Only

Zanaflex® is the registered trademark of Elan Pharmaceuticals Inc.. Zanaflex Capsules™ is the trademark of Elan Pharmaceuticals Inc..

Manufactured by:
Elan Pharma International, Ltd.
Athlone, Ireland

672 Marketed and Distributed by:
673 Acorda Therapeutics Inc.
674 Hawthorne, NY 10532
675

677 Draft - ZanaflexTabCap0001 Rev. 7/06
678

ACORDA®
679 THERAPEUTICS
680
681

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW OF SUPPLEMENT

ORGANIZATION:	HFD-120
NDA NUMBER:	**20-397**
SUPPLEMENT NUMBER:	**SCM-004**
LETTER DATE	24-FEB-99
STAMP DATE	26-FEB-99
AMENDMENT (FA):	
LETTER DATE	20-MAR-01
STAMP DATE	21-MAR-01
RECEIVED BY CHEMIST:	22-MAR-01

APPLICANT NAME AND ADDRESS: Elan Pharmaceuticals Inc.
800 Gateway Boulevard
South San Francisco, CA 94080

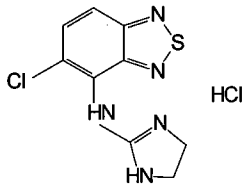
NAME OF DRUG: Zanaflex®

NONPROPRIETARY NAME: Tizanidine HCl

CHEMICAL NAME / STRUCTURE: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole HCl

Mol. Formula: $C_9H_8ClN_5S.HCl$

Mol. Weight: 290.2



DOSAGE FORM(S): Tablets

POTENCY(IES): 2 (new strength), 4 mg

PHARMACOLOGICAL CATEGORY: α_2-adrenergic agonist with myotonolytic properties / Treatment of spasticity of spinal cord origin

SPECIAL PRODUCTS: ___(YES) XX (NO)

HOW DISPENSED: XX (Rx) ___(OTC)

RECORDS / REPORTS CURRENT: XX (YES) ___(NO)

RELATED IND / NDA / DMF(S): DMF # 9242 (Novartis)

SUPPLEMENT PROVIDES FOR: The original submission (AP 4-FEB-00) provided for addition of the 2 mg strength. The current amendment provides the Final Package Insert and Labels.

COMMENTS:
The Approval Letter of 4-FEB-00 contained the commitment:
"The Final Printed Labeling (FPL) must be identical, and include minor editorial revisions indicated, to the submitted draft labeling (package insert submitted February 1, 2000 and February 2, 2000; immediate container and carton labels submitted February 24, 1999). These revisions are terms of the NDA approval". The firm fulfilled the above commitment with this submission and provided 20 copies of FPL as approved on 4-FEB-00. The recommended storage conditions read: "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled Room Temperature]. Dispense in containers with child resistant closure." A common Package Insert is used for both Tablet strengths, as approved. Container Labels are attached.

CONCLUSIONS AND RECOMMENDATIONS: NAI. FPL is identical with the approved.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Danae Christodoulou, Ph.D.		April 10, 2001

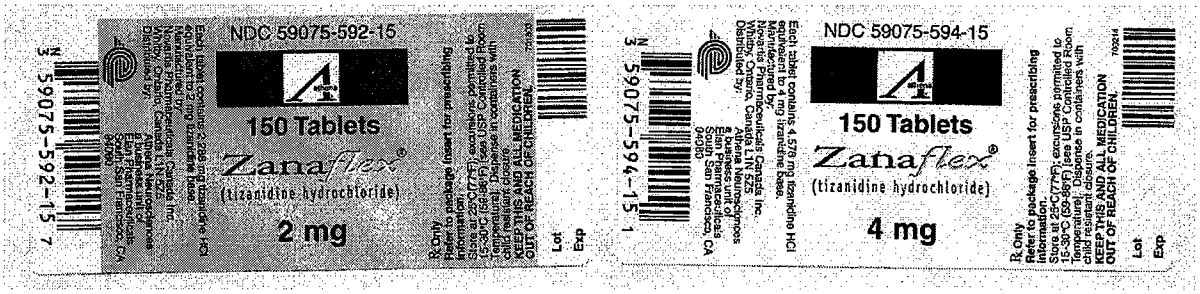
cc: Orig.; NDA 20-397
HFD-120/Div. File
HFD-120/LChen
HFD-120/DChristodoulou
INIT: MGuzewska/

Filename: N20397S4.FA.doc

ATTACHMENT

FPL for Approved Supplement NDA 20-397/SCM-004

Container Labels



/s/

Danae Christodoulou
4/10/01 11:27:58 AM
CHEMIST

Maryla Guzewska
4/10/01 01:04:59 PM
CHEMIST

CHEMIST'S REVIEW OF SUPPLEMENT

ORGANIZATION:	FEB - 3 2000	HFD-120
NDA NUMBER:		20-397
SUPPLEMENT NUMBER:		SCM-004
LETTER DATE		24-FEB-99
STAMP DATE		26-FEB-99
AMENDMENTS:		
LETTER DATE		01-FEB-2000
LETTER DATE		02-FEB-2000
RECEIVED BY CHEMIST:		01-FEB-2000

APPLICANT NAME AND ADDRESS: Elan Pharmaceuticals Inc.
800 Gateway Boulevard
South San Francisco, CA 94080

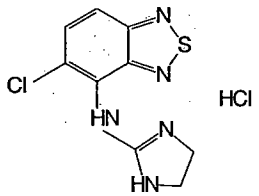
NAME OF DRUG: Zanaflex®

NONPROPRIETARY NAME: Tizanidine HCl

CHEMICAL NAME / STRUCTURE: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole HCl

Mol. Formula: $C_9H_8ClN_5S.HCl$

Mol. Weight: 290.2



DOSAGE FORM(S): Tablets

POTENCY(IES): 2 (new strength), 4 mg

PHARMACOLOGICAL CATEGORY: α_2-adrenergic agonist with myotonolytic properties / Treatment of spasticity of spinal cord origin

SPECIAL PRODUCTS: __ (YES) XX (NO)

HOW DISPENSED: XX (Rx) __ (OTC)

RECORDS / REPORTS CURRENT: XX (YES) __ (NO)

RELATED IND / NDA / DMF(S): DMF # 9242 (Novartis)

SUPPLEMENT PROVIDES FOR: The original submission provided for addition of the 2 mg strength. The current amendments provide the package insert (not included in the original submission), and proposed revisions.

COMMENTS: REVIEW # 3.
The package insert includes both tablet strengths, 2 (new) and 4 mg. "Description" section is adequate. "How Supplied" section has been revised to reflect more accurately appearance of the tablets, storage statement to comply with current USP requirements, and implementation of the "Elan" logo to reflect acquisition of Athena by Elan. Revisions are to be submitted with the FPL and implemented with the next package insert printing. (See Review Notes and telocons between Ms. Octavia Norris and Louise Johnson of Elan and Drs. D. Christodoulou and M. Guzewska of FDA).

CONCLUSIONS AND RECOMMENDATIONS: Recommend approval of N20-397/SCM-004 as amended.
The following revision should be communicated to the sponsor:
"Store at 15-30°C (59-86°F). Dispense in containers with child resistant closure." REVISE TO:
"Store at 25° (77°F); excursions permitted to 15-30°C (59-86°F)". [See USP controlled Room Temperature].
Dispense in containers with child resistant closure."

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Danae Christodoulou, Ph.D.	D. Christodoulou	February 3, 2000

cc: Orig.; NDA 20-397
HFD-120/Div. File
HFD-120/LChen
HFD-120/DChristodoulou
INIT: MGuzewska/ 2/3/00

Filename: N20397S004.3.doc

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of trade secret and/or

confidential commercial

information from

Chemistry Review #3- 2/3/00

OCT 15 1999

CHEMIST'S REVIEW OF SUPPLEMENT

ORGANIZATION:	HFD-120
NDA NUMBER:	20-397
SUPPLEMENT NUMBER:	SCM-004
LETTER DATE	24-FEB-99
STAMP DATE	26-FEB-99
AMENDMENT:	05-OCT-99
RECEIVED BY CHEMIST:	26-FEB-99

APPLICANT NAME AND ADDRESS: ELAN PHARMACEUTICALS
800 Gateway Boulevard
South San Francisco

NAME OF DRUG:	ZANAFLEX®
NONPROPRIETARY NAME:	Tizanidine hydrochloride
CHEMICAL NAME / STRUCTURE:	5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole hydrochloride
DOSAGE FORM(S):	Tablets
POTENCY(IES):	2 mg (new strength), 4 mg
PHARMACOLOGICAL CATEGORY:	Treatment of spasticity of spinal cord origin
HOW DISPENSED:	XX (Rx) ___(OTC)
RECORDS / REPORTS CURRENT:	XX (YES) ___(NO)
RELATED IND / NDA / DMF(S):	DMF 9242 (Novartis)

SUPPLEMENT PROVIDES FOR: The original submission provided for the addition of the 2 mg strength. This amendment provides the missing manufacturing information requested in the NAE letter.

COMMENTS: The manufacturing process description and in-process controls and tests are in agreement with batch records provided in the original submission. See CMC Review Notes.

CONCLUSIONS AND RECOMMENDATIONS: Recommend Approval contingent upon Approval recommendation of the Division of Biopaharmaceutics.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Mona Zarifa, Ph.D.	Mona Zarifa	October 14, 1999

cc: Orig.; NDA 20-397
HFD-120/Div. File
HFD-120/LChen
HFD-120/MZarifa

Filename: 20397S04.doc

INIT: MGuzewska/ 10.15.99

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of trade secret and/or

confidential commercial

information from

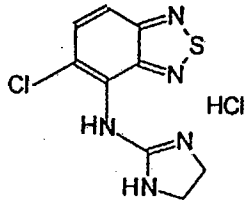
Chemistry Review #2 - 10/14/99

2/11

CHEMIST'S REVIEW OF SUPPLEMENT

ORGANIZATION: JUN 17 1999 HFD-120
NDA NUMBER: 20-397
SUPPLEMENT NUMBER: SCM-004
LETTER DATE 24-FEB-99
STAMP DATE 26-FEB-99
RECEIVED BY CHEMIST: 10-MAR-99

APPLICANT NAME AND ADDRESS: ELAN PHARMACEUTICALS
800 Gateway Boulevard
South San Francisco
NAME OF DRUG: ZANAFLEX®
NONPROPRIETARY NAME: Tizanidine hydrochloride
CHEMICAL NAME / STRUCTURE: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole hydrochloride



DOSAGE FORM(S): Tablets
POTENCY(IES): 2 mg (new strength), 4 mg
PHARMACOLOGICAL CATEGORY: Treatment of spasticity of spinal cord origin
HOW DISPENSED: XX (Rx) ___ (OTC)
RECORDS / REPORTS CURRENT: XX (YES) ___ (NO)
RELATED IND / NDA / DMF(S): DMF 9242 (Novartis)
SUPPLEMENT PROVIDES FOR: The addition of a new dosage strength, 2 mg tablets.

