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NDA-020397

FIRM: ATHENA NEUROSCIENCES

1 OF 7

TRADE NAME: ZANAFLEX ORAL TABS. 4MG

GENERIC NAME: TIZANIDINE HCL

Summary Basis of Approval
Cover Form

Appl #: 020397

Firm: ATHENA NEUROSCIENCES

Reviewing Div: 120

Trade Name: ZANAFLEX (TIZANIDINE HCL) ORAL TABS. 4MG

Generic Name:

TIZANIDINE HCL

Approval Letter: Y

Statistician Review: Y

SBA Form: N

Bio/Dissolution Review: Y

Final Printed Labeling: N

Microbiologist Review: N

Medical Officer Review: Y

NAS/NRC Review: N

Chemist Review: Y

Pharmacologist Review: Y

Federal Register Notice: N

Completion Date: 11-APR-97

20397

Zanaflex

Approval Letter And Related Correspondence



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 27 1986

NDA 20-397

Athens Neurosciences, Inc.
Attention: Ms. Kathy Dumas
800F Gateway Blvd
South San Francisco, CA 94070

Dear Ms. Dumas:

Reference is made to your new drug application dated December 3, 1983 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Zanaflex® (tizanidine hydrochloride) 4 mg Tablets

We also acknowledge receipt of the following amendments and correspondence which were submitted in response to our "approvable" letter of March 11, 1986

03-12-86	08-26-86	10-09-86	10-28-86
05-01-86	09-12-86	10-10-86	10-29-86
06-03-86	09-23-86	10-23-86	11-01-86
08-09-86	10-04-86	10-25-86	11-05-86

This new drug application provides for the following indication:

Tizanidine is a short acting drug for the acute and intermittent management of increased muscle tone associated with spasticity.

We have completed the review of this application including the enclosed draft labeling 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 draft labeling included with this letter (Attachment 1). Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (Attachment 1). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen 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

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designated "FINAL PRINTED LABELING" for approved NDA 20-397. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

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Please submit one market package of the drug when it is available

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

If you have questions, please contact:

**Ms. Katurah Higgins, R.Ph.
Project Manager
(301) 594-5504**

Sincerely yours,

Robert Temple 11/27/96

**Robert Temple, M.D.
Director
Office of Drug Evaluation and Research
Center for Drug Evaluation I
Center for Drug Evaluation and Research**



NDA 20-397

Athena Neurosciences, Inc.
Attention: Ms. Kathy Dumas
800F Gateway Blvd.
South San Francisco, CA 94080

MAR 11 1996

Dear Ms. Dumas:

Please refer to your New Drug Application (NDA) dated December 3, 1993 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zanaflex™ (tizanidine hydrochloride) 4 mg Tablets.

We also refer to your submissions dated December 14, 1994, January 4, 13, 16, 20, and 24, 1995 and February 3 and 8, 1995, received prior to the not approvable letter dated March 6, 1995 but received during the ninety-day extension period granted to your application under the User Fee Act and therefore not considered in our March 6, 1995 not approvable decision.

We further refer to your subsequent submissions dated March 10, May 2, June 2, July 19, August 7, September 8 and 11, October 10, 18, and 27, and November 27 and 30, 1995.

GENERAL

We have completed our review of this application and find that it is approvable for the management of spasticity provided that Zanaflex is marketed under the conditions of use described in the draft labeling attached to this letter. Why we have modified your proposal for product labeling in the manner that we have requires explication.

Effectiveness issues:

The results from study 005 suggest that a single dose of 8 or 16 mg effectively reduces muscle tone. The effects appear to begin within one hour, peak after 2 to 3 hours and essentially disappear within 6 hours. Study 003 in patients with spinal cord injury supports a similar conclusion. Although the recommended tid dosing regimen has not been shown to reduce muscle tone over the entire dosing interval, your consultants argue persuasively that a treatment providing even a relatively short term reduction of muscle tone can be of benefit as a part of the overall management of some individuals with spasticity. For example, a reduction in muscle tone of the kind demonstrated in clinical trials may help some patients

transfer from bed to wheelchair, or participate more effectively in physical therapy. An implication of this is that Zanaflex needs to be thought of as a drug for repeated single dose use, with use targeted to specific intended benefits over a few hours, rather than as round the clock treatment for spasticity.

We remain uncertain moreover, about the extent of the benefit that will be provided to the typical patient with spasticity of spinal cord origin.

The studies providing evidence of effectiveness do not provide an estimate of the proportion of patients treated with tizanidine who are likely to experience a net clinical benefit from its muscle tone reducing effects. A reduction in muscle tone may be valuable but can be harmful (e.g., interfere with walking, standing) in some patients. Moreover, even in patients who benefit from a reduction in muscle tone, the side effects caused by tizanidine may be so severe as to outweigh that benefit. For example, hypotension, seen in a substantial proportion of patients at the doses recommended in labeling, and at least sometimes orthostatic, may prevent patients from being able to maintain an upright position. Sedation, also common, may impair cognitive function, even interfere with a patient's capacity to participate in physical therapy sessions.

Accordingly, although Zanaflex may be approved for use in the management of patients with spasticity of spinal cord origin, it is critical that labeling make clear to prescribers the mix of benefits and risks its use imposes.

Safety issues:

Zanaflex is not a risk free drug. Its use, as your clinical development program documents, is associated with a high incidence of dysphoric, even disabling, side effects. As a consequence, many patients, even on a regimen of slow titration to dose, may be unable to tolerate effective doses of the drug. Labeling must alert prescribers to this problem.

Furthermore, Zanaflex has not been extensively studied at the doses that have been shown in controlled trials to produce an effect on muscle tone of a size that may be useful for some patients. Thus, we must alert prescribers to the limited assurance that can be given concerning Zanaflex's safety for use in the management of spasticity. Only 350 patients in the database have been exposed to one or more daily doses of 24 mg or more. Fewer than 170 patients have been exposed to this dose or greater for 3 months, and only 75 patients have been exposed for at least 3 months to doses of 36 mg or more per day. Thus, Zanaflex

might cause serious adverse events at relatively high incidence post marketing that were not detected even once in the course of its premarketing development. Labeling must provide a clear warning of this possibility.

We realize you believe our concerns about the safety of Zanaflex are unwarranted because Zanaflex has been marketed widely throughout the world for a number of years. We find this experience less reassuring than you do because most such use has been at much lower doses than will be recommended in Zanaflex's U.S. labeling.

Post Marketing Study Commitment:

Because of the limited information available about the risks of tizanidine under the actual conditions of its use, and uncertainty about the link between dose and reductions of muscle tone, we seek a commitment from your firm to conduct, post-approval, a dose response study that will examine the effectiveness, within individuals, of a wide range of doses (e.g., a crossover study examining the effects of single doses of 2 mg, 4 mg, 8 mg, and 12 mg of tizanidine).

In addition, it is critically important to gain additional experience with patients treated with tizanidine at the highest recommended dose of 36 mg a day. A cohort of patients titrated to 36 mg and followed for several months would provide valuable information. The clearly superior single-dose effect of 16 mg in Study 005 also suggests further study of that dose, especially in repeated doses.

Labeling:

With regard to the draft labeling attached to this letter, when specific wording is employed, please use the text verbatim, save for minor matters of grammar or style. Additional requests for proposed wording as well as for analyses to support other necessary statements are embedded within the text of the proposed labeling. Also, please revise the draft labeling to include those important adverse events not currently in labeling but that have been reported since your last safety update.

BIOPHARMACEUTICS

We have the following comments and requests for information that should be addressed:

1. You have investigated the potential for inhibition of the major CYP450 isoforms following tizanidine administration, which will aid in predicting the potential *in vivo* drug interactions. However, isoenzymes involved in the metabolic oxidative processes of tizanidine have not yet been determined. You are requested to investigate and fully characterize the isoenzymes involved in the metabolic processes of tizanidine, *in vitro*.
2. Please provide information regarding ethnic differences on the pharmacokinetics and pharmacodynamics of tizanidine.

FOREIGN REGULATORY UPDATE/LABELING

We require a review of the status of all tizanidine actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us current foreign labeling for tizanidine, along with the English translations when needed. If tizanidine labeling is uniform worldwide, it would, of course, be sufficient to provide only the English translation of that standard labeling.

UPDATE OF LITERATURE

Please review and provide a summary of all published reports bearing on the safety and effectiveness of tizanidine that have appeared since your last comprehensive review. Please alert us to any reports of adverse events or reactions that have not previously been reported in association with its use.

SAFETY UPDATE

Please submit a Safety Update. In the update, please include only a cumulative report of serious adverse events and deaths, as well as any other adverse events, serious or not, that have not been previously reported.

MISCELLANEOUS

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and package insert to the Division of Drug Marketing, Advertising, and Communications, HFD-140.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with the Division to discuss what further steps are needed to secure approval. At least 15 days advance notice should be given for said conference.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, the FDA may take action to withdraw the application. Any amendment should respond to any deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies, if any, have been addressed.

The drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

If any questions should arise concerning this NDA, please contact Mr. Grilley, Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enc: Draft labeling



NDA 20-397

MAR - 6 1995

Athena Neurosciences, Inc.
Attention: Kathy Dumas
800F Gateway Blvd.
South San Francisco, CA 94080

Dear Ms. Dumas:

Please refer to your New Drug Application (NDA) dated December 3, 1993 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zanaflex™ (tizanidine hydrochloride) 4 mg Tablets.

We acknowledge receipt of your additional communications (see Enclosure 1).

We also acknowledge the following submissions as correspondence to your NDA :

December 14, 1994, January 4, 1995, January 13, 1995, January 16, 1995, January 20, 1995, January 20, 1995, January 24, 1995, February 3, 1995, and February 8, 1995.

Please note, these submissions were received during the ninety-day extension period granted to your application under the User Fee Act and were not considered in our decision. These submissions need not be resubmitted in your response but may be incorporated by reference.