COMMENTS: The new proposed formulation for the 2mg tablets is of the same qualitative composition as the NDA formulation but [ ]. The sponsor provides no year stability manufacturing information on the new formulation. No information is provided in the supplement for the manufacture of the 2 mg tablets (the DMF referenced in the submission is not the correct DMF). The sponsor committed to provide the correct DMF reference or the manufacture information in an amendment to the supplement (Telephone contact June 14, 1999). The sponsor provides 3-year supportive stability data performed on the commercial 2 mg tablets marketed in Europe (manufactured at Novartis, Switzerland as proposed for this supplement) and the acceptance for packaging specifications/test methods for the proposed U.S. commercial tablets. CoAs are provided for the European commercial lots. The sponsor bases bioequivalence of the two strengths on comparative dissolution data profiles. The bioequivalence study has been reviewed by the Biopharmaceutical group and was found not adequate to support the bioequivalence of the two strengths (See Biopharmaceutical Review for details)

CONCLUSIONS AND RECOMMENDATIONS: The Office of Compliance's recommendation for the manufacturing site is Acceptable (see attached EER). Recommend NDA 20-397 S-004 to be Approvable contingent upon receipt of the pending manufacture information and satisfactory recommendation of the Division of Biopharmaceutical See Bio-pharmaceutical Review for final recommendation and the CMC Review Notes for our input to the action letter.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Mona Zarifa, Ph.D.	Mona Zarifa	June 17, 1999

cc: Orig.; NDA 20-397
HFD-120/Div. File
HFD-120/Lchen/MZarifa
INIT: MGuzewska/ 6.17.99

Filename: 20397004.doc

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of trade secret and/or

confidential commercial

information from

Chemistry Review #1 - 6/17/99

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20397/004**
Priority: **1S**
Org Code: **120**
Stamp: **26-FEB-1999** Regulatory Due: **26-JUN-1999**
Action Goal:
District Goal: **22-MAY-1999**
Applicant: **ELAN PHARMA**
C/O ATHENA NEUROSCIENCES INC
800 GATEWAY BLVD
SOUTH SAN FRANCISCO, CA 94080
Brand Name: **ZANAFLEX (TIZANIDINE HCL) ORAL TABS. 4MG**
Established Name:
Generic Name: **TIZANIDINE HCL**
Dosage Form: **TAB (TABLET)**
Strength: **2MG, 4MG**

FDA Contacts:

L. CHEN	**(HFD-120)**	**301-594-5529**	**, Project Manager**
M. ZARIFA	**(HFD-120)**	**301-594-2850**	**, Review Chemist**
M. GUZEWSKA	**(HFD-120)**	**301-594-5571**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 25-MAR-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9611204**
NOVARTIS PHARMA INC (SANDOZ)
LICHTSTRASSE 35
BASEL, , SZ ch-4002
DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **25-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

MEMORANDUM OF TELEPHONE CONTACT

DATE:	June 14, 1999
SUBJECT:	NDA 20-397 S-004
COMPANY:	Elan Pharmaceuticals Phone # (800-)435-5108
COMPANY REPRESENTATIVES:	Octavia Norris

I asked Ms Octavia Norris to clarify the reference to DMF 9242 in S-004. The subject DMF is a Type II DMF for the drug substance manufactured by Novartis and does not include any information on the manufacture of the 2 mg tablet. Ms. Norris said she agrees and she will send the correct reference or an amendment to the supplement with the manufacture information.

Mona Zarifa, Ph.D., Review Chemist

CC: NDA 20-397 file
Init. MGuzewska

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

1/19/00

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 10/4/99, 12/1/99

NDA:	20-397/S-004
Name of Drug:	Zanaflex (Tizanidine), 2 mg and 4 mg Tablets
Indication of Drug:	Anti-spasticity
Sponsor:	Elan Pharmaceuticals, South San Francisco, CA
Type of Submission:	Response to Not Approvable Letter
Reviewer:	Hong Zhao, Ph.D.

Introduction

NDA, 20-397, for Zanaflex (tizanidine HCL) 4 mg tablets, was approved on November 27, 1996. On February 24, 1999, the sponsor submitted a supplement (S-004) which intended to add a 2 mg tablet dosage strength. A Not Approvable letter from the Agency was issued on June 23, 1999 and a meeting was held on July 16, 1999 with the sponsor. In this submission, the sponsor responds to comments presented in the Not Approvable letter. These comments are listed below, with the sponsor's response to each comment.

Review of Responses to the Comments in Agency's Not Approvable Letter

Comment: The sponsor may choose to provide dissolution data to show both the 2 mg and 4 mg Zanaflex tablets dissolve 85% or more of the label amount in ≤ 15 min in the three recommended dissolution media: (1) acidic media, such as 0.1 N HCL or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Response: Zanaflex 2 mg tablets show much slower release in pH 4.5 and 6.8 media (see Attachment I) compared to Zanaflex 4 mg tablets.

At the July 16 meeting, the sponsor was requested to demonstrate comparable dissolution performance between Zanaflex 4 mg and 2 mg tablets using the currently established method (Apparatus I at 100 rpm in 500 ml 0.1 N HCL) for the 4 mg tablets. The sponsor provides data in this submission to show that both dosage strengths of Zanaflex tablets are rapidly dissolving in 0.1 N HCL, ie., average dissolution ≥ 85% in 15 minutes (see Attachment II).

Comment : Failing to show comparability of the two strengths on the basis of dissolution, the sponsor may use an in vivo bioequivalence assessment to support the addition of the 2 mg tablet strength. The sponsor can make their bioequivalence assessment based on the data obtained from the clinical study (Study DS-0008).

The sponsor submitted this clinical study (Study DS-0008) in their submissions of original NDA and of February 25, 1999 and March 31, 1999 without bioequivalence assessment.

Response: A bioequivalence assessment based on the data from Study DS-0008 is provided in this submission as supportive justification for approval of the 2 mg dosage strength (see Attachment III for the results). This study was conducted by Sandoz/Novartis. Mean pharmacokinetic parameters of tizanidine are listed below:

Parameter	2 mg (A)	4 mg (B)	8 mg (C)
C_{max} (ng/ml)	4.9±1.8	8.9±5.5	16.8±4.9
T_{max} (h)	1.5	1.0	1.5
AUC_{0-t} (ng.hr/ml)	13.0±5.0	22.5±7.0	44.5±14.2
$AUC_{0-\infty}$(ng.hr/ml)	14.0±5.4	23.8±7.6	47.8±15.2
*C_{max} (A/B) (90%CI)	1.09 (99.4, 117)		
*$AUC_{0-\infty}$ (A/B) (90% CI)	1.08 (105.6, 124.0)		

* Dose normalized parameter, N=17.

The results of data analysis show that Zanaflex 2 mg and 4 mg tablets are bioequivalent. However, dissolution profiles from the 2 mg biobatch (No. 3700 028.01009, provided by Novartis) were not available to enable comparison with recent production lots. This 2 mg biobatch was made in June 1981. The component and composition of the clinical supply 2 mg lot are the same as the proposed commercial formulation for Zanaflex 2 mg tablets with one minor exception (see Attachment IV) that [ ] mg/tablet [ ] in the biobatch was substituted for [ ] mg/tablet silicic anhydride in commercial formulations).

Comment: In the NDA 20-397, the dissolution specification was set for Zanaflex 4 mg tablets as NLT [ ]% in 15 minutes. The sponsor is requested to clarify why a different specification was used for 2 mg tablets (NLT [ ]% at 30 minutes).

Response: The sponsor accepts a common specification of NLT [ ]% dissolved in 15 minutes for Zanaflex 4 mg and 2 mg tablets.

This specification has been used in all of the above mentioned responses for dissolution tests of both 2 mg and 4 mg tablets.

Review Comments:

Comment 1
The sponsor has satisfactorily responded to the Agency's Comments.

Comment 2
The dissolution results show that both dosage strengths of Zanaflex tablets are rapidly dissolving in 0.1 N HCL, ie., average dissolution ≥ 85% in 15 minutes. The data analysis of the in vivo study (DS-0008) demonstrated bioequivalence between the 2 mg and 4 mg tablets.

Recommendation

The approval of the addition of the 2 mg tablet strength of Tizanidine (Zanaflex 2 mg Tablets) can be granted. The sponsor is requested to adopt the following dissolution method and specification for both Zanaflex 2 mg and 4 mg tablets:

Apparatus:	USP Apparatus I (basket) at 100 rpm
Medium:	500 ml 0.1 N HCL at 37°C±0.5°C
Specification:	Not less than [ ]% in 15 minutes

Please convey this Recommendation to the sponsor.

Hong Zhao, Ph.D. Hong Zhao 1/14/2000

RD/FT Initialed by Raman Baweja, Ph.D. R. Baweja 1/18/2000.

cc: NDA 20,397/S-004, HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

Figure 2 Zanaflex 4 mg and 2 mg Tablets
Dissolution Profile in 0.1 M Potassium Phosphate,
without enzyme, pH = 4.5