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

Effectiveness in use:

Under section 505(d) of the Act and 21 CFR 312.125(b), you have failed to provide substantial evidence consisting of adequate and well controlled studies, as defined in 21 CFR 314.126, that Zanaflex™ will have the effect it is represented to have under the conditions of use prescribed, recommended or suggested in its proposed labeling.

Your application identifies the results of three controlled clinical investigations, studies 021-001, 021-003, and DS-0502, as the sources of substantial evidence of tizanidine's effectiveness in the management of spasticity of spinal cord origin.

Although these studies provide some evidence of pharmacologic activity, they do not demonstrate tizanidine's effectiveness as a treatment of spasticity of spinal cord origin because the results are inconsistent and because the findings, even if accepted at face value, do not clearly represent a meaningful clinical benefit in the patients studied. There has, in addition, been little attempt to discover the dose-response relationship of tizanidine for its beneficial and adverse effects.

1. Measures of Effectiveness:

It is not clear that the outcomes measured in the three studies, and found to differ to a statistically significant degree between tizanidine and placebo treated patients, are valid measures of the efficacy of a drug product identified as a treatment for spasticity of spinal cord origin.

Evidence of a pharmacologic effect, even one potentially pertinent to a disease, does not necessarily imply clinical value. Spasticity, for example, can be a clinical problem but can also allow certain activities to be carried out. It is therefore important, and this was considered in pre-NDA discussions about tizanidine's development in 1992, that outcome measures in clinical trials of tizanidine not only have the capacity to show that tizanidine exerts an effect on a widely recognized measure of spasticity, (e.g., the Ashworth scale), but also be able to show that the drug produces a clinically meaningful effect. This assessment strategy is similar to one developed for the assessment of antidementia drug products, in which a dual measure of outcome is used: a measure of cognitive performance (e.g., the ADAS cog) and a measure of clinical utility (e.g., a clinician's global or ADL assessment).

In our discussions, we indicated that spasm frequency might serve as a measure of usefulness, but even more pertinent would be ADL assessments and global assessments that took into account the patients' overall clinical state.

None of the 3 studies identified as pivotal in your application prospectively designate a compound measure of effectiveness of the sort recommended and, in general, did not show effects on both the Ashworth scale and such other measures. Study DS-502, for example, which reported a significant effect on the Ashworth scale, found no effect on spasm frequency, pain and disability due to spasm, in patients' global assessment, ADL, walking time, or muscle strength. There was a reported effect on the prescriber's global but, as will be explained below, there is concern about potential bias in this evaluation. Study 021-001 showed a borderline effect on spasm frequency, despite showing no effect at all on the Ashworth scale, and no effect on ADLs or the blinded assessor's global. There were reported effects on patients' and prescriber's global evaluations, but potential bias in these evaluations is a concern. Study 021-003 reported an effect on the Ashworth scale, but no effect on spasms and no effect on patient or therapist global scores, or on pain and disability due to spasm or ADL.

2. Consistency of Evidence:

Even if we were to accept your view that a single outcome measure (the Ashworth scale) is a sufficient basis for approval, the evidence would still not be deemed substantial. Our examination of the evidence reveals an important internal inconsistency that undermines this case for effectiveness: specifically, the two, seemingly identically designed studies, DS-0502 and 021-001, that evaluated tizanidine's effects on spasticity in patients with multiple sclerosis provide conflicting results.

Study 021-001 is virtually identical in design to study DS-502. This was not accidental. Study 021-001 was conducted in an effort to replicate and confirm the positive findings of DS-502 in

spasticity occurring in patients with multiple sclerosis; it failed to do so. This does not seem to be a matter of study size or random differences. Patients assigned to placebo actually fared better than those randomized to tizanidine as assessed by the Ashworth scale.

Studies DS-502 and 021-001, although very similar, differed in one critical respect. In DS-502, Ashworth scores are based on clinical examinations made by physicians who were responsible for the management of the patients over the course of the clinical trial. In 021-001, because it was recognized that side effects of tizanidine could unblind observers, assessments were based on examinations made by independent physicians who had no responsibilities for the care and management of the patients in the study. This difference may explain the discrepant results of the studies. Investigators who have conducted clinical trials with tizanidine report that it is virtually impossible to maintain a treatment blind because of the characteristic profile of side effects (dry mouth, somnolence, and asthenia) exhibited by patients on the drug (e.g., see the discussion section on pages S42 and S43 of the special supplement (#9) to the November 1994 issue of Neurology; it addresses this point explicitly.).

Accordingly, there is good reason to be concerned that penetration of the treatment blind allowed a systematic bias to affect the Ashworth scale ratings, which are at least somewhat subjective, in Study DS-502. We sought to assess the likelihood of this bias by examining the level of improvement observed among placebo patients exhibiting and not exhibiting side effects. We reasoned that if such a bias were operative, the magnitude of favorable change would be greater among placebo recipients reporting adverse events than those not reporting them. This reasoning proved correct; in Study DS-502, patients on placebo who reported AE were observed to improve almost twice as much on average than those who did not. Furthermore, the relationship between improvement and side effect occurrence was not observed to a similar extent among patients randomized to placebo in either study 021-001 or 021-003.

In light of these observations, Study DS-502 cannot be viewed as an adequate and well controlled clinical investigation. By regulation, [21 CFR 314.126(b)(5)] an adequate and well controlled trial employs "adequate measures ...to minimize bias on the part of subjects, observers and analysts of the data." Study DS-502 fails to meet this standard because it did not take appropriate steps to keep assessors from becoming aware of treatment assignment.

Study 021-003 did find an effect by a blinded assessor and is a potential source of substantial evidence supporting the effectiveness of tizanidine. Its findings, however, are not persuasive. The assessor was a physical therapist who was responsible for completing the ADL by interviewing the patient. This level of communication might have unblinded this observer. Moreover, although there was a greater reduction in Ashworth scores and the frequency of daytime spasms in the tizanidine group when compared to placebo, the reduction of spasms over the entire plateau phase of the study was not statistically significantly different. Furthermore, as noted above, there were no statistically significant differences in favor of the drug on the other assessments of functional improvement including the global assessments by the blinded assessors or by the patients themselves.

In sum, we are unable to conclude that the NDA provides substantial evidence of tizanidine effectiveness in the treatment of spasticity. I should note also that the studies all use a titrational

design that tends to obscure dose-response relationships. This will be discussed further below.

Safety In Use

Under section 505(d) of the Act and 21 CFR 314.125(b), there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

a. Safety reports: Clinical experience

The application does not contain sufficient information on the use of the drug at the doses that your data, if accepted, suggest would be needed. Although the labeling submitted in the NDA proposes recommendations for dosing of 12 to 24 mg/day, these recommendations do not correspond to the doses used in the studies you identified as documenting the effectiveness of the drug; in these studies patients could be titrated to 36 mg. In study 021-003, for example, only 10% of patients received 24 mg or less, the mean plateau dose was 32 mg/day and 69% of patients received 36 mg/day. Thus, there must be evidence that 36 mg of tizanidine can be used safely in chronic use.

The evidence you have presented does not appear to reflect exposure of a reasonable number of patients treated in the 30 - 36 mg range for 6 - 12 months. I should note that we did advise you, prior to the submission of the NDA, to provide an accounting of the extent of experience with tizanidine, not only by numbers of individuals exposed over time of use, but by numbers of individuals exposed in various dose ranges. No such analysis has been provided. Accordingly, we are unable to determine precisely what experience you have, although as noted, exposure at the relevant doses seems insufficient.

I should note that concern about these higher doses may not be necessary. Your studies all used a titration design that would have obscured any dose-response relationship if one existed. There has been no attempt to examine effects over time to see if there is any evidence of greater effect with time; although such an analysis of titration studies confounds dose and time effects, it might be informative. For example, if no added effect is seen with time, this could suggest higher doses are not necessary. Please consider, in developing further evidence of effectiveness, use of a randomized, parallel, dose-response study design to relate favorable and unfavorable effects to dose. In a similar case, it has been possible to separate the therapeutic and toxic effects of the antihypertensive central alpha agonist, guanfacine.

I should add that the seeming 'safe passage' inferred from the benign profile of post-marketing experience gained with tizanidine in countries where it has been marketed largely is irrelevant to our evaluation of the safety of tizanidine for the indication you propose in the current application. Post-marketing experience in other countries has been gained at much lower doses than those likely to be employed if the product is marketed domestically.

b. Safety reports: Preclinical

There is insufficient data to evaluate the adequacy of the carcinogenicity studies in predicting risk to humans due to the differences in metabolic profiles across species. In order to determine the adequacy of these studies, the extent of exposure in humans and in the mouse and rat to both the parent drug and the major human metabolites at steady state must be known. Except for the parent drug in humans, you have not provided this data in your application.

We requested in August of 1994 that you measure plasma levels of the parent and its major metabolites in the ongoing rat 6 month toxicity study and that you conduct a 4-6 week toxicokinetic study in mice. In recognition of the likelihood that rodent and human exposure will not be very similar for all or most metabolites, we also requested that you conduct specific gene mutation assays (Ames and mouse lymphoma) for metabolites 3, 4, 9, and 10. We will be pleased to discuss with you whether the latter can substitute for some or all of the metabolite data.

Please note, we conducted a recent literature search and found two references describing the synthesis of metabolite 10. (P. Koch, D.R. Hirst and B.R. von Wartburg: *Biological Fate of Sirdalud in Animals and Man*, *Xenobiotica*, 1989, 19(11), 1255-1265. and P. Koch, J.J. Boeiserli, D.R. Hirst, and M.D. Walkinshaw: *A Novel Metabolic Pathway for Benzothiadiazoles: X-Ray Molecular Structure of 5-Chloro-4-(4,5-dihydroimidazol-2-ylamino)-1,3-dimethyl-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide*, *J. Chem.Soc.,Perkin Trans. 2*, 1990, 1705-1708.)