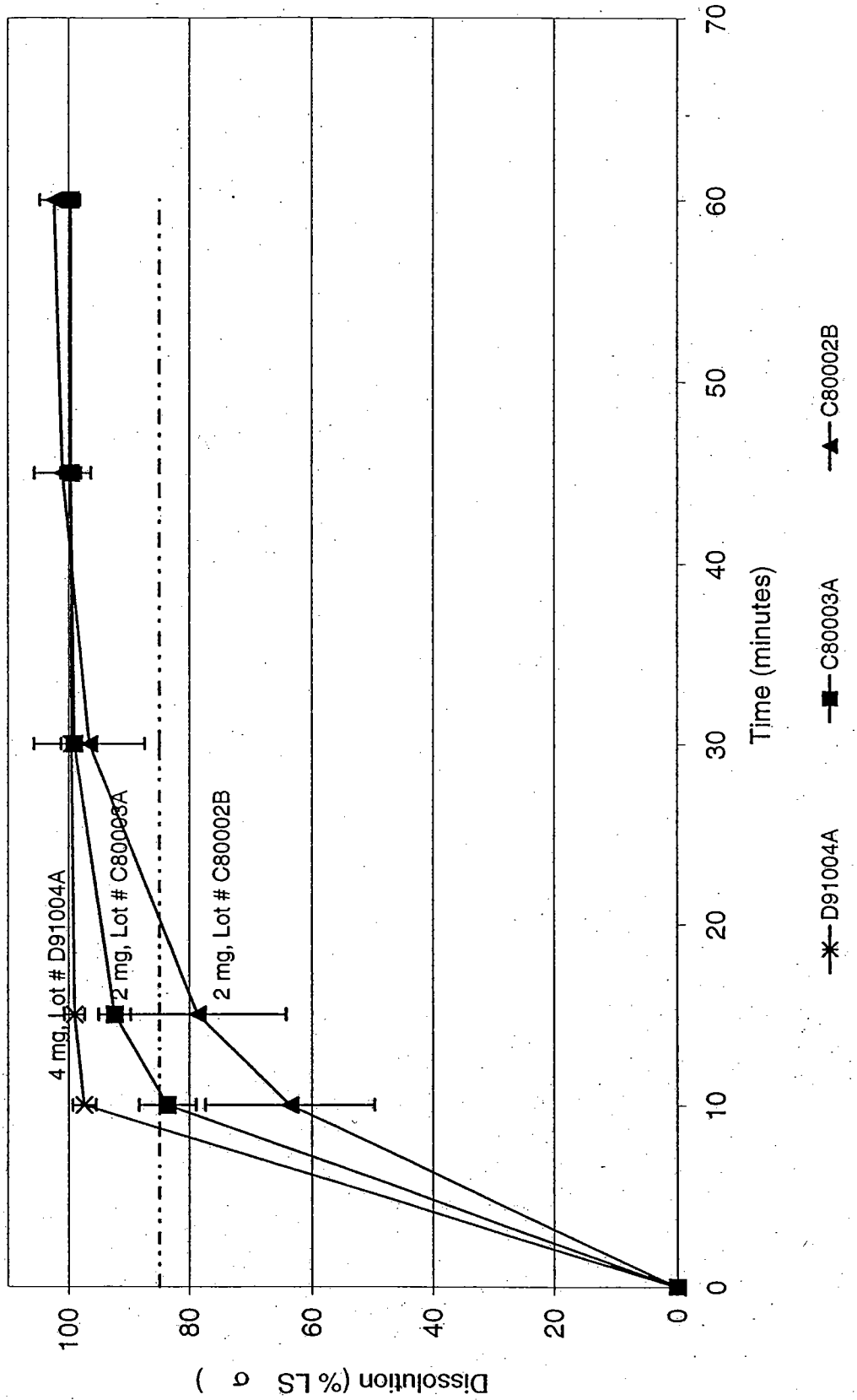
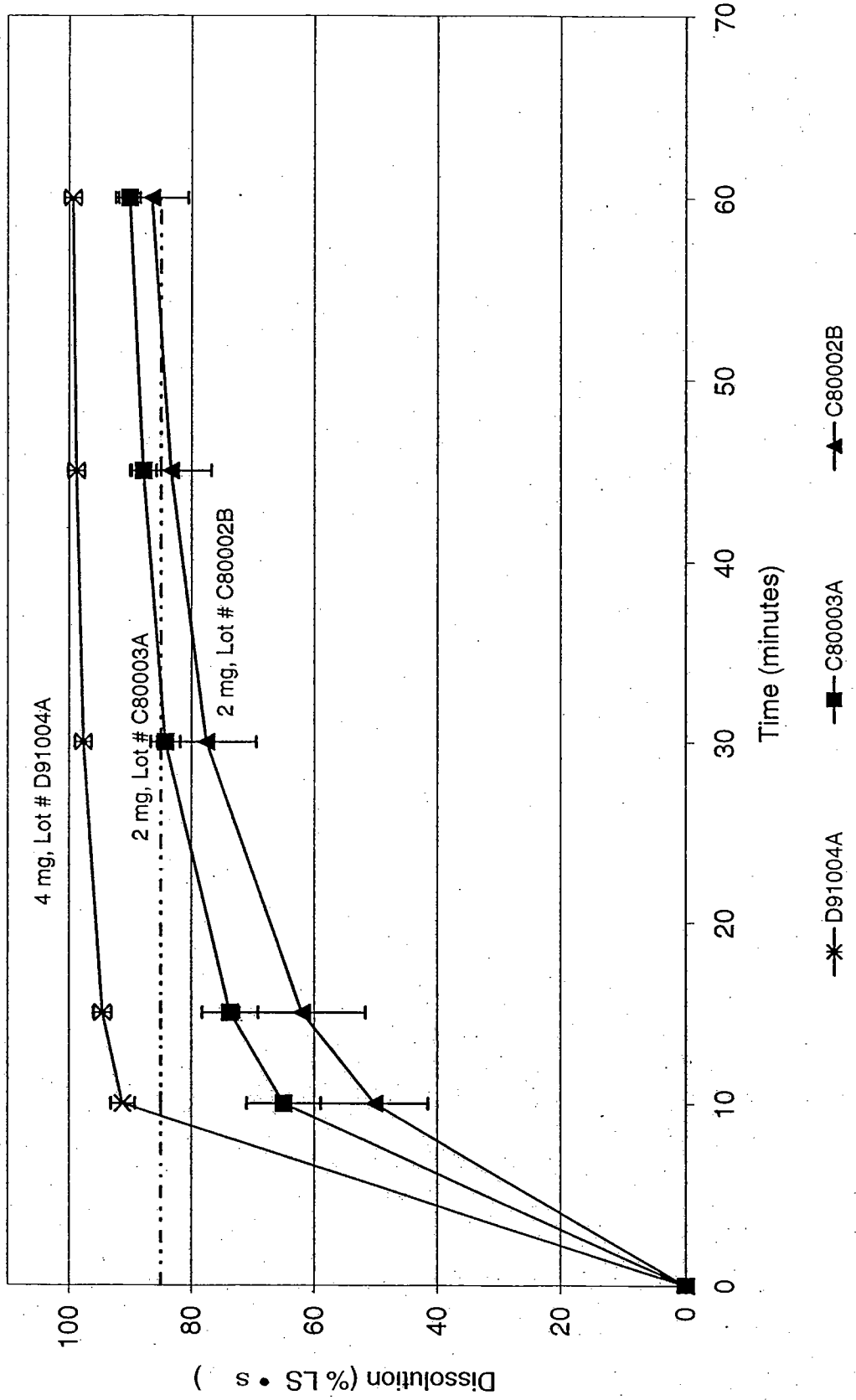


Figure 3 Zanaflex 4 mg and 2 mg Tablets
Dissolution Profiles in 0.1 M Potassium Phosphate,
without enzyme, pH = 6.8



Attachment 1 of 3

Figure 1 Zanaflex 4 mg and 2 mg Tablets
Dissolution Profiles in 0.1N HCl

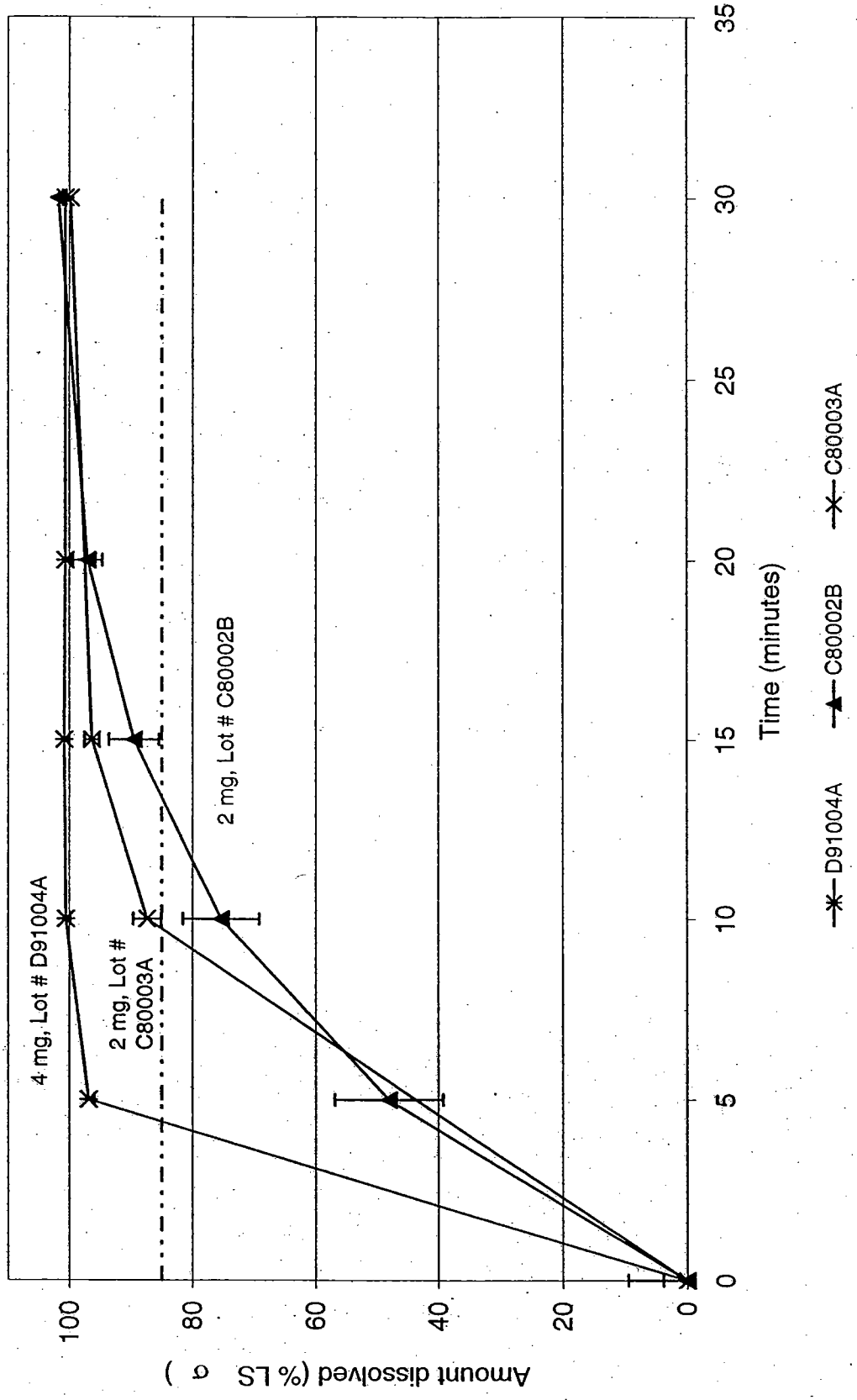


Table 4 Zanaflex Tablets, 4 mg and 2 mg - Recent Production Lots
Summaried Dissolution Profiles in 0.1 N HCl Including Calculated Similarity Factor, f_2

Tablet Dosage	Lot No.	Manufacture Date	Dissolution Profile 10 min	15 min[1]	30 min	45 min	Similarity Factor (f_2 Metric)[2]
4 mg (reference product)	21179	Sept. 1998	94	97 [ ]	99	99	-
	21180	Oct. 1998	96	99 [ ]	99	99	-
	21181	Jan. 1999	97	98 [ ]	99	99	-
Grand Average of 4 mg Tablet Reference Lots			96	98	99	99	-
2 mg	21158	Jun. 1999	96	98 [ ]	99	99	100
	21159	Jun. 1999	90	93 [ ]	98	98	70
	21160	Jun. 1999	88	95 [ ]	100	100	68
	21161	Jun. 1999	99	100 [ ]	101	100	80
	21162	Jun. 1999	92	95 [ ]	97	98	78
	21182	Jun. 1999	98	100 [ ]	99	100	86
	21183	Jun. 1999	97	98 [ ]	99	99	96
	21191	Jun. 1999	96	98 [ ]	98	99	97
	21192	Jun. 1999	98	98 [ ]	98	98	89

[1] The range of the individual dissolution data at 15 minutes is provided to facilitate an assessment of whether USP Stage 2 criteria is indicated

[2] The grand average of the mean dissolution results for three 4 mg tablet lots, Nos. 21179, 21180, and 21181 was used in the calculation of the f2 metric

Attachment D
2 of 3

Table 1 Zanaflex Tablets, 4 mg and 2 mg
Dissolution Profiles in 0.1 N HCl Including Calculated Similarity Factor, f_2

Tablet Dosage	Lot No.	Manufacture Date	Dissolution Profile 5 min	10 min	15 min[1]	20 min	30 min	Similarity Factor (f_2 Metric)
4 mg (reference product)	D91004A	Jan. 1999	97	101	101 [ ]	101	101	-
2 mg	C80003A	Apr. 1998	ND[2]	87	96 [ ]	ND[2]	100	-
	C80002B	Jan. 1998	48	75	90 [ ]	97	102	27.6

[1] The range of the individual dissolution data at 15 minutes is provided to facilitate an assessment of whether USP Stage 2 criteria is indicated

[2] No data was obtained for 5 and 20 minutes timepoints during dissolution profile testing.