Chemistry and Manufacturing Controls

Under section 505(d) of the Act and 21 CFR 314.125(b) and in compliance with current good manufacturing practice regulations in 21 CFR 210 and 211, we cannot conclude that the methods, facilities, and controls used for the manufacture, processing, packing, or holding of the drug substance or the drug product are adequate to preserve its identity, strength, quality and purity of the product.

- a. Deficiencies described in our letters dated August 24, 1994 to Sandoz's DMF and August 25, 1994 to your NDA need to be addressed.
- b. Recently, our investigators made an inspection of Sandoz with respect to the applicable methods, facilities and controls, and observed a number of important departures from FDA current good manufacturing practice regulations. Sandoz was advised at that time of the deficiencies which need to be addressed.

Although not reasons for concluding that your application is not approvable, we have the following comments and requests for information that should be addressed:

Chemistry and Manufacturing Controls

1. Environmental assessment deficiencies described in our letter of September 13, 1994 and discussed in a meeting held between representatives of your firm and the Agency on October 25, 1994 need to be addressed.

Biopharmaceutics

1. Tizanidine undergoes extensive metabolism with multiple metabolites. Only four metabolites have been identified. Identified metabolites account for about 50% of the dose administered. The total radioactivity has a long half-life (43-90 hours) leading to concerns about accumulation of unidentified species. We strongly recommend that you identify these unidentified species.
2. Metabolite 10, which is a major metabolite in humans, has not been characterized for its activity. Therefore, you should ascertain the activity of major metabolite 10.
3. The specific enzymes involved in the metabolic oxidative processes have not yet been determined. The specific enzymes involved can predict drug-drug interactions and, in some cases, inter-individual differences in pharmacokinetics. Please investigate and fully characterize the enzymes involved in the metabolic processes of tizanidine. It may be possible to use in vitro methods for some of this characterization.
4. Since the drug undergoes extensive metabolism, the effect of liver disease on its pharmacokinetics should be investigated.
5. Please adopt the following dissolution methodology and specification for Tizanidine 4 mg tablet:

Medium:
Apparatus:
Specification:
6. Initially, the NDA contained several illegible and unreadable figures which upon request were corrected in your resubmission and all future submissions, please provide legible and readable figures.

Clinical

1. We request that you supply additional, detailed information on the number of patients receiving specific doses as well as the duration for which these patients have been exposed.
2. Please provide additional, detailed information to characterize the serious adverse events including deaths, hepatotoxicity, cardiovascular effects, psychiatric effects, hypersensitivity reactions and hematological reactions.

Within 10 days of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the

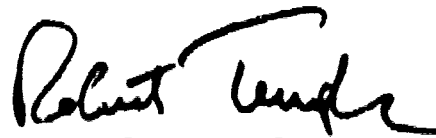
absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the invoice.

Should you have any questions, please contact:

Katurah H. Higgins
Consumer Safety Officer
Telephone #: (301) 594-2777

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure



NDA 20-397

Athena Neurosciences, Inc.
Attention: Ms. Kathy Dumas
800 Gateway Boulevard
South San Francisco, California 94080

AUG 25 1994

Dear Ms. Dumas:

Reference is made to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zanaflex™ (tizanidine hydrochloride) Tablets.

We have completed our review of the chemistry manufacturing and controls (CMC) section of your NDA and have found the following deficiencies which we request you respond to:

Drug Substance

Please note that comments and requests regarding the CMC for Tizanidine HCl drug substance will be communicated to Sandoz, the manufacturer and packager of the drug substance. In addition, the following deficiencies were identified in your submission:

1. We note several discrepancies between the values provided in NDA 20-397 (Athena) and DMF (Sandoz) describing the physical characteristics of Tizanidine HCl drug substance. Examples: pKa value and solubility data provided in Vol. 1.3 on pp. 10 and 9, respectively. Please clarify.
2. We note that the levels of impurities in Tizanidine HCl Lot No. 88006 reported on p. 17 in Vol. 1.3 differ from those provided by Sandoz in DMF. Please clarify.
3. We note that information on the container/closure system for the drug substance is incorrectly referenced to DMF. Specifications and testing methods for the will be requested directly from Sandoz.

Drug Product

1. To facilitate the evaluation of the production and controls of the drug product, please submit a copy (in English) of the actual records of the batch production and controls for representative batches used in pivotal clinical, or bioavailability/bioequivalency or primary stability studies. The records should include a description of the equipment used and information on the critical control parameters, i.e., cycle times, holding times between steps, operating temperatures, etc.

2. Please describe the in-process sampling plan for the proposed commercial scale batches. The plan should specify the number of samples, time point in the manufacturing process, and location where samples are collected. Test methods and limits of acceptance used during each stage of manufacturing and processing of Zanaflex Tablets should be fully described.
3. Please submit a proposal for reprocessing procedures for Zanaflex tablets. We recommend that all possible foreseeable deviations from specifications be covered (e.g., weight variation, content uniformity, moisture content, etc.) and the proposed reprocessing procedures be based on the manufacturing experience with Tizanidine HCl Tablets.
4. We have the following requests and comments regarding the analytical methods used to assess the identity, strength, quality, and purity of the drug product:
 - a. Identity: We request that a specific method for identification of Tizanidine HCl in Zanaflex Tablets be developed and validated. Please refer to the Agency Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances: "The specific identity test(s) (i.e., IR, NMR, and MS) should be capable of distinguishing the new drug substance from related compounds. If only one specific identity test is performed, an IR spectrum is preferred. Other identity tests (such as UV spectra, or relative mobility by various chromatographic methods are considered confirmatory rather than specific. Doing additional confirmatory tests is encouraged; however, doing several confirmatory tests will not substitute for a specific identity test." We note that you attempted to employ _____ as an additional test but found it not suitable. Since the description of the _____ you provided in the NDA submission is illegible, the suitability of the _____ for identification of Tizanidine HCl drug substance in the drug product can not be evaluated by the reviewer.
 - b. Assay: We request that a specific assay method(s) capable of separating Tizanidine HCl drug substance from all known by-products and excipients be developed and validated. We note that the currently used method is capable of separating Tizanidine from three known related compounds:

5. **Please provide the results of analytical testing for all batches of Tizanidine HCl tablets used in pivotal clinical, bioavailability and stability studies. We recommend that the following information be included: a. batch size, b. date of manufacture, c. date of latest analysis, and d. the results for all specifications (including the dissolution profile). We recommend that all dates be unambiguously given as, e.g., August 11, 1993, to avoid confusions which may result from the digital mode 08.11.1993 (or 11.08.1993 in Europe).**
6. **The provided description of the packaging component test procedures is ambiguous. In order to expedite the review process, we request a summary tabulation of the test procedures for the incoming packaging components performed before a given lot is accepted. The following information should be included: a. address of the testing facility; b. sampling frequency, and c. listing of all testing methods used for each component type, i.e., HDPE bottles, closures, and unit dose blister packs. We recommend that the test procedures for the incoming packaging components include both: the physicochemical tests of the components (according to USP <661> and <671>) and a material identity test (by IR). The testing methods should be either described or referenced (if compendial).**
7. **Please provide information on the stability batches (size, date of manufacture) used in studies conducted by**
8. **Please describe the analytical methods used for stability testing of the drug product.**

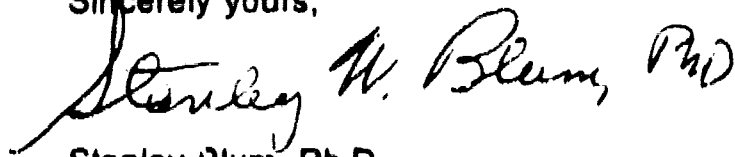
9. Please provide explanation of the following statement (Vol. 1.3, pp. 385 and 388):

e

es

If questions should arise concerning this letter, please contact Mr. Grilley, Regulatory Management Officer, at 301-594-2777.

Sincerely yours,



Stanley Blum, Ph.D.
Supervisory Chemist
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 11, 1996

FROM: Paul Leber, M.D.
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: Your memorandum of March 8, 1996 on NDA 20-397

TO: File, NDA 20-397 Zanaflex (tizanidine)
 &
 Robert Temple, M.D.
 Director,
 Office of Drug Evaluation 1

Your assertion that the Division waited until the "last minute" to 1) communicate its concerns about the limited amount of safety data provided in this NDA and 2) present its strategy for dealing with them through labeling is inaccurate.

You have known for well over a year that the information provided by the sponsor in this NDA concerning exposure to higher doses of Zanaflex is limited. Your issuance of the March 1995 not approvable action letter on this NDA, a letter which describes the agency's concerns about the limited safety information available, speaks to this point directly.

Moreover, prior to your recent trip, I told you explicitly that the Division, despite the team leader's recommendation to the contrary, would recommend approval of the NDA, provided the firm was required to adopt labeling for Zanaflex that 1) would take note of the limited experience gained with daily doses at the higher end of the recommended dosing range, and 2) calls attention to the limitations this less than robust experience imposes on the warrant of safety in use implied by the NDA approval.

I fail to understand, therefore, how you can assert that the Division brought a major problem to your attention at the last minute. Your schedule is exceedingly demanding, and you spend little of your time

meeting with me or my staff. In fact, over the last year, you have cancelled any number of scheduled "one on one's" with me. Accordingly, if you are not as well informed about the ongoing work of the division as you would like to be, the fault is hardly ours.

Given the work load faced by the Division, it was only through extraordinary personal effort that a review action package was available as soon as it was, 11 days prior to the PDUFA action date (on 2/26/96). I note that this falls just short of the two weeks that you regularly cite as all the time that you require to review an NDA package from our Division. Thus, I believe it was your trip, not our late delivery of the action package, that kept you from reviewing the NDA in a more timely fashion.

As to your specific comments and questions:

1. There is no reliable experience on which to assess the effects of the 16 mg dose which, as you are aware, was given at night in but one study. We chose, therefore, not to provide information about its benefits. Moreover, the data upon which the graph displayed in labeling is based reflects experience gathered in a laboratory experiment. It is difficult to know to what extent that experience reflects what is to be expected when that dose is used. Accordingly, we elected to display only the 8 mg data in an effort not to promote the use of a dose that may be too high for many.