Attachment II
3 of 5

Table 1: Subject Demography and Randomization

Patient #	Weight (kg)	Gender	Randomization Sequence (Trt)	Treatment (mg)
1	60.3	Female	ABDC	2/4/P/8
2	80.4	Male	BCAD	4/8/2/P
3	73.2	Male	CDBA	8/P/4/2
4	59.7	Female	DACB	P/2/8/4
5	61.2	Female	CBDA	8/4/P/2
6	48.3	Female	BACD	4/2/8/P
7	77.5	Female	ADBC	2/P/4/8
8	51	Male	DCAB	P/8/2/4
9	53.5	Female	BCAD	4/8/2/P
10	93.1	Female	CDBA	8/P/4/2
11	61.2	Male	DACB	P/2/8/4
12	59.9	Female	ABDC	2/4/P/8
13	49.6	Female	BACD	4/2/8/P
14	88.9	Female	CBDA	8/4/P/2
15	53.1	Female	DCAB	P/8/2/4
16	62	Female	ADBC	2/P/4/8
102	75.8	Female	BCAD	4/8/2/P

Treatment: A = 2mg
B = 4mg
C = 8mg
D = Placebo

Figure 3

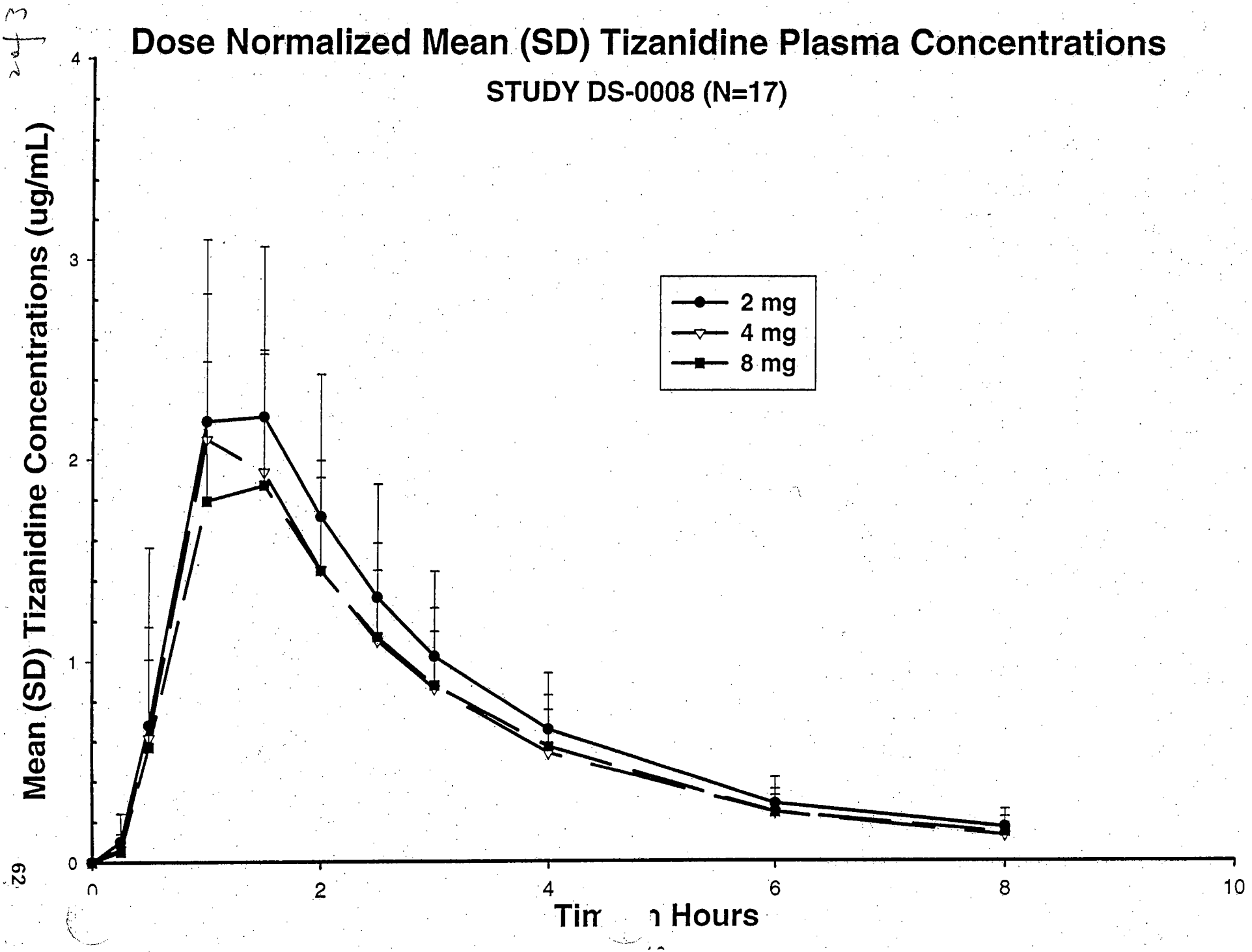

Dose Normalized Mean (SD) Tizanidine Plasma Concentrations
STUDY DS-0008 (N=17)
Mean (SD) Tizanidine Concentrations (ug/mL)
2 mg
4 mg
8 mg
0
1
2
3
4
2
4
6
8
10
Time in Hours

Table 9: 90% Confidence Interval of Tizanidine PK Parameters

Parameter	Treatment	Ratio of LS Means	90% Confidence Interval	
			Lower	Upper
NC_{max}	A/B	1.09	99.37	117.0
$NAUC_{0-t}$	A/B	1.07	104.8	121.3
$NAUC_{inf}$	A/B	1.08	105.6	124.0

*A=2 mg treatment
B=4 mg treatment

Table A

Mean (SD) Pharmacokinetic Parameters of Tizanidine

Parameter	Treatment		
	2 mg	4 mg	8 mg
@T_{max} (hr)	1.5	1.0	1.5
C_{max} (ng/mL)	4.89 (1.77)	8.85 (5.52)	16.77 (4.92)
$AUC_{(0-t)}$ (ng.hr/mL)	12.98 (5.01)	22.45 (6.99)	44.50 (14.21)
AUC_{inf} (ng.hr/mL)	13.99 (5.42)	23.83 (7.59)	47.81 (15.16)

@ Median Value

Attachment IV

- Other than the differences in process scale, the process used to produce the clinical supply lot is representative of the commercial manufacturing process. Both processes involve the [ ]. In process controls applied to the biobatch (weight, shape and hardness) are equivalent to controls used commercially.

Composition of Tizanidine Hydrochloride 2 mg Tablets, Biobatch and Commercial Formulations

	Lot No. 3 700 028.01.009		Current Commercial Formula
	Mg/tablet		Mg/tablet
Tizanidine Hydrochloride	2.29		2.29
Silicon Dioxide	[ ]		[ ]
Stearic Acid	[ ]		[ ]
Microcrystalline Cellulose	[ ]		[ ]
Lactose, Anhydrous	[ ]		[ ]
Tablet Weight	160.00		160.00

[1] In biobatch Lot No. 3 700 028.01.009, [ ] was substituted for Silicic anhydride (Silicon dioxide, SiO_2)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 2/25/99, 3/31/99

NDA:	20,397/S-004&S-005
Name of Drug:	Zanaflex (Tizanidine), 2mg Tablets
Indication of Drug:	Anti-spasticity
Sponsor:	Elan Pharmaceuticals, South San Francisco, CA
Type of Submission:	Prior Approval Supplement
Reviewer:	Hong Zhao, Ph.D.

Background

NDA, 20-397, for Zanaflex (tizanidine HCL) 4 mg tablets, was approved on November 27, 1996. At this time, the sponsor wishes to add a 2 mg tablet dosage strength. The expected use of the 2 mg tablet will be in the early stage of treatment of spasticity to allow patients to titrate more slowly to a clinically effective dose and thereby minimize side effects. The sponsor also proposes to add an alternate packaging site for commercial product. Elan Holdings, Inc., Gainesville, Georgia will perform the packaging operations for the 2 mg and 4 mg tablets.

Information to Support the Addition of the 2 mg Tablet

A three-page documentation of bioavailability/bioequivalence was submitted for supporting the addition of the 2 mg tablet (see Appendix I). The sponsor claims that the 2 mg tablet is made by the same manufacturer of the currently approved 4 mg tablet, Novartis Pharma AG, Basel, Switzerland. Zanaflex 2 mg tablets have the same qualitative composition as the marketed 4 mg tablets. [ ]. The percentage of each excipient relative to total tablet weight is the same in 2 mg and 4 mg tablets (information in the additional submission sent on March 31, 1999). In vivo bioequivalence study of 2 mg tablets was not conducted. In vitro dissolution test was used to support the addition of the 2 mg tablet. Dissolution data were generated for the 2 mg and 4 mg tablets at the 5, 10, 15 and 30 minutes time points with only mean data reported (Appendix I). The sponsor claims that the results show compliance with the specification set for dissolution of tizanidine HCL (Q=[ ]% within 30 minutes) for both formulations.

Initial Review

The information for supporting the addition of the 2 mg tablet submitted by the sponsor is insufficient. A teleconference between OCPB and the sponsor was held on March 19, 1999 and the sponsor was requested to provide the following information:

1. Request a waiver of in vivo bioavailability/bioequivalence studies for their 2 mg tablet.
2. Provide quantitative and qualitative formula for the 2 mg and 4 mg tablets.
3. Provide documentation of the current dissolution method and specification for the 4 mg tablet.

4. Provide written confirmation of the "new process" (i.e., new drug synthesis) referred to in the dissolution data submitted (Appendix I).
5. Provide individual unit data for the batches of 2 mg and 4 mg strengths provided earlier with mean dissolution data only. Give the number of units tested per batch. Include a dissolution comparison using the f2 metric value to show that the profiles of the 2 mg and 4 mg tablets are similar. Also, include a plot of dissolution profiles.

Review on the Additional Submission

In response, the sponsor submitted some dissolution data and selected volumes of the original NDA 20-397 on March 31, 1999. See Appendix II for the dissolution method and specification. The sponsor provided 2 batches of individual dissolution data for each strength (2 mg and 4 mg) without f2 values (Appendix III). The sponsor claims that a profile comparison is unnecessary since both test and reference products dissolve 85% or more within 15 minutes according to the FDA draft Guidance for Industry, Waiver of in Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System.

The above mentioned draft guidance is not in implementation stage. Nevertheless, the guidance says "When both the test and the reference products dissolve 85% or more of the label amount in ≤ 15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary." The three dissolution media are: "(1) acidic media, such as 0.1 N HCL or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes." In this submission dissolution tests were only performed in one medium (0.1 N HCL). No data were submitted to show both the 2 mg and 4 mg Zanaflex tablets dissolve 85% or more of the label amount in ≤ 15 min in the three recommended dissolution media.

Using the dissolution data for Zanaflex 2 mg tablets, Lot C80002B and 4 mg tablets, Lot D91004, which have multiple time points (5, 10, 15, 20, and 30 min), the calculated f2 metric value is 24. Since this f2 metric value is below the similarity criteria of 50-100, it suggests that the dissolution profile of the 2 mg tablets is different from that of the 4 mg tablets.

Review of the Clinical Study (Study DS0008)

In addition to the dissolution data, the sponsor also claims a clinical study (Study DS0008) was performed with the proposed commercial formulation (2 mg) in patients with established multiple sclerosis to evaluate the relationship between dose, plasma levels and antispastic effects. In this study, single doses of 2, 4, and 8 mg of tizanidine HCL were administered to 16 patients either as 2 mg or 4 mg tablets in a double blind, placebo controlled, cross over fashion. The blood sampling time was up to 8 hours post dosing in each treatment. Since this study was not designed to evaluate bioequivalence between the 2 mg and 4 mg, no $AUC_{0-\infty}$ was calculated and data was not analyzed and compared for bioequivalency.

Comments

1. Since the excipients in 2 mg and 4 mg formulations are the same on a percentage (w/w) basis, a dissolution profile comparison can be used to show the similarity of the

two formulation strengths. However, using the dissolution data for Zanaflex 2 mg tablets, Lot C80002B and 4 mg tablets, Lot D91004, which have multiple time points (5, 10, 15, 20, and 30 min), the calculated f2 metric value is 24. This f2 metric value is below the similarity criteria of 50-100, which suggests that the dissolution profile of the 2 mg tablets is different from that of the 4 mg tablets.

2. The sponsor may choose to provide dissolution data to show both the 2 mg and 4 mg Zanaflex tablets dissolve 85% or more of the label amount in ≤ 15 min in the three recommended dissolution media: (1) acidic media, such as 0.1 N HCL or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.
3. Failing to show comparability of the two strengths on the basis of dissolution as outlined above, the sponsor may use an in vivo bioequivalence assessment to support the addition of the 2 mg tablet strength. The sponsor can make their bioequivalence assessment based on the data obtained from the above mentioned clinical study (Study DS-0008). From the plasma drug concentration-time data, AUC_{0-t}, $AUC_{0-\infty}$, C_{max} T_{max}, K_{el} and $t_{1/2}$ should be estimated. Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence and treatment effects. The 90% confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) should be calculated, using the two one-sided t-test procedure.
4. If the clinical study (Study DS0008) fails to show bioequivalence between the 2 mg and 4 mg formulation strengths, a new in vivo bioequivalence study is suggested for supporting the addition of the 2 mg tablet strength.
5. In the NDA 20-397, the dissolution specification was set for Zanaflex 4 mg tablets as NLT □% in 15 minutes. The sponsor is requested to clarify why a different specification was used for 2 mg tablets (NLT □% at 30 minutes).

Recommendation

The approval of the addition of the 2 mg tablet strength can not be granted at this time based on the dissolution data submitted.

Please convey this Recommendation and Comments 1-5 to the sponsor.

Hong Zhao, Ph.D. Hong Zhao 6/14/99 IG3

RD/FT Initialed by Raman Baweja, Ph.D. R. Baweja 6/14/99.

cc: NDA 20,397/S-004&S-005, HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (Barbara Murphy)

4. BIOAVAILAILABILITY/BIOEQUIVALENCE

The bioavailability of the 4 mg tablet of Zanaflex has been demonstrated in the pharmacological, pharmacokinetic and therapeutic studies included in the original NDA filing and cross-referenced to in this supplement. The 2 mg tablet of Zanaflex is the same pharmaceutical form as the 4 mg tablet, which was approved by the FDA on November 27, 1996 (NDA 20-397). In addition, both dosage strengths are made by the same manufacturer, Novartis Pharma AG., Basel, Switzerland. Zanaflex 2 mg tablets are produced from the same components and have the same qualitative composition as the marketed 4 mg tablets. [ ] [ ]. The expected use of the 2 mg tablet will be in the early stages of treatment of spasticity to allow patients to titrate more slowly to a clinically effective dose and thereby minimize side effects. The evidence to support the bioavailability of the 2 mg tablet is discussed below.

Reference No.	Title	Location in Original NDA
1.	103-282-^{14}C, Absorption, Blood Levels, and Excretion in Man. February 1980. Strauss R, Holder A. (Sandoz Study No. 3)	Vol 1.25, Page 350
2.	Pharmacokinetic Characteristics of 103-282 During Multiple Oral Administration of 103-282-^{14}C in Healthy Male Volunteers. April 1985. Cohen A. (Sandoz Study No. 303)	Vol 1.36, Page 2
3.	^{14}C-103-282 Pharmacokinetic Studies in Mice. June 1980. Wagner O, Rietech D, Thomaier K (Sandoz Report No. 303-015)	Vol 1.19, Page 1
4.	^{14}C-103-282 Pharmacokinetic Studies in Rats. March 1979. Wagner O. (Sandoz Report No. 303-007)	Vol 1.19, Page 47
5.	^{14}C-103-282 Pharmacokinetic Studies in Dogs. March 1979. Wagner O. (Sandoz Report No. 303-008)	Vol 1.19, Page 157
6.	Tizanidine-^{14}C in Female Rabbits: Absorption, Blood Levels and Excretion Following Single Oral and Intravenous Dose. January 1985. Ballard FH. (Sandoz Report No. 303-038)	Vol 1.19, Page 136
7.	A Double-blind, Placebo-controlled, Randomized, Crossover, Clinical Experimental Study to Assess the Correlation Between Pharmacodynamic Actions and Blood Levels of Oral Sirdalud® (tizanidine) (Study DS0008). July 1991. Roberts (Sandoz Report No. 603-140)	Vol 1.126, Page 1
8.	A Multi-center, Double-blind, Randomized, Placebo-controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity Due to Multiple Sclerosis. November 1993 (Study DS0502)	Vol 1.114, Page 1

The active ingredient, tizanidine hydrochloride, is water soluble. Pharmacokinetic studies in man show rapid absorption after single oral doses of 5 mg and 20 mg, with mean peak blood concentrations occurring approximately one hour after dosing (1). The plasma half-life is approximately three hours and no evidence of drug accumulation is observed following multiple dosing (1;2). Similar pharmacokinetics, rapid absorption, peak plasma concentrations at one hour and short half-life, were also observed in the animal species investigated (3, 4, 5, 6). In addition to the pharmacokinetic studies, a study was also performed, with the proposed commercial formulation, in patients with established multiple sclerosis, to evaluate the relationship between dose, plasma levels and antispastic effects. Single doses of 2, 4, and 8 mg of tizanidine HCl were administered as either 2 mg or 4 mg tablets (see attached publication by Emre et al., Correlation Between Dose, Plasma Concentrations, and Antispastic Action of Tizanidine, *Journal of Neurology, Neurosurgery, and Psychiatry*). The full report for this study may be found in Volume 1.126, page 1 of the original NDA submission. The results show that a linear relationship between single doses, plasma levels, and antispastic effects of tizanidine over the dose range studied (Figures 2 and 4 in the attached publication). The study also demonstrated that peak antispastic effects appear 1.5 hours after drug administration and the effects last about three hours. In addition to this study, the commercial formulation of the 2 mg tablet was also used by Novartis during the dose titration phase of one of the pivotal trials in patients suffering from spasticity due to multiple sclerosis (7).

same study

In addition, dissolution profiles of the 2 mg and 4 mg tablets were compared at the 5, 10, 15 and 30 minutes timepoints (see attached report), using dissolution method specified in Section 2.D (QUALITY CONTROL) of this submission, for both tablet strengths. The results show compliance with the specification set for dissolution of tizanidine HCl (Q=[ ]% within 30 minutes) for both formulations. ?

It is therefore concluded that the 2 mg and 4 mg tablets are bioequivalent. The 2 mg tablet will be used primarily during the early stages of treatment to allow patients to carefully titrate to a dose producing the desired therapeutic effect.

ANALYTICAL DATA

SIRDALUD®/ZANAFLEX Tablets 2 mg
Dissolution profile of Tizanidine HCl:

Batch No.	5 min m ± ST (in %)	10 min m ± ST (in %)	15 min m ± ST (in %)	30 min m ± ST (in %)
064 Previous process				
065 Previous process				
066 Previous process				
079 Improved process				
080 Improved process				

* Complies to the requirement Q = [ ]% within 30 minutes, acceptance plan according to USP

SIRDALUD®/ZANAFLEX Tablets 4 mg
Dissolution profile of Tizanidine HCl:

Batch No.	5 min m ± ST (in %)	10 min m ± ST (in %)	15 min m ± ST (in %)	30 min m ± ST (in %)
062 Improved process				
079 Improved process				
080 Improved process				

* Complies to the requirement Q = [ ]% within 30 minutes, acceptance plan according to USP

Comment:
The results obtained show that the requirement set for dissolution of Tizanidine HCl was met independently of the manufacturing process of the active ingredient.

DISSOLUTION TESTING OF 2 MG ZANAFLEX TABLETS

Procedure

1. Dissolution parameters

   1.1 Apparatus: USP apparatus 1, baskets

   1.2 Rotation speed: 100 RPM

   1.3 Medium: 0.1N Hydrochloric Acid

   1.4 Medium volume: 500 mL

   1.5 Sampling time: 30 minutes

   1.6 Sample volume: approximately 5 mL

   1.7 Samples tested: Six 2 mg Zanaflex tablets

   1.8 Vessel temperature: 37 ± 0.5°C

2.

3.

4.

Appendix III

Dissolution Comparison of Zanaflex® 2 mg and 4 mg Tablets (AQS-812)

Introduction:

Elan Pharmaceuticals, Inc. recently submitted an NDA supplement for the Zanaflex 2 mg tablet dosage form. A study was conducted at Elan Pharmaceuticals, Inc., South San Francisco to evaluate the in vitro dissolution of the new Zanaflex 2 mg tablet dosage form compared to the commercially available Zanaflex 4 mg tablet. Two lots of each strength were run per a 12 unit dissolution assay. The Zanaflex 4 mg tablets were taken from lots D91004 (Novartis lot 128MFD0199) and D91005 (Novartis lot 129MFD0199). The Zanaflex 2 mg tablets were taken from lots C80002B (Novartis lot 091MFD0198) and C80003A (Novartis lot 092MFD0498). One lot of each strength was run with dissolution clock points of 5, 10, 15, 20 and 30 minutes. The second lot of each strength was run with dissolution clock points of 10, 15 and 30 minutes.