2 and 3. I don't understand your point. We know relatively little about single daily doses greater than 8 mg. In fact, the only information I have about dosing and daily exposures comes from the firm's tables on the average plateau doses in the 3 randomized controlled trials. I reproduce it here:

dose	502	21-001	21-003	Total	cumulative
<8	4	5	0	9	9
8 to 12	6	7	3	15	24
13-16	6	12	1	19	43
17-20	10	12	1	23	66
21-24	12	4	2	18	84
25-28	7	12	5	24	108
29-32	3	7	6	16	124
33-36	30	32	26	88	212
>36	1	4	3	8	220

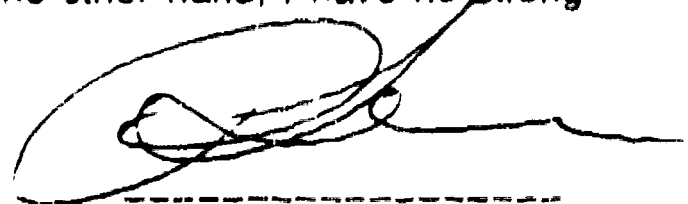
As you can observe, there are only about 96 patients who were maintained in the plateau phase of all three studies at the high end of the dosing range (e.g., greater than 33 mg/day).

As to whether or not the warning is "overdone," it's clearly a matter of personal sentiment. The team leader believes the application should not be approved. I take a different view, but only because I believe that what is or is not sufficient evidence to show that an effective drug product is "safe for use" is a more a political than a scientific or medical question. However, my personal quid pro quo for allowing effective products with limited clinical experience on the market is labeling that is candid about the limited amounts of information available, and the consequences of that limitation vis a vis any warrant of safety implied by the drug's marketed status.

Your stated reluctance "to ad hoc the use of the inverse rule of 3," makes no sense to me. It's no more than an innovative way to deal with a situation in which we making a drug available at a point where we have less information than we would ordinarily prefer to have about its safety in use. By the way, the rule applies to any binomial process in which one assumes that the proportion of patients suffering an event is fixed at some value, p . It has nothing to do with rarity, but is, admittedly, ordinarily used in such circumstances.

Conclusion:

As Office Director, you have the final say on whether, and if so under what conditions, this product can be approved for marketing. You have my recommendations; I stand by them. On the other hand, I have no strong objection to the approach you prefer.



Paul Leber, M.D.
3/11/96

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **February 21, 1996**

FROM: **Paul Leber, M.D.**
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: **Recommendation for Approvable Action**

TO: **File, NDA 20-397 Zanaflex (tizanidine)**
 &
 Robert Temple, M.D.
 Director,
 Office of Drug Evaluation 1

This memorandum conveys the Division's assessment of the Zanaflex NDA, resubmitted on 9/11/95.

BACKGROUND:

The sponsor's original NDA for Zanaflex as a treatment for spasticity (filed in December of 1993) was found not approvable (letter of 3/6/95) because, among other deficiencies, under the conditions of use proposed, 1) the evidence of effectiveness was inadequate¹ to show that the drug would be effective in use, and 2) there was inadequate clinical experience to support a conclusion that the drug would be safe for use under the

¹ See also, my memorandum to the file of February 10, 1995. The sponsor relied on 3 randomized controlled clinical studies. Upon review, the two conducted in patients with MS were determined to provide contradictory results. Specifically, DS-0502, in which there was evidence of penetration of the treatment blind, was positive; 021-001, in which there had been specific protocol described procedures to protect the blind, was a total wash. The third study, 021-003, which was conducted in patients with spinal cord injury, was positive. Our review team also had concerns about the validity of the outcome measures used to assess tizanidine's clinical effect, concerns of which the sponsor had been repeatedly advised during the drug's development, but had chosen to disregard. The division's concerns arose from our inability to know how, if at all, effects detected on the outcome measures employed, were linked to the clinical state of the patients being treated.

conditions of use at which it would have been necessary to recommend that it be used had the evidence of effectiveness been deemed substantial.

After the issuance of the not approvable action letter, representatives of the firm met (July 27, 1995) with Division staff and the Office Director. The firm argued that the agency's conclusion that tizanidine lacked effectiveness was manifestly incorrect. To support their argument they showed videotapes of patients with spasticity that had been made before and after they were treated with single oral doses of tizanidine.

These video clips left little doubt in the minds of those viewing them that the acute administration of tizanidine had a substantial effect on muscle tone in the patients presented. This did not answer the question, however, of how representative the changes shown on the tapes were of the expected effects of tizanidine in a typical patient with spasticity.

Moreover, the substantively more important question remained whether or not the effect observed was a clinically useful one. Although consultants who accompanied the sponsor to the meeting readily acknowledged the agency's point that it is critical to distinguish between a drug with an effect and an effective drug², they argued that, for at least for some patients with spasticity, tizanidine's acute effects on muscle tone would offer an invaluable clinical benefit (e.g., make possible transfer from bed to wheelchair without uncontrolled spasms).

Prior to the conclusion of the meeting, the Office Director agreed that an acute effect on muscle tone of the sort shown was an appropriate clinical endpoint and he invited the sponsor, therefore, to repair the deficiencies in the NDA by submitting a report of the clinical trial documenting that tizanidine produced the kinds of effects that had been illustrated in the videotapes presented during the meeting.

² A dramatic reduction in muscle tone need not be a clinically useful effect. Specifically, for the patient who requires a minimum degree of spasticity to stand or move, tizanidine's effect on muscle tone might be harmful rather than helpful. Moreover, a change in muscle tone may occur without any corresponding clinical benefit.

DISCUSSION:

Effectiveness:

The NDA contains reports of more than one adequate and well controlled clinical trial that show that tizanidine, administered at a single dose of 8 mg or more orally, can have a substantial effect on muscle tone in patients with spasticity of spinal cord origin (secondary to MS or trauma).

1) Study AN021-005 [submitted to the file after the non approvable action]: This was a randomized, controlled, multiclinic trial comparing the effects of a single oral dose (one dose study) of 8 mg [N=45] or 16 mg [N =49] of tizanidine against placebo [N= 48] in MS patients with disabling spasticity. Highly statistically significant differences favoring both doses of tizanidine were found on the Ashworth scale and pendulum test (each a measure of muscle tone). No effect on the incidence of spasm or clonus was detected, but the interval of evaluation was hardly long enough to capture enough events to allow a statistically significant difference to be found, even if one existed in the face of the high inter and intra-subject variation associated with these outcome variables. This study cannot, by virtue of its single dose design, speak to the effect of tizanidine in extended use (i.e., that is, whether, after repeated use, the patient will continue to respond to single oral doses to the same extent and degree as he or she did to the first oral dose).

2) Study 021-003 [submitted in the original NDA: This was a multiclinic (14 centers in US and Canada), 7 week long, parallel, randomized, placebo controlled, balanced study (N= 59 placebo, N= 59 tizanidine) in patients with spinal cord injury. The primary measures of treatment outcome were the Ashworth scale (a clinical measure reflecting the results of a standardized physical examination of muscle group strength) and the pendulum test.

Dosing in the study began at 4 mg/d. Over a period of 3 weeks, patients were titrated to a maximum of 36 mg / day as tolerated. Thereafter, they were maintained at their maximum tolerated dose

over a 4 week 'plateau' or maintenance phase. During this period, those receiving the maximum dose were given it on a tid schedule in unequal amounts: 10 mg given in the morning and afternoon and 16 mg given at night.

Throughout the maintenance phase, muscle tone was assessed on the Ashworth score within a period of 2 and one half hours following either the morning or afternoon dose. At the last time point at which measurements of muscle tone were made during the maintenance phase (protocol specified time of outcome assessment), a statistically significant difference in the extent of reduction in muscle tone was seen favoring patients receiving tizanidine. This reduction in muscle tone was not associated with a reduction in muscle strength (a good outcome); on the other hand, no consistent advantage for tizanidine relative to placebo randomized patients were obtained on measures of activities of daily living or flexor spasm frequency.

In sum, Study 021-003 provides unequivocal evidence that tizanidine can reduce muscle tone for a period of 2 to 4 hours or so following a single oral dose of 10 mg, that dose being delivered as one dose in a tid dosing regimen that 'forced' patients to or towards a plateau dose of 36 mg a day.³

Two other nominally adequate and well controlled clinical trials, DS0502 and 021-001 are also included in the NDA file. These studies, each conducted in MS patients with spasticity, were reviewed when the original NDA was submitted and were found, upon review by the acting neurology team leader, Dr. Levin, to provide contradictory results. I concurred in that judgment (see my memorandum of 2/10/85).

³ The effects of the single dose of 16 mg given h.s. were not evaluated in this study. Furthermore, not all patients in 021-003 were maintained on a daily dose of 36 mg during the plateau phase. The fact that the distribution of average doses during the plateau phase was less than 36 mg a day is a center piece of the firm's argument (see discussion of dose that follows) that tizanidine is effective at daily doses lower than 36 mg a day.

DS0502 was nominally positive as analyzed by the firm, but 021-001, a larger, domestic trial that was specifically intended to confirm DS0502's positive results, was not. We have no certain explanation for the contradictory findings of these 2 trials, but in view of the fact that muscle strength assessment was performed by physicians caring for patients in DS0502, it is almost certain that the treatment blind was penetrated in that study. I make note of this because Athena continues, in its resubmission, to rely on the results of DS0502.

Specifically, in their 9/8/95 submission, Athena cites data from the study's plateau (i.e., maintenance) phase in support of its argument that doses as low as 12 mg / day (4 mg tid) of tizanidine are effective. The firm also cites the positive results of the clinician's global in this study as a basis to support its view that Zanaflex produces a valuable clinical effect in extended use.