Discussion:

Dissolution profiles for the Zanaflex 2 mg (Tables 1 and 2) and 4 mg tablets (Tables 3 and 4) were generated for the purpose of determining equivalency of the two dosage strengths as outlined in the Guidance for Industry, *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, FDA, CDER, August 1997. However, both dosage strengths are such rapidly dissolving tablets that the criteria for doing similarity calculation, such as three or four clock points with only one clock point having a % dissolved ≥ 85%, can not be met for the dissolution comparison. Therefore, Elan referred to the draft Guidance for Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System*, FDA, CDER, January 1999, which comments that a profile comparison is unnecessary when both test and reference products dissolve 85% or more within 15 minutes. Thus, the f_2 equation was not completed. Plots of the dissolution profiles are provided on the following pages.

Conclusion:

The dissolution study for the Zanaflex dosage strengths demonstrate that the 2 mg tablet is equivalent to the 4 mg tablet, and a waiver of the in vivo BA/BE studies should be granted for the Zanaflex 2 mg tablet.

Table 1: Dissolution Results for Zanaflex 2 mg Tablets, Lot C80002B

Unit Number	Percent of Labeled Strength				
	5 minutes	10 minutes	15 minutes	20 minutes	30 minutes
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	48	75	90	97	102
SD	9.5	8.8	6.2	4.1	2.3

Table 2: Dissolution Results for Zanaflex 2 mg Tablets, Lot C80003A

Unit Number	Percent of Labeled Strength		
	10 minutes	15 minutes	30 minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	87	96	100
SD	3.9	2.3	1.2

Appendix III

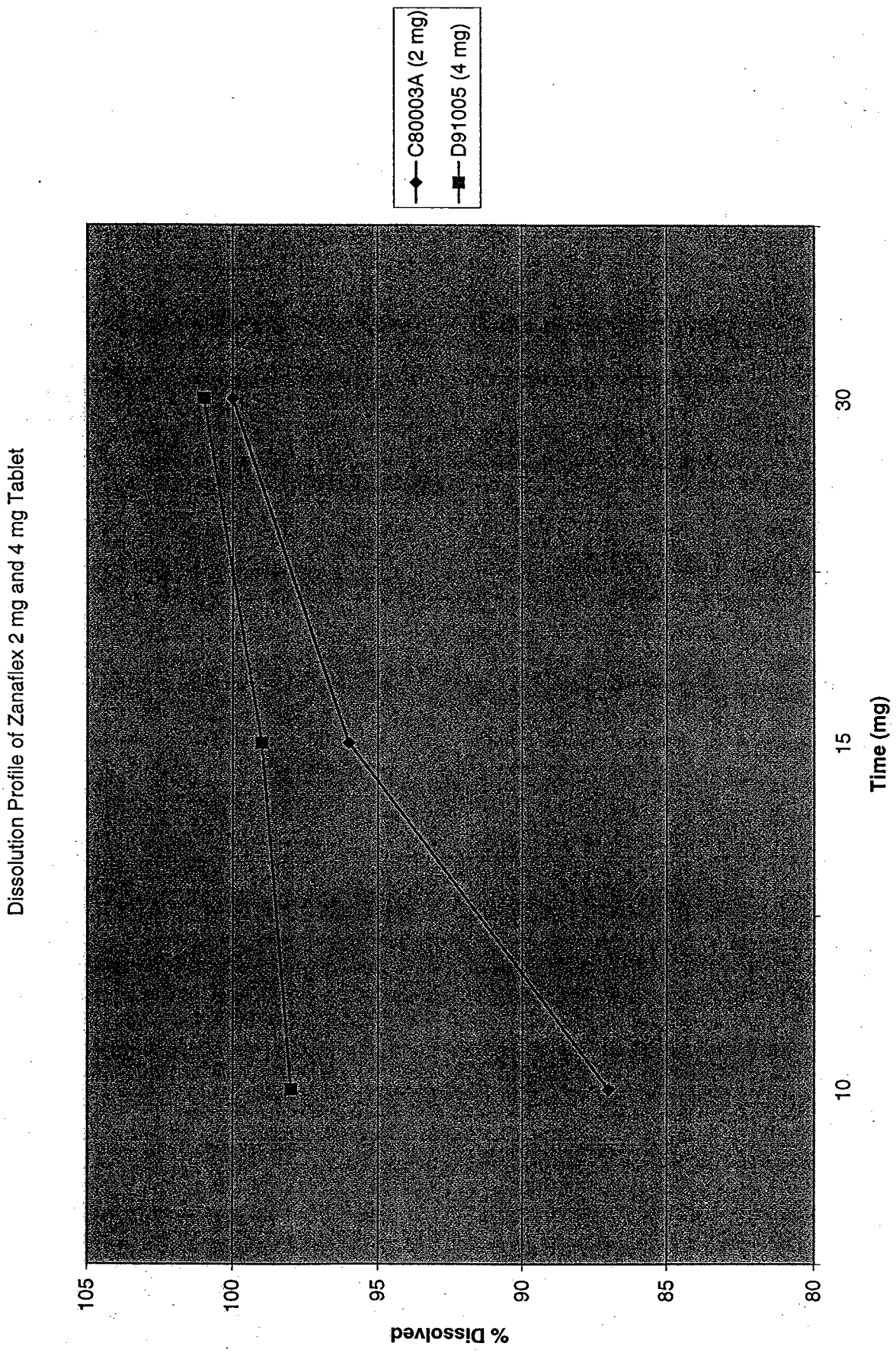
Table 3: Dissolution Results for Zanaflex 4 mg Tablets, Lot D91004

Unit	Percent of Labeled Strength				
Number	5 minutes	10 minutes	15 minutes	20 minutes	30 minutes
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	97	101	101	101	101
SD	1.6	0.9	0.7	0.8	0.8

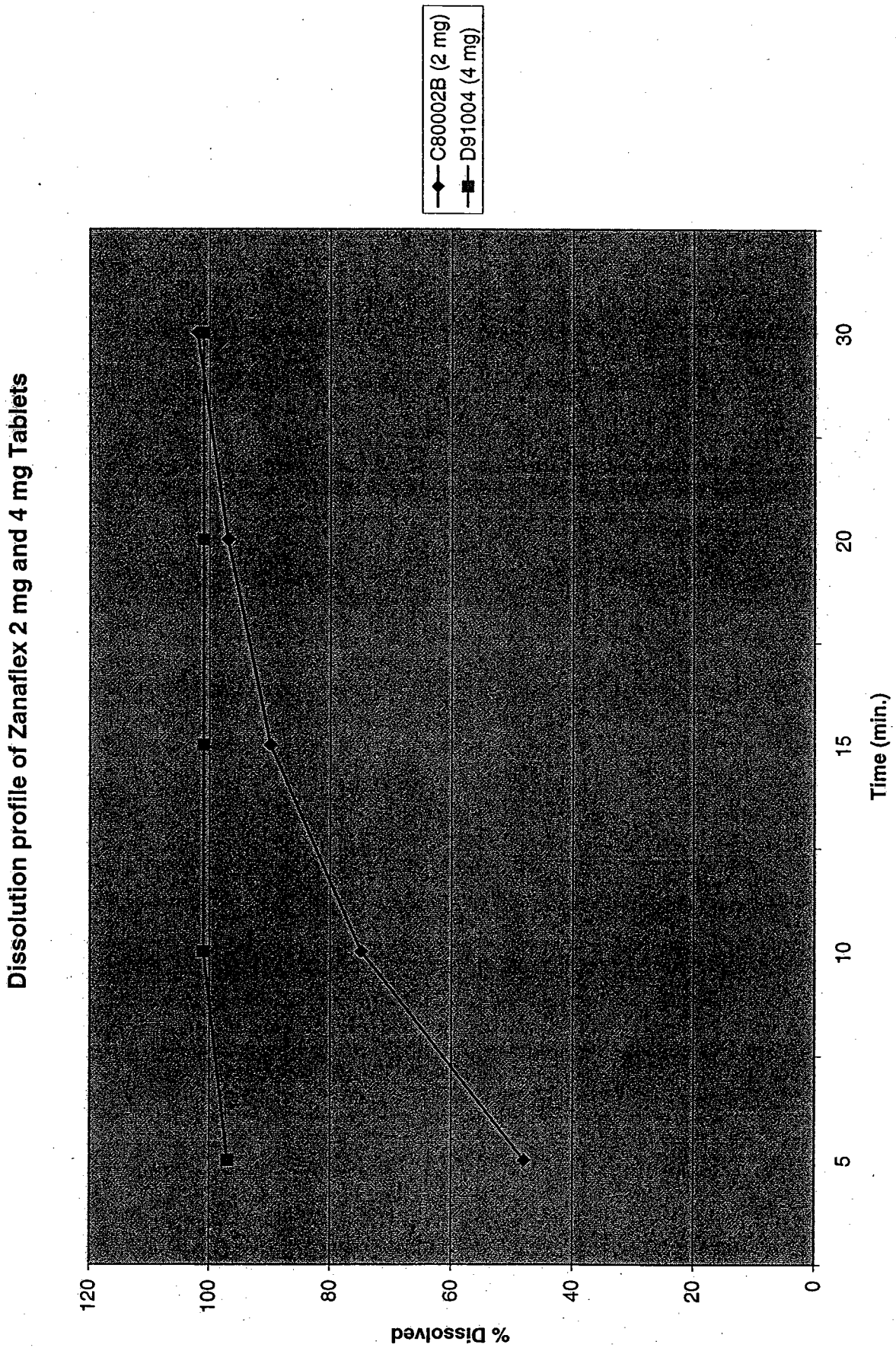
Table 4: Dissolution Results for Zanaflex 4 mg Tablets, Lot D91005

Unit	Percent of Labeled Strength		
Number	10 minutes	15 minutes	30 minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	98	99	101
SD	9.0	5.7	2.0

Appendix III



Appendix III



2. DRUG PRODUCT

2.1 Composition and Dosage Form

The quantitative composition of the drug product (4 mg tablets) is as follows:

Component	mg/ tablet	% w/w
Tizanidine.HCl[1]	4.576	2.08
Silicon dioxide colloidal, Ph. Eur.	[ ]	[ ]
Stearic acid, NF		
Cellulose, microcrystalline, Ph.Eur.		
Lactose, anhydrous, NF		
Total	220.0 mg	100.00%

[1]Corresponds to 4.0 mg tizanidine base

Zanaflex (tizanidine.HCl) will be marketed as a 9 mm, flat faced, bevelled-edge, round, white, non-coated tablet embossed with [ ] on one side and cross-scored on the other.

2.2 Manufacturers

Zanaflex (tizanidine.HCl) tablets will be manufactured and packaged (bulk tablets, [ ] [ ]) by:

Pharmaceutical Production Department
Sandoz, Ltd.
CH-4002
Basel, Switzerland

Zanaflex (tizanidine.HCl) bulk tablets will be packaged and labeled into trade size and professional sample packaging by:

[ ]

2. DRUG PRODUCT

The components and qualitative composition of Zanaflex 2 mg tablets are the same as for Zanaflex 4 mg tablets. Tizanidine hydrochloride tablets are formulated with common pharmaceutical excipients used in oral solid dosage forms. The excipients were selected to provide a [ ]. Refer to Novartis' Type II Drug Master File (DMF), No. 9242, for information regarding the manufacture of drug product.

2.A COMPOSITION

The composition of Zanaflex 2 mg tablets is presented in Table 1. Its active ingredient corresponds to 2.0 mg tizanidine base.

Table 1: Tablet Composition

Ingredients	Grade	Weight (mg) /Tablet
Active ingredient		
Tizanidine hydrochloride	In-house	2.29
Inactive Ingredients		
Silica, colloidal anhydrous	USP23 NF18	[ ]
Stearic acid	USP23 NF18	
Cellulose, microcrystalline	USP23 NF18	
Lactose, anhydrous	USP23 NF18	
Total		**160.00**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

ADMINISTRATIVE

FEB - 9 2000

Division of Neuropharmacological Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 20-397/S-004
Name of Drug: Zanaflex (tizanidine) Tablets
Sponsor: Elan Pharmaceuticals

Material Reviewed

Submission Date(s): February 24, 1999
Receipt Date(s): February 27, 1999

Background and Summary Description:

A supplemental new drug application of February 24, 1999 was submitted for Zanaflex (tizanidine) Tablets. The purpose of this supplement was to provide for the new 2 mg tablet, a new strength. The Not Approvable letter for this supplement issued June 23, 1999, and the Sponsor's response dated October 4, 1999 was submitted with carton and container labeling. Draft labeling was subsequently submitted in on February 1, 2000 and February 2, 2000. Additionally, the draft labeling included changes reported in Postmarketing Periodic Report submitted March 27, 1998.

Draft labeling submitted by Sponsor on February 1, 2000 and February 2, 2000 was compared to the last approved labeling of November 27, 1996.

Review

A line-by-line comparison was done to compare draft labeling submitted on February 1, 2000 and February 2, 2000 with the last approved labeling of November 27, 1996. The following changes were made:

1. Those changes specified in the in Postmarketing Periodic Report submitted March 27, 1998:

    a) In CLINICAL STUDIES, "spasm counts" as a measure recorded by patients in the clinical studies, and their results, were added.

b) In INDICATIONS AND USUAGE, the previous version:

"Tizanidine is a short-acting drug for the acute and intermittent management of increased muscle tone associated with spasticity. 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 to 6 hours. Use must therefore be individualized, directed to those activities and times when relief of spasticity is most important and titrated to avoid intolerance. Evidence demonstrating the effectiveness of tizanidine is derived from a single dose study and from a seven week multiple dose study conducted in patients with multiple sclerosis and spinal cord injury, respectively."

was replaced with:

"Tizanidine is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important (see DOSING AND ADMINISTRATION)."

a) In INFORMATION FOR PATIENTS, the following new precaution was included:

"Zanaflex should be used with caution where spasticity is utilized to sustain posture and balance in locomotion or whenever spasticity is utilized to obtain increased function".

b) In ADVERSE REACTIONS, the term "asthenia" was replaced with "asthenia (weakness, fatigue and/or tiredness)" in several instances throughout the section.

2. In the CLINICAL PHARMACOLOGY section, "about" was replaced with "approximately" in several instances throughout the PHARMACOKINETICS section.

3. Changes to include the 2 mg tablet in the Header, DESCRIPTION and HOW SUPPLIED sections. These changes are described in Dr. Christodoulou's review dated February 3, 2000.

Conclusions

The changes noted above are acceptable. An approval letter should issue.

Lana Chen, R.Ph.
Project Manager

Supervisory Comment/Concurrence:

John Purvis
Supervisor, Project Management Staff

Clinical Team Leader Comment/Concurrence:

Randy Levin, M.D.
Neurology Team Leader

cc:
Original
HFD-120/Div. Files
HFD-120/Katz/Levin
HFD-120/Guzewska/Zarifa/Christodoulou
HFD-120/Chen

draft: lyc/February 3, 1999
final: 2/9/00

C:/wpfiles/tizan.nda/s4lbl_rev.doc

CSO REVIEW

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA/IND #:	N20-397/SCM-004
DATE:	01-FEB-2000
PRODUCT NAME:	Zanaflex®
FIRM NAME:	Elan Pharmaceuticals Inc.
SUBJECT:	Request for information on the package insert
CONVERSATION WITH:	Ms. Octavia Norris
TELEPHONE #:	650-794-5757

01-FEB-2000 I contacted Ms. Norris of Elan, to clarify:

1. Are the tablets embossed with the Athena logo and "592" or "A592" as in the appearance specification?
2. Has the package insert been printed yet?
3. Is revision of the storage statement to "Store at 25° (77°F); excursions permitted to 15-30°C (59-86°F)", possible?

01-FEB-2000 Ms. Norris left me a message with the requested information:

1. The tablets are embossed with "A592" and "A594" respectively for 4 mg, as in the appearance specification.

2&3. A supply of package insert has already been printed; the firm is planning to exhaust the supply and make the recommended revisions during printing of the next lot.

02-FEB-2000 4. In the absence of Ms. Norris I spoke with Ms. Louise Johnson, (650-794-5709) in order to verify if the 2 mg tablets were [ ] (appearance spec., original N20-397/SCM-004). Ms. Johnson (Director, Reg. Affairs) sent a 13-page fax with the drawings of the tablets and the current appearance specification, where they are described as [ ].

The appearance specification terminology is inconsistent with the description in the original submission and also inconsistent with the single score on the 2 mg tablets. Further revisions/clarifications are required.

D. Christodoulou

D. Christodoulou, Ph.D., Chemist

cc. Orig. NDA 20-397/SCM-004
HFD-120/Division File
HFD-120/DChristodoulou
HFD-120/LChen
HFD-120/MGuzewska
R/D Init. by: MG 2/3/00

Filename: N20397S004.3t.doc

MEMORANDUM

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

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

Date: February 3, 2000
From: Randy Levin, M.D., Neurology Team Leader
Subject: Zanaflex NDA 20-397 Supplement 004
To: File

Background

Zanaflex 4 mg tablet was approved in November 1996. The sponsor submitted supplement 004 on February 24, 1999 to add a 2 mg tablet. A not approvable letter was sent on June 23, 1999. The not approvable action was discussed with the sponsor on July 16, 1996. This October 4, 1999 submission is a response to the not approvable letter.

Chemistry and biopharm issues

Following review of the submission, the chemists (Drs. Zarifa and Guzewska) and biopharm reviewers (Drs. Zhao and Baweja) now recommend that the supplement be approved.

The chemists found the submitted manufacturing process description and in process controls and tests in agreement with the batch records. This information was not provided in the original submission. The biopharm reviewers concluded that the sponsor now satisfactorily demonstrated that the both tablets rapidly dissolving in 0.1 N HCL and provided information from an in vivo study to demonstrate bioequivalence between the 2 and 4 mg tablets. Both of these factors were not adequately addressed in the original submission. The biopharm reviewers requested that the sponsor adopt their specified dissolution methods and specifications.

Labeling

The sponsor provided an updated package insert following our request. Dr. Guzewska also reviewed this labeling along with the draft carton and container labeling and agreed with the changes except for minor changes regarding storage temperatures.

The package insert was also reviewed by the project manager, Ms. Chen who found the text to be the same as the labeling provided in the March 27, 1998 periodic report and subsequent annual report with the exception of the addition of wording for the new 2 mg dosage strength in the description and how supplied section. It should be noted that the labeling text added in the periodic and annual report includes text changes that the division previously agreed to including information about spasm counts, clarification of the indication section, clarification of asthenia adverse event classification, and additional precautions.

Recommendation:

The 2 mg tablet strength should be approved with the changes to labeling recommended by Dr. Guzewski. In addition, Drs. Zhou and Baweja's requested dissolution methods and specifications should be conveyed to the sponsor.

Randy Levin, M.D.
Neurology Team Leader

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-397/S-004

CORRESPONDENCE

fax

élan
pharmaceuticals

800 Gateway Blvd
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-7699

Maria Guzewska

To: Danae Christodoulou

From: Louise Johnson

Re: Zanaflex 2mg Tablet

Fax: 301-594-2859

Date: Feb. 2, 2000

Page: 8 total

The original documents will be sent via FedEx tomorrow as a formal submission.

If transmission was faulty, please call 1-650-877-0900.

élan
pharmaceuticals

Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

February 2, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Document Control Center (HFM-99), Room 200N
Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20852-1448

Attn.: **Russell G. Katz, M.D.**
Director
HFD-120

Subject: **Zanaflex® (tizanidine HCl)**
NDA 20-397
Response to FDA Request

Dear Dr. Katz:

Please refer to the supplement (S-004) to the NDA to add a 2 mg dosage strength. The supplement was submitted to the Agency on February 24, 1999. Please also refer to telephone conversations with Drs. Danae Christodoulou and Maria Guzewska of the Division today.

This letter responds to their requests for clarification of the description of the 2 mg tablet and its appearance specification.

1. All experiments conducted with the 2 mg tablet have used the tablet with a single score on one side (release testing, stability studies and the bioequivalence study number DS-008).

2. The current 2 mg tablet appearance specification refers to the 2 mg tablet as [ ]. In response to today's requests, we propose to revise the terminology as indicated in the following table, to reflect the nomenclature defined in the "Tableting Specification Manual" (previously referred to as the IPT Standard Specifications for Tableting Tools). Copies of pertinent pages from this book are attached following this letter.

If you have any questions or comments, please contact me at (650) 794-5709 or (800) 435-5108. I can be reached via pager at (888) 515-2869. Alternatively, I can be reached by facsimile at (650) 616-5053.

Sincerely,

Louise C. Johnson

Louise C. Johnson
Director, Regulatory Affairs

3 page(s) have been removed from this portion of the review to comply with copyright laws.

Correspondence - Response to FDA Request 2/02/00

fax

élan pharmaceuticals

800 Gateway Blvd.

South San Francisco, CA 94080
Telephone (800) 435-5108
Fax (650) 616-5053

To:	Lana Chen	Fax:	301-594-2858
From:	Octavia Norris	Date:	February 1, 2000
RE:	Zanaflex® 2 mg Tablets	Pages:	6

Per your request, attached is the Zanaflex package insert that includes reference to the 2 mg tablet strength in the Header, Description and How Supplied sections.

If you have any questions or comments, please contact me at (800) 435-5108. Alternatively, I can be reached by facsimile at (650) 616-5053.

Regards,

Octavia Norris

5 page(s) of draft labeling has been removed from this portion of the review.

Correspondence- Zanaflex 2mg Tablets

2/01/00

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ORIGINAL

Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

SCM-004 (BL)
NDA SUPP AMEND

February 1, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Document Control Center (HFM-99), Room 200N
Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20852-1448

CENTER FOR DRUG EVALUATION AND RESEARCH

FEB 02 2000

RECEIVED HFD-120

Attn.: **Russell G. Katz, M.D.**
Director
HFD-120

Subject: **Zanaflex® (tizanidine HCl)**
NDA 20-397
Response to FDA Request

Dear Dr. Katz:

This is in reference to the supplement (S-004) to the NDA for Zanaflex to add the 2 mg dosage strength. The supplement was submitted to the Agency on February 24, 1999.