Admittedly, the global results would be of interest had we concluded that DS0502 provided an unbiased estimate of tizanidine's effects, but we did not. Moreover, the fact that DS0502 is nominally positive by some measure of outcome is not, indeed, never was, in dispute. The critical issue is what caused this nominally positive result--drug effect or bias? The fact that another physician⁴ based measure of outcome obtained in DS0502 had a nominally positive result does not address the issue of assessor bias.

In any case, my persisting concerns about DS0502 notwithstanding, I am personally persuaded that the data considered in their entirety provide support for a conclusion that 1) Zanaflex can for a few hours following oral administration of an 8 mg or greater dose, reduce muscle tone in some patients with spasticity, 2) an effect of a single 10 mg dose does not dissipate with repeated dosing over an interval of at least 7 weeks, and 3) the degree of reduction in muscle tone produced by the

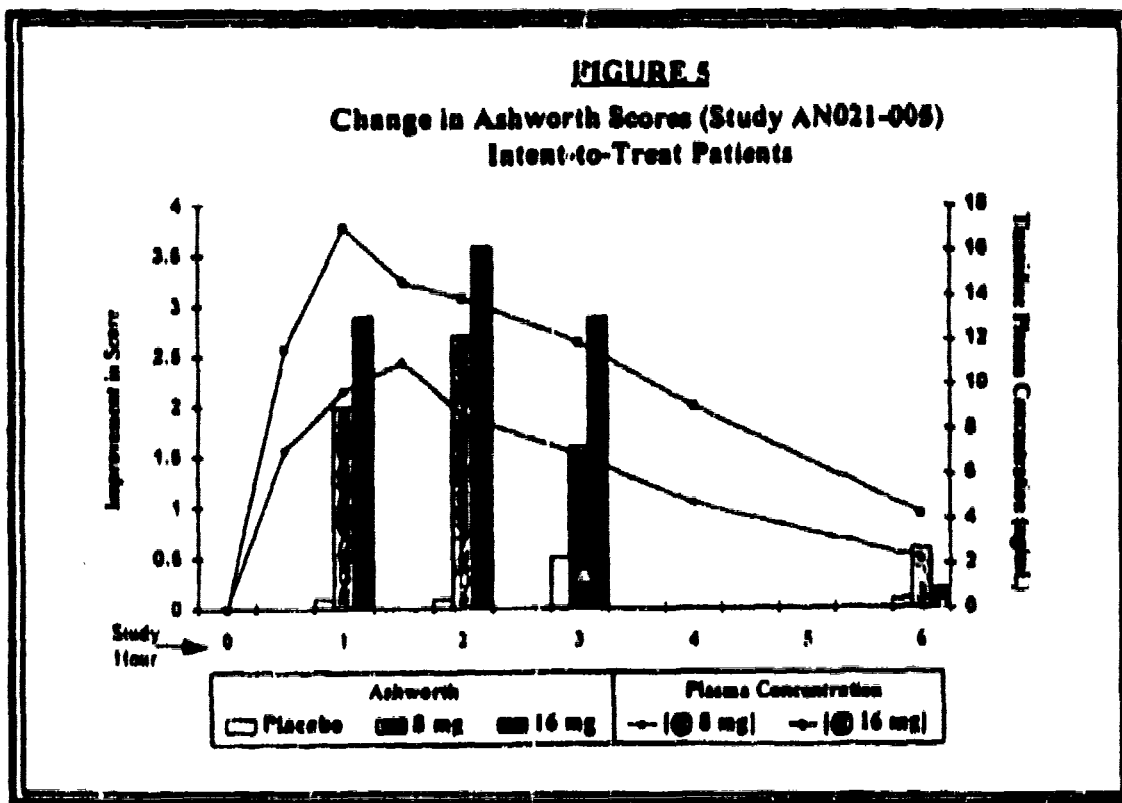
⁴ Had a treatment effect been found on an objective measure like the pendulum test (one was not done in this study), we would be reasonably reassured that at least some of the observed between treatment difference was drug induced. We would still be unsure as to the relative contribution of drug effect and bias to the nominal effect size of subjective measurements that were the study's protocol specified primary outcomes, however.

administration of an 8 mg single dose can be beneficial in the management of some patients with spasticity of spinal cord origin.

In sum, I believe the case for effectiveness has been made .

Dose response relationship:

The dose range over which tizanidine can produce a clinically meaningful reduction in muscle tone remains incompletely defined. As noted in earlier discussion, evidence from at least 2 controlled trials (i.e., 003 and 005) documents that single oral doses of 8 mg or more, produce effects on muscle tone of sufficient size to be useful in some situations for some



patients with spasticity. It is clear, however, (see the preceding figure, Figure 5 from page 16 of the sponsor's letter of 9/8/95) that the effect of a single 8 mg oral dose, (a dose which, if given on a tid regimen would represent the typical upper limit of the daily dose the sponsor seeks to have labeling identify as required to obtain the claimed benefits of use), does not persist throughout the entire 8 hour dosing interval. In fact, the

effect of an 8 mg dose may well be gone within 5 hours and certainly by 6.

The sponsor asks us to conclude, nonetheless, that other evidence shows Zanaflex to be effective at lower single doses. They point, in particular, to the distribution of daily doses among patients in the maintenance phase of 003, and two other extended use studies, including, in particular data from the pair of studies, 001 and DS0502 that we find contradictory. (Table 4, page 12 of their 9/8/95 letter, Reproduced below)

TABLE 4
Distribution of Average Doses of Tizanidine - Plateau Phase

Dose (mg/day)	Number of Patients			
	DS0502	AN021-001	AN021-003	All
< 8	4	5	0	9
8 - 12	6	6	3	15
13 - 16	6	12	1	19
17 - 20	10	12	1	23
21 - 24	12	4	2	18
25 - 28	7	12	5	24
29 - 32	3	7	6	16
33 - 36	30	32	26	88
> 36	1	4	3	8

They argue that the fact patients in the plateau phase were maintained at daily doses below the maximum supports a conclusion that these doses were effective. While adequate clinical response could be an explanation for the distribution of doses among patients in a titration study based on response, it seems just as, if not more, likely that achieved maximum tolerable daily doses reflect tolerance to side effects in a forced titration study of a drug that causes a high incidence of dose related dysphoric effects. The most reasonable explanation of all, of course, is that the distribution of doses in the plateau phase of forced titration studies is the result of a mix of effects that cannot be untangled.

The sponsor also argues that the data adduced in these 3 studies can be

analyzed in a way that reveals something it defines as the dose at which there was an "initial onset of efficacy." I have no idea how this outcome was defined, let alone when. I suspect it reflects a post hoc assessment of responses, but whatever it may be, it suffers from every one of the flaws just discussed.

In sum, the firm's arguments about dose are not persuasive; in fact, they are logically inconsistent, even specious. To illustrate, if their reasoning about plateau dose distribution is applied to all treatment conditions in these studies, is not one forced to conclude that the daily doses of placebo at which patients randomized to it were maintained were also effective? A basic flaw in all the firm's arguments about dose is the fact that they turn on the interpretation of evidence gathered in studies that employed dose titration. Dose titration designs do not ordinarily provide a valid means to evaluate dose response relationships. To the contrary, they typically produce a distorted, even inverted, relationship between dose and response because poor responders and non responders within the sample being studied are generally titrated to the highest doses allowed (or tolerated)⁵.

In any case, although I find the firm's arguments about dose largely specious, I am persuaded that doses of tizanidine of 8 mg or more do produce an effect on muscle tone that will be deemed by some experts to be clinically useful. Furthermore, given the variability of pharmacokinetic parameters and pharmacodynamic responses among individuals, it seems highly likely that some patients with spasticity of spinal cord origin will respond in a satisfactory way to single oral doses

⁵ There are exceptions, admittedly. When a series of graded doses of a drug can be administered to the same patient, it is sometimes possible to construct a within subject dose response curve that is valid. This requires, however, that 1) the disease condition be stable, and 2) there be a characteristic response to treatment that appears promptly and consistently within each patient after treatment administration and dissipates rapidly upon treatment withdrawal (i.e., there must be no residual or carryover effects from one dose to the next and order of treatment must be irrelevant.) Even in this situation, if treatment is adjusted on responses other than those reflecting the intended therapeutic effect, the results will be uninterpretable. The latter proviso is critical because it applies to the studies of Zanaflex where side effects clearly were dose limiting.

of tizanidine of less than 8 mg. The prevalence of such individuals in the population of patients with spasticity of spinal cord origin, however, is unknowable given the kind of information that has been gathered by the sponsor.

Safety in use

Known risks of use.

Zanaflex is not a risk free drug. Its use at doses that we know are effective in reducing muscle tone, causes severe sedation, dizziness, weakness, and dry mouth in a substantive proportion of those treated. Less commonly tizanidine may cause bradycardia, hypotension, syncope, transaminitis and hallucinosis. A substantial proportion of patients are unable, as a result, to tolerate Zanaflex at doses they need to obtain a clinically beneficial reduction in muscle tone.

None of these risks, however, is a bar to approval, provided that they are fully and prominently described in labeling.

Risk of events not seen

The extent of clinical experience with Zanaflex at doses that are documented to reduce muscle tone is limited. Accordingly, it is not possible to exclude the possibility that Zanaflex's use at these doses will be associated with an incidence of serious adverse events that would render it a danger to the public health.

Opinion on whether Zanaflex is safe for use is divided

Dr. Levin, the neurologist serving as the team leader for the Zanaflex NDA, finds the evidence submitted insufficient to show that Zanaflex will be safe for use as a chronic treatment for spasticity ⁶ when administered at

⁶ See the recommendation section (pages 22 to 25) of Dr. Levin's 1/7/96 review for an explication of his reasons. Note, too, that Dr. Levin also has concluded that the firm has failed to adduce the evidence necessary to develop a regimen for the safe effective use of the Zanaflex that can be recommended in

the doses known (necessary) to produce a clinically meaningful reduction in muscle tone.

Although I clearly share Dr. Levin's views about the sparseness of the information bearing on Zanaflex's safety at doses we know it to work, I do not believe the NDA needs to be disapproved.

I am mindful that judgments about matters of drug safety are highly subjective. Moreover, I am aware, too, that agency/Office policy has long favored the approval of effective drugs, even those with very serious risks of use, provided those risks are outweighed by the benefits of use and can be fully described in labeling.

Accordingly, I believe a credible case can be made for approving the NDA on the condition that the sponsor agrees to market Zanaflex under labeling that makes explicit the limitations of our knowledge about its risks of use at the doses we know to be effective.

Labeling.

Dosing recommendations

The sponsor proposes that "the optimum therapeutic response [with Zanaflex] is generally achieved with a daily dose between 12 and 24 mg administered in 3 equally spaced doses. The maximum recommended daily dose is 36 mg." As discussed in the earlier section on Dose response relationship, I do not believe the firm can justify this assertion.

I do believe, however, that the product can be approved with recommendations that describe what is known about effective doses and which recommends titration. My suggestion is as follows:

"A single oral dose of 8 mg of tizanidine reduces muscle tone in patients with spasticity for a period of several hours. This effect is likely to be undetectable 6 hours after dosing, however.

labeling.

Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical trials, the dose related nature of tizanidine's common dysphoric side effects make it prudent to begin treatment with single oral doses of 4 mg. If this dose is tolerated and reduction in muscle tone is unsatisfactory, the single oral dose may be increased gradually (2 mg steps) to a maximum of 12 mg. In no case should the total daily dose exceed 36 mg. "

Warnings about risks not seen:

The circumstances surrounding our action on Zanaflex are complicated by the fact that the product is marketed world-wide with recommendations for use under which we cannot be certain it is effective. Under the conditions of use recommended elsewhere, however, the product is likely to be "safe⁷" in the sense that the vast majority of patients exposed to the recommended dose are unlikely to suffer lasting injury as a result of using the drug.

There is, however, very little clinical experience at the doses that we believe the sponsor must recommend Zanaflex be administered to ensure that it will be effective in use as labeled. Indeed, it is this fact that has led Dr. Levin to recommend that the NDA be disapproved.

As noted earlier, although I do not believe the NDA should be disapproved, I do believe we need, if we are to keep faith with the Act's requirement that labeling not be false or misleading in any particular, to have labeling state clearly the limitations on our implied warrant that Zanaflex has been shown to be safe for use.

Accordingly, the draft labeling upon which the Division conditions its

⁷ I use the term safety within quotation marks because I personally find it illogical to assert that the use of a pharmacologically active substance is safe if its use as recommended has no documented benefit. My position is a logical extension of our risk to benefit approach to drug safety; for a drug without a demonstrated benefit, the analysis must be unfavorable.

recommendation that Zanaflex be declared approvable, provides, in the Warnings Section, a discussion of the incidence of adverse events that can reasonably be excluded under the conditions of use that are being recommended.

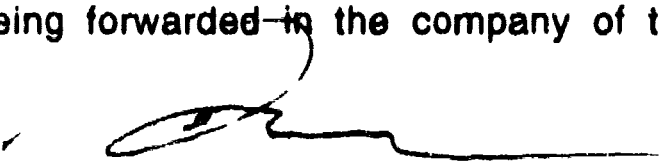
I am mindful that this approach is innovative, but I believe it is fully consistent with the requirements of 21 CFR 201.57 as to the permissible content of the Warnings Section. Even more importantly, it serves the interests of the public health; patients and physicians who contemplate the use of a new drug product need to be informed about both what is and what is not known about its benefits and risks.

Post-marketing Study requests

The draft approvable action letter asks the firm, post-approval, to 1) conduct studies of appropriate design to describe tizanidine's dose response curve (e.g., a cross over study that would examine the effects of 2, 4 and 8 mg single doses would be of interest), and 2) to carry out more extensive safety trials with doses at high end of the recommended labeling (i.e., an open cohort to examine the consequences of a 16 mg dose given orally).

Recommendation:

Issue the approvable action letter being forwarded ~~in~~ the company of this memorandum.



Paul Leber, M.D.
2/21/96

NDA 20-379

HFD-100

Temple

HFD-120

Katz

Levin

Rouzer-Kammeyer

Fitzgerald

Atrakchi

Blum

Guweska

Grilley

HFD-710

Nevius

Sahlroot

Mele

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 10, 1995

FROM: Paul Leber, M.D.
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: Disapproval Action Recommendation

TO: File, NDA 20-397 Zanaflex (tizanidine)
 &
 Robert Temple, M.D.
 Director,
 Office of Drug Evaluation 1

The Division's review team, headed by Randy Levin, M.D.¹, has completed its review of NDA 20-397, and has concluded that the application should not be approved. I concur in that judgment and recommend that the not approvable action letter accompanying this memorandum be issued.

Basis for refusing to approve the Application:

The Division's disapproval recommendation is based on my determination that the application is deficient in regard to 1) chemistry and manufacturing controls, 2) the adequacy of preclinical tests conducted to show the product is safe for use, 3) the adequacy of the clinical experience presented to show that the drug will be "safe for use" under the conditions of use that would, in all likelihood, have to be recommended in labeling were it approved² for the

¹ At my request, Dr. Levin agreed to assume the role of supervisory reviewer and/team leader for the Zanaflex NDA review project. I took this step to assure that the Division's Neurology Group, which is faced with a large number of pending applications, could take action upon them within the time frames established by agency management for applications that are subject to User Fee goals.

² This deficiency requires further explication and qualification. It is logically absurd to discuss the conditions that would allow an ineffective drug to be used safely. According, the statement made is a conditional one based on the presumption that if Zanaflex can eventually be shown to be effective,

claims sought, and 4) the required showing of substantial evidence that Zanaflex is effective for use as a treatment for spasticity of spinal cord origin.

It is important to note that the review team is not in unanimous agreement concerning each of these enumerated deficiencies. Specifically, Drs. Levin (memorandum of 2/2/95), Rouzer-Kammeyer (review of clinical data of 9/7/94) and Mele (Statistical Review of 12/23/94), disagree about whether the evidence adduced in the sponsor's so-called "pivotal" controlled clinical trials support its claims for the efficacy of Zanaflex. I have spoken with each of them concerning the basis for their conclusions, and I am persuaded that their conflicting views arise not from disagreements about the accuracy of the sponsor's reports or the method of statistical analysis applied to the clinical data, but to differences in values and beliefs about measures of efficacy and standards of evidence that each brings to the interpretation of the findings. In addition, Dr. Levin has specific concerns about the adequacy of blinding in one of the 3 pivotal studies, DS-502.

As a practical matter, however, the disagreements among staff about the weight of the evidence bearing on the effectiveness of Zanaflex do not have any immediate consequence on the proposed regulatory action³. Specifically, even if there were unanimity among the clinical and statistical reviewers that the sponsor had provided 'substantial evidence' of tizanidine's effectiveness, there would be inadequate grounds to conclude that the product is safe for use on the basis of the information provided in the NDA.

First, as Dr. Levin's review documents, clinical experience with the drug at the very doses at which the firm contends effectiveness has been demonstrated (circa 36 mg/day) is extremely limited, far too limited to

it will be at doses far larger than those to which the vast majority of patients described in the NDA have so far been exposed.

³ Of course, our conclusion about the evidence adduced in the controlled trials will have an effect on the advice we can give the firm concerning the subsequent repair of the application.

support a conclusion that Zanaflex will be safe for use⁴.

The firm is unlikely to share this view and will undoubtedly argue that reassurance about the safety of tizanidine can be taken from its extensive and apparently uneventful use at lower doses and the seemingly benign profile of post-marketing reporting associated with its marketing world wide.

We would disagree, of course. The experience that can be cited by the firm is almost entirely at doses well below 36 mg a day. Furthermore, as Dr. Levin notes, the vast majority of clinical experience has been gained in the treatment of conditions other than spasticity. For example, about 50% of tizanidine's marketed use occurs in Japan where it is primarily employed at doses of less than or equal to 9 mg/day. Moreover, Athena estimates that 80% of tizanidine's marketed use is for the management of low back pain, presumably at doses far below and for much briefer intervals than those used to treat spasticity.

Second, as Dr. Fitzgerald notes (her supervisory overview memorandum of 1/23/95), the preclinical testing ordinarily required to evaluate the tumorigenic potential of a product intended for chronic use is less than satisfactory. Specifically, the in-vivo life time carcinogenicity studies conducted in rodents are flawed because the rat and mouse appear (based on the results of a single dose study) to metabolize tizanidine in a way that does not result in their being exposed to the same level and profile of metabolites to which humans are exposed. (Following oral administration to humans, tizanidine is extensively metabolized.). The problem presented by the inadequacy of systemic exposure to metabolites was discussed with the CAC and while its members did not entirely agree with the position taken by Dr. Fitzgerald, I personally favor her approach to the resolution of the matter. Accordingly, I endorse her conclusion that the application be disapproved because it fails to provide 1) evidence that the level of metabolite exposure obtained in the carcinogenicity studies is adequate (the firm will have to conduct and/or obtain plasma level data from repeat dose animal studies) and 2) results of in vitro mutagenicity tests on the major metabolites found in

⁴ How limited is not precisely known because the firm has failed, despite previous requests for the information by the division, to provide a precise accounting of the actual experience (numbers of patients and time of exposure by dose) at or above the modal doses used in the so-called pivotal clinical trials (e.g., around 36 mg/day).

human plasma. Incidentally, the firm was informed of the division's views concerning the deficiencies in the carcinogenicity tests prior to August of 1994. They have not, however, at least as of this date, provided the information requested.

In sum, it is my conclusion that the NDA has failed to provide all reasonable preclinical tests required to show that tizanidine will be safe for use.