Pursuant to the request of Ms. Lana Chen of the Agency, the revised package insert for Zanaflex that includes reference to the 2 mg tablets in the HEADER, DESCRIPTION, and HOW SUPPLIED sections is provided on the following pages. Please incorporate this information in our file.

If you have any questions or comments, please contact me at (800) 435-5108. Alternatively, I can be reached by facsimile at (650) 616-5053.

Sincerely,

for Louise C. Johnson
Director, Regulatory Affairs

Enclosure

5 page(s) of draft labeling has been removed from this portion of the review.

Correspondence - Response to FDA Request (2/01/00)

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800 Gateway Blvd., South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

NDA SUPP AMEND
(BB)
SCM-004
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CENTER FOR DRUG EVALUATION
AND RESEARCH

DEC 02 1999

RECEIVED HFD-120

December 1, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Document Control Center (HFM-99), Room 200N
Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20852-1448

Attn.: **Russell G. Katz, M.D.**
Director
HFD-120

Subject: **Zanaflex® (tizanidine HCl)**
NDA 20-397
Response to FDA Request

Dear Dr. Katz:

Please refer to a voice message today from Dr. Ray Baweja to Dr. Jaymin Shah of Elan Pharmaceuticals, Inc. Dr. Baweja requested a copy of the dissolution method used for Zanaflex tablets.

Enclosed are copies of the dissolution methods used for the 2 mg and 4 mg tablets. These are copied from the submission of March 31, 1999.

If you have any questions or comments, please contact me at (800) 435-5108. Alternatively, I can be reached by facsimile at (650) 616-5053.

Sincerely,

for Louise C. Johnson
Director, Regulatory Affairs

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800 Gateway Blvd., South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

NDA SUPP AMEND

SCM-004 (AC)

ORIGINAL

October 4, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Document Control Center (HFM-99), Room 200N
Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20852-1448

Attn.: **Russell G. Katz, M.D.**
Acting Director
HFD-120, Room 10B45

Subject: **Zanaflex® (tizanidine HCl)**
NDA 20-397
Response to Not Approvable Letter

Dear Dr. Katz:

Reference is made to the supplement to New Drug Application 20-397 for Zanaflex® (tizanidine hydrochloride) 2 mg tablets, which was submitted to the Agency February 24, 1999. Reference is also made to the Not Approvable letter from the Agency dated June 23, 1999 and the meeting of July 16, 1999 with Dr. Ray Baweja and Ms. Lana Chen of the Agency. At this time, we wish to respond to all comments presented in the Not Approvable letter.

This submission includes additional dissolution data for the 2 mg and 4 mg tablet dosage strengths, in addition to Chemistry, Manufacturing, and Controls (CMC) information for the 2 mg drug product (Appendix 2). The CMC information is provided since the Novartis Drug Master File (DMF# 9242) does not contain information in regard to the tizanidine drug product.

Effective January 1, 1999, Athena Neurosciences, Inc. (Athena) transferred NDA ownership and all rights to its wholly owned subsidiary Elan Pharmaceuticals, Inc. (Elan). Consequently, Athena and Elan are used interchangeably until all documentation (e.g., DMF authorization letters) has been updated to carry the Elan designation.

Should you have any questions pertaining to this communication do not hesitate to contact Octavia Norris at (650) 794-5757 or me at (650) 794-5709. Alternatively, we can be reached at (800) 435-5108 or by facsimile at (650) 616-5053.

Sincerely,

Louise C. Johnson

Louise C. Johnson
Director, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-397/S-004 & S-005

Elan Pharmaceuticals, Inc.
800 Gateway Boulevard
South San Francisco, CA 94080

MAR 11 1999

Attention: Louise C. Johnson, Associate Director

Dear Ms. Johnson:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zanaflex

NDA Number: 20-397

Supplement Number: S-004 & S-005

Date of Supplement: February 24, 1999

Date of Receipt: February 26, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 27, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Attention: Document Control Room, HFD-120
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

for John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-397/S-004 & S-005
HFD-120/Div. Files
HFD-120/CSO/Chen

filename:

SUPPLEMENT ACKNOWLEDGEMENT

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800 Gateway Blvd., South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

February 24, 1999

NDA SUPPLEMENT

NDA NO. 20-397 REF NO. SCM-004 SCM-005
NDA SUPPL FOR Manufactur

CENTER FOR DRUG EVALUATION
AND RESEARCH

FEB 26 1999

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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
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Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20852-1448

Attn.: **Russell G. Katz, M.D.**
Acting Director
HFD-120, Room 10B45

Subject: **Zanaflex® (tizanidine HCl)**
NDA 20-397
Prior Approval Supplement

Dear Dr. Katz:

Reference is made to the New Drug Application, 20-397, for Zanaflex® (tizanidine hydrochloride) 4 mg tablets, which was approved by the Agency November 27, 1996. At this time, we wish to add a 2 mg tablet dosage strength. The 2 mg tablet is made by the same manufacturer of the currently approved 4 mg tablet, Novartis Pharma AG, Basel, Switzerland. Zanaflex 2 mg tablets are produced from the same components and have the same qualitative composition as the marketed 4 mg tablets. [ ]. The expected use of the 2 mg tablet will be in the early stages of treatment of spasticity to allow patients to titrate more slowly to a clinically effective dose and thereby minimize side effects. Information to support the addition of the 2 mg tablet is provided pursuant to the proposal submitted to the Agency on September 5, 1997. S-004

Information is also provided to add an alternate packaging site for commercial product. Elan Holdings, Inc., Gainesville, Georgia will perform the packaging operations for the 2 mg and 4 mg tablets (refer to Section 2.C, METHOD OF MANUFACTURE AND PACKAGING). S-005

Effective January 1, 1999, Athena Neurosciences, Inc. (Athena) transferred NDA ownership and all rights to its wholly owned subsidiary Elan Pharmaceuticals, Inc. (Elan). Consequently, Athena and Elan are used interchangeably until all documentation has been updated to carry the Elan designation.

Should you have any questions pertaining to this communication do not hesitate to contact Octavia Norris or me at (800) 435-5108. Alternatively, we can be reached by facsimile at (650) 877-7699.

Sincerely,

for Louise C. Johnson
Associate Director, Regulatory Affairs

élan
pharmaceuticals

800 Gateway Blvd., South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

March 31, 1999

ORIGINAL

Food and Drug Administration
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Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20852-1448

Attn.: **Russell G. Katz, M.D., Acting Director**
HFD-120, Room 10B45

NDA SUPP AMEND

Subject: **Zanaflex® (tizanidine HCl)**
NDA 20-397
Response to FDA Request

SCH-004-(BB)
SCH-005-(BB)

Dear Dr. Katz:

Reference is made to the supplement to New Drug Application 20-397 for Zanaflex® (tizanidine HCl), which was submitted to the Agency February 24, 1999. This supplement contained a request to add a 2 mg tablet dosage strength of tizanidine HCl. Reference is also made to the teleconference of March 18, 1999 between Dr. Ray Baweja and Dr. Hong Chao of the Agency and representatives from Elan Pharmaceuticals, Inc. (Elan).

At this time, we wish to provide a response to the requests made by Dr. Baweja and Dr. Chao. Each item is listed below in bold type, followed by Elan's response.

1. Request a waiver of in vivo Bioavailability/Bioequivalence studies.

Elan requests FDA to waive the requirement for submission of evidence demonstrating the in vivo bioavailability or bioequivalence of the Zanaflex 2 mg tablet. Refer to Attachment 1 for the waiver request.

For your information, Elan is also providing a desk copy of the following volumes of the original NDA submission for Zanaflex 4 mg tablets. These volumes contain the bioavailability/bioequivalence studies submitted in support of the original NDA, which include those studies referenced in Volume 2, Section 4, page 309 of the February 24, 1999 NDA supplement.

Volume 1.19 Volume 1.36
Volumes 1.21-1.26 Volume 1.114

2. Provide quantitative and qualitative formula for the 4 mg tablet.

The qualitative composition of Zanaflex 2 mg and 4 mg tablets is as follows:

Tizanidine hydrochloride
Silica, colloidal anhydrous, NF
Stearic acid, NF
Cellulose, microcrystalline, NF
Lactose, anhydrous, NF

The quantitative compositions of Zanaflex 2 mg and 4 mg tablets are presented in Table 1 below.

Table 1: 2 mg and 4 mg Tablet Composition

Ingredients	**Grade**	**Weight (mg) /Tablet**	**Weight (mg) /Tablet**
Active ingredient		**2 mg**	**4 mg**
Tizanidine hydrochloride	In-house	2.29	4.58
Inactive Ingredients			
Silica, colloidal anhydrous	USP23 NF18	[redacted]	[redacted]
Stearic acid	USP23 NF18		
Cellulose, microcrystalline	USP23 NF18		
Lactose, anhydrous	USP23 NF18		
Total		**160.00**	**220.00**

3. Provide documentation of the current dissolution method for the 4 mg tablet.

The dissolution specification is the same for the 2 mg and 4 mg tablet strengths. The dissolution procedures are the same, except for the sample analysis. An UV spectrophotometer is used in the sample analysis of the 2 mg tablets. An HPLC system is used in the sample analysis of the 4 mg tablets. The analytical methods for dissolution testing of the Zanaflex 2 mg (AAM-002-00469) and 4 mg (AAM- 002-00056) tablets are provided as Attachment 2.

4. Provide written confirmation of the "new process" (i.e., new drug synthesis) referred to in Volume 2, page 311 of the supplement dated February 24, 1999.

Due to a change in environmental regulations in Switzerland, Novartis made a slight modification in the drug substance synthesis for tizanidine. Early in the synthesis, [redacted] was substituted for [redacted].

Data were presented in supplement S-001 to the FDA on March 7, 1997 to support the comparability of the drug substance manufactured from the "new" and "old" processes. This supplement was approved by the Agency on September 2, 1997. Attachment 3 contains a copy of the approval letter for supplement S-001.

5. Provide individual unit data for the batches provided in the dissolution data included in the 2 mg sNDA (submitted February 24, 1999, Volume 2, Page 311). Give the number of units tested per batch. Include a dissolution comparison using the f_2 equation to show the profiles of the 2 mg and 4 mg tablets are similar. Also, include a plot of dissolution profiles.

The dissolution data included in this supplement were provided by Novartis Pharma AG. Because we do not have immediate access to the individual unit data, Elan conducted a dissolution comparison of the 2 mg and 4 mg tablets. The Zanaflex lots used in this study were manufactured using the new drug substance synthesis. Refer to Attachment 4 for the dissolution comparison.

Should you have any questions pertaining to this communication do not hesitate to contact Octavia Norris or me at (800) 435-5108. Alternatively, we can be reached by facsimile at (650) 616-5053.

Sincerely,

Octavia Norris

for Louise C. Johnson
Associate Director, Regulatory Affairs