Finally, the application can be disapproved for chemistry manufacturing and controls deficiencies. Although the firm was made aware of the deficiencies early on in the review process, they did not submit the required information and data to the NDA file within 12 months of the application's date of submission (i.e., within the cut-off date for consideration of submissions to the NDA file). Although not critical to the proposed regulatory action, the chemists on the review team believe it likely that these deficiencies can be readily repaired.

Some speculations concerning the genesis of the divergent views on the question of Zanaflex's effectiveness among the review team.

With the possible exception of drug products that reduce the incidence of concrete, unequivocally undesirable, discretely and unambiguously countable, clinical events (e.g., deaths, major strokes, massive myocardial infarctions), decisions on effectiveness may turn as much on opinions about the assessments employed to measure a treatment effect as on the empirical evidence adduced in a clinical experiment. Evidently, we must come to grips with this problem in dealing with the evidence put forward by Athena in its NDA for Zanaflex.

What, for example, constitutes a meaningful clinical measure of an antispasticity drug action? As is often the case, there are an abundance of instruments alleged to measure spasticity, but it is not a matter of general agreement among experts which, if any, of these, taken alone or in combination, provide an adequate measure of a treatment's efficacy in the management of spasticity.

In pre-NDA communications with the firm, the Division noted its oft expressed concerns about the issue (i.e., citing the distinction to be made between drugs with detectable pharmacological effects and drugs that are effective treatments). Indeed, my notes of meetings held as early as 1992

with Athena indicate that we advised the firm to document its claims for efficacy with compound outcome assessments, a strategy very much akin to the one we typically advise sponsors to use to evaluate antimentia drug products. Basically, in addition to a measure to show that Zanaflex induces a beneficial effect on some sign/symptom of spasticity, we asked them to collect information that would allow us to conclude that the effect was clinically beneficial (e.g., an effect on incidence of clonus and spasms as rated by patients in diaries, ADLs, a clinical or patient rated global, etc.). The Division probably noted as is its custom, although my notes provide no confirming documentation, that its advice constituted a recommendation, not a demand. Athena was in all likelihood told, too, that we could not refuse to accept an application merely because they did not follow our recommendations. In short, we probably made clear that they had the right to ignore our advice and submit any evidence they believed appropriate provided it was derived from more than one adequate and well controlled clinical investigation.

As it turned out, Athena did not choose to employ a compound outcome assessment strategy although it may have attempted to follow some of the division's suggestions (e.g., the designation of spasm and clonus counts as a primary outcome variable).

By inference, the Ashworth scale, a measure of muscle tone provided by a clinician based on his/her subjective opinion of the quality of muscle tone elicited upon the passive manipulation of as many as 10 different muscle groups examined bilaterally, serves as the primary outcome measure in all 3 clinical studies identified as pivotal by Athena.

The Ashworth scale is a measure of a clinical sign, however, and, as such, it is not obvious what degree of change in its score represents an effect of clinical value or importance. Accordingly, the use of the Ashworth as the primary basis for evaluating the effectiveness of a drug's antispasticity action is arguable. This fact alone may account for some portion of the disagreement among the members of the review team.

To illustrate, if we assume for the moment that the Ashworth scale is, in and of itself, an adequate measure of effectiveness of a drug intended for the treatment of spasticity, it may appear that there is unequivocal evidence of Zanaflex's efficacy in that statistically significant drug placebo differences on the Ashworth favoring Zanaflex exist in two of the sponsor's 3 controlled clinical trials (DS-502 and 021-003). Indeed, I believe this is why Dr.

Rouzer-Kammeyer finds the evidence of Zanaflex's effectiveness persuasive.

Dr. Levin, however, viewed the evidence from another perspective. First, like myself, he has, for the reasons stated above, substantive reservations about the use of the Ashworth as the sole measure of a treatment's effectiveness in spasticity. Accordingly, he is not persuaded by a finding on the Ashworth in the absence of accompanying findings showing the change is associated with meaningful clinical benefit. By this test, only DS-502 is a nominally positive study; however, Dr. Levin believes that its seemingly positive results may be explained by systematic bias rather than drug effect.

Perhaps even more important to Dr. Levin is the lack of internal consistency in the efficacy data base.

Viewed from the perspective of Zanaflex's sequential development, DS-502, conducted by Sandoz in patients with MS, is the initial positive controlled trial, the trial that we would ordinarily expect Athena to replicate to confirm the effectiveness of tizanidine. Athena's attempt, however, failed. The intended confirmatory trial, 021-001, which was conducted domestically, not only fails to show an effect of tizanidine on the Ashworth, but at some time points actually favors placebo. This failure occurs despite the fact that 021-001 is larger than DS-502. The failure to replicate is viewed as uniquely important by Dr. Levin because 021-001 was by design superior to DS-502 in the precautions taken to ensure that those assessing the Ashworth scale would be blind to treatment assignments. In DS-502, physicians responsible for the care of patients and dose titration served as assessors; in 021-001, assessors were independent and unfamiliar with the patients they assessed. Dr. Levin argues that knowledge of treatment assignment can be easily deduced from knowledge of the unique profile of side effects exhibited by patients on tizanidine. Dr. Levin's concern, importantly, is not an idiosyncratic one; to the contrary, it is one held by investigators who have actually conducted controlled trials with tizanidine.

Accordingly, DS-502 and 021-001 are at best contradictory; at worst they provide no probative evidence of efficacy whatsoever.

As to 021-003, a study in patients with spinal cord injury, Dr. Levin agrees that the trial shows an effect on the Ashworth that can reasonably be attributed to tizanidine; however, in the absence of evidence from outcome measures reflecting meaningful clinical benefit, he is only able to accept the trial as a source tentatively supporting tizanidine's effectiveness in use.

Upon further discussion, however, I gather that Dr. Levin, presented with a second positive study in patients with spinal cord injury, would find the combination of the two studies to constitute substantial evidence of an effect in spasticity of spinal cord origin. I am not yet persuaded he is correct, in large part because I still have no sense of the clinical importance of the treatment effect reflected by a difference in change scores (drug versus placebo) recorded on the Ashworth Scale.

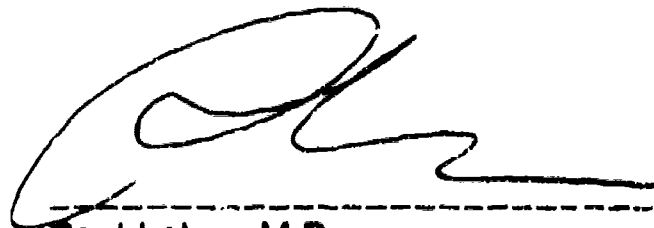
Overall, however, I fundamentally agree with Dr. Levin. Accordingly, I am recommending that the NDA be disapproved and that a lack of substantial evidence of effectiveness be included among the reasons cited for doing so.

I am mindful, however, that what makes evidence substantial is the extent to which fair minded and impartial individuals, expert in the area of therapeutics involved, can conclude fairly and responsibly from the evidence that the drug will have the effect claimed. Obviously, I cannot know how other experts would evaluate this data. Thus, if the firm can provide clinical reports of "safe passage" from several hundred patients exposed for reasonably long intervals (i.e., months) to the doses of tizanidine used in 021-003 (the one study in which statistically significant between group changes unequivocally attributable to treatment with tizanidine were found on the Ashworth Scale), and the deficiencies in pharmacology and chemistry are repaired, I would be willing to consider a resubmission of the NDA as a means to secure the views of the PCNS AC about the existing effectiveness data.

With the exception of this last suggestion, the issues covered in this memorandum are conveyed in the not approval action letter.

Recommendation:

Issue the not approval action letter.



Paul Leber, M.D.

February 10, 1995

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: November 14, 1996
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-397 (Tizanidine)
To: File

Introduction:

Athena submitted NDA 20-397 on 12/3/93. A non approval letter, describing deficiencies in both the safety and efficacy data base was sent on 3/6/95. The sponsor responded to the non approval letter in May of 1995. In this submission, the sponsor provided an additional efficacy study, 005, that characterized the brief time course of the efficacy of the drug in reducing muscle tone associated with spasticity. In this response, the sponsor also provided additional information on the safety of the drug from data collected in long term safety studies 002 and 004. I concluded that the data did not provide evidence of efficacy to support the labeling provided by the sponsor. The labeling was subsequently changed to reflect the brief nature of the drug's efficacy. I also concluded that the safety data base was too small to provide assurance for the safe use of the drug as described in labeling. The labeling was subsequently changed to warn patients and prescribers on the limited nature of the safety data base.

Based on the limitations described in labeling, the sponsor was sent an approvable letter on 3/11/96. On 8/19/96, the sponsor met with members of the division and Dr. Temple to discuss labeling and post marketing commitments.

On 8/21/96, the sponsor's response to the Approvable letter was received by the division. This document did not provide for a complete response to the approvable letter. A safety update and a detailed description of the actions from

the foreign regulatory authorities was not provided.

On 8/23/96, we asked the sponsor to provide the safety update. A safety update without CRFs for deaths and discontinuations was received on 8/27/96. A request for CRFs was provided on 9/24/96. From a review of the safety update and CRFs, it was discovered that additional cases of hepatitis had occurred. After discussion with Dr. Leber and Dr. Temple, an outside hepatology consult was requested. While this consult was being arranged, the sponsor obtained their own consult from Dr. Maddrey. A copy of Dr. Maddrey's consult was provided on 10/28/96 and the division's consult was canceled. During the time between the receipt of the initial information on 8/21/96 and Dr. Maddrey's consult, a dialog between the sponsor and myself, took place to address differences of opinion regarding the labeling. The labeling changes were based on discussions that took place between the sponsor, Dr. Leber and Dr. Temple. The safety update and CRFs were also reviewed.

Comments:

I have provided a review of the information provided by the sponsor on the safety and efficacy of the drug in the treatment of increased muscle tone in patients with spasticity. The efficacy data demonstrate that the drug is effective in reducing muscle tone. The effect is brief, peaking at 1 to 2 hours and gone between 3 to 6 hours and is associated with significant adverse events in many patients. Many of these adverse events such as sedation and hypotension may defeat any positive benefits from the drug.

This efficacy data presented does not support the recommended three times a day dosing regimen. An effective dosing regimen may require treatment every 2 to 4 hours in order to maintain an antispasticity effect. The efficacy data supports treatment of spasticity on a prn, or as necessary basis. The safety data does not support dosing at intervals more frequent than three times a day. It is not known if patients can even tolerate dosing at intervals of less than three times a day, let alone producing serious adverse effects.

The sponsor has not evaluated the drug adequately to provide prescribers with instructions for optimal treatment. The sponsor has not adequately evaluated the dosing range of the drug. This includes the use of both lower doses (2 to 4 mg) and higher doses (16 mg) and more frequent dosing intervals (every 2, 4 or 6 hours).

While the safety data provided by the sponsor describes safety problems, its lack

of long term experience leaves doubts on true safety profile of the drug. While these doubts are described in the labeling, additional information is needed regarding the long term experience with doses in the 24 to 36 mg/day range as well as single doses of 8 to 16 mg. Patients and prescribers should be aware of the potentially serious problems of sedation, hypotension and liver toxicity as well as the occurrence of AEs not yet identified as drug related.

Recommendations:

Because of an inadequate evaluation of the safety and efficacy of this drug, prescribers and patients will not have the information necessary to use this drug optimally. While I do not recommend approval of the drug, I feel that, if approved, the labeling should make patients and prescribers aware of these deficiencies and provide the most accurate information on use of the drug with the data on hand. Therefore, I suggest that in the Indication section of labeling, the use of this drug should be specifically for the acute and intermittent treatment of spasticity to reflect the short duration of effect and the lack of effect over the course of chronic three times a day dosing. Any discussion of a chronic treatment regimen, by this I mean regular tid dosing, should not be included in labeling as this is not consistent with the duration of effect. Without specifying acute and intermittent use or by discussing chronic treatments, prescribers may assume that the drug could maintain a reduction in muscle tone over the course of a day. Discussions of repeated dosing should focus on prn dosing to be consistent with an acute and intermittent treatment. In the Dosage and Administration section, the brief duration of effect should be emphasized and the role of the drug as an intermittent treatment should be made clear. The lack of safety information should be contained in the Warning section as well as the Dosage and Administration section.

This labeling should also encourage the sponsor to conduct the appropriate studies to fully characterize the efficacy of the drug so that prescribers and patients will know the most effective way to use the drug. I would suggest conducting studies similar in design to study 005 to evaluate doses of 2 and 4 mg. If these doses are effective, the sponsor should assess the efficacy of different dosing regimen (every 2, 4 or 6 hours) in multiple dose studies to evaluate the ability of the drug to provide a consistent benefit without significant AEs over the day. In addition to evaluating the efficacy adequately, the sponsor should also commit to collecting long term safety data on patients taking higher doses of the drug, 28 to 36 mg/day and single doses of 16 mg/day.

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 26, 1996

FROM: Paul Leber, M.D.
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: Approval Action Recommendation

TO: File, NDA 20-397 Zanaflex (tizanidine)
 &
 Robert Temple, M.D.
 Director,
 Office of Drug Evaluation 1

This memorandum provides my formal recommendation to the file concerning the approval of NDA 20-397.

Background

Athena's NDA for Zanaflex was originally submitted in December of 1993. The Division's initial review of the application determined¹ that it failed to provide the information that, by law, is required to allow the approval of an NDA². Nevertheless, although the NDA was disapproved (3/6/95), we were mindful at the time that tizanidine was an active drug substance that could reduce muscle tone, and, therefore, a drug that might well, given an appropriate dosing regimen, provide clinical benefit³.

¹ The deficiencies are summarized in my memorandum to the file of 2/10/95

² The NA letter cited deficiencies involving CMC, the extent of preclinical toxicology/carcinogenicity testing, and the quality, validity and consistency of the evidence the sponsor advanced to support its claims that Zanaflex would be safe for use and effective in use as recommended in proposed labeling.

³ We regularly distinguish between drugs that exert an effect and those that are effective treatments. The fact that a drug can reduce muscle tone is not sufficient, in and of itself, to establish that it exerts a beneficial effect, let alone safe

At a meeting in July 1995, videotapes of patients treated acutely with tizanidine were shown that persuasively illustrated that tizanidine can bring about a dramatic reduction in muscle tone; it appeared, too, that in these patients, the reduction in muscle tone was accompanied by an increased capacity to participate in what are reasonably characterized as activities of daily living (e.g., moving from bed to a wheel chair without suffering painful spasms).

The Office Director, presumably persuaded by the visual evidence provided in the video tapes that tizanidine could have a meaningful clinical effect, invited the firm to submit evidence from a controlled clinical trial that would not only document tizanidine's effects as seen on the tapes but provide quantitative information about the relationship between its dose and the magnitude and duration of its effects on muscle tone.

The NDA was resubmitted in September of 1995; it provided results of a single dose study that documented the acute effects on the muscle tone of patients with severe spasticity of a single oral dose of 8 or 16 mg. In addition, the submission provided further information and argument about clinical data that had been presented in reports made to the original NDA. Upon review of the evidence and arguments, I concluded that (page 6, 2/21/96):

"the data considered in their entirety provide support for a conclusion that 1) Zanaflex can for a few hours following oral administration of an 8 mg or greater dose, reduce muscle tone in some patients with spasticity, 2) an effect of a single 10 mg dose does not dissipate with repeated dosing over an interval of at least 7 weeks, and 3) the degree of reduction in muscle tone produced by the administration of an 8 mg single dose can be beneficial in the management of some patients with spasticity of spinal cord origin."

for use. Subjects with upper motor neuron disease often rely on the presence of spasticity to allow them walk and/or to maintain body posture. Moreover, the reduction of muscle tone induced by tizanidine can be associated with decreased blood pressure and marked sedation, findings that raised concerns about its safety for use under the conditions of use proposed by the sponsor.

Questions about tizanidine's safety for use remained, however, to a large degree because only limited clinical experience had been gained at the very doses (36 mg a day or so) that we had concluded would be necessary to recommend be used to obtain the drug's beneficial effects. Moreover, it was suspected that the use of higher doses of tizanidine would be associated with an increased incidence of more troublesome, untoward effects (e.g., bradycardia, hypotension, syncope, transaminitis and hallucinosis.)

Based on his overall assessment of the evidence, Dr. Levin recommended that the application not be approved, essentially arguing that the documented benefits of tizanidine were not sufficient to outweigh its known risks. The small number of patients exposed to tizanidine at higher doses for extended times only served to heighten Dr. Levin's concerns.

I disagreed with Dr. Levin. Although I shared his view that the sponsor's safety data base was smaller than we might prefer, in particular in regard to the extent of clinical experience that had been gained at the higher end of the dosing range (circa 36 mg a day--12 mg tid or 16, 10, 10), I concluded the application was approvable. I did, however, condition my recommendation on the firm's agreement to adopt product labeling that 1) fully and candidly described tizanidine's known risks, and 2) openly acknowledged the limited experience upon which our regulatory warrant of safety for use was based.

Despite some additional minor disagreements about the precise wording of labeling and conditions of approvability among Office and Division staff, an approvable action letter issued on 3/11/96. The letter conditioned final approval of the NDA for ZANaflex on the firm's agreement to 1) market Zanaflex under labeling developed by the Division, 2) its commitment to conduct, post approval, and 3) to

Post Approvable Action Issues and considerations.

Athena had multiple objections to the conditions of approval announced in

the agency's March 1996 approvable action letter. Following a meeting (8/19/96) with the agency that was attended by the Office Director, Athena submitted (8/21/96) what it represented to be a "Response" to the Approvable Action letter. As Dr. Levin records in his 10/21/96 review, Athena's "response" was incomplete, not only lacking the reports and information ordinarily provided in a "safety update," but failing to provide information about the actions, pending or taken, on tizanidine by foreign drug regulatory agencies.

Moreover, Athena refused to make all the commitments sought in the approvable action letter.

5

Eventually (late September), Athena provided the safety information required. A review of this and other information raised new concerns. Specifically, Dr. Levin was impressed by additional reports of hepatitis and liver injury; accordingly, the firm was advised to have a recognized expert in drug induced liver injury review these cases. Dr. Levin was also concerned about the severity of the sedation associated with higher doses of the drug.

Discussion:

Dr. Levin continues to believe that the risks of tizanidine have yet to be shown to be outweighed by its benefits as a treatment for spasticity. Accordingly, he continues to recommend that the NDA not be approved⁴. I, in contrast, continue to believe that tizanidine, albeit not an ideal treatment for every patient, has been shown to have an action that makes it a potentially useful treatment for some patients with spasticity, and, accordingly, I believe the agency is obliged to conclude that tizanidine has been shown to be effective in use.

⁴ I take note for the record that Dr. Levin is not alone in his views; it seems that neither Canadian nor UK drug regulatory authorities are, at least so far, willing to approve Zanaflex as a treatment for spasticity.

A conclusion that Zanaflex is effective in use (i.e, that the NDA provides substantial evidence of effectiveness) is, of course, a necessary but not a sufficient requirement for NDA approval. The approval of an NDA also requires a determination that the product will be, within the meaning of the Act, safe for use. Clearly, Zanaflex is not risk free; the issue, therefore, is whether tizanidine's benefits outweigh these risks under the conditions of use recommended in product labeling.

The answer to this question is determined more by personal sentiments and values than evidence. In my opinion, and it is no more than that, tizanidine's risks are not so great as to bar its marketing under product labeling that fully and accurately describes its risks and the limits of the warrant that can be made about its safety. (For a more extensive development of the evolution of my views about tizanidine, see my memoranda to the file of 2/10/95, 2/21/96 and 3/11/96).

Mindful that the Office Director shares my view, Dr. Levin has worked diligently and carefully to develop product labeling that will describe the risks of tizanidine fully and accurately. He has not only discussed his suggestions for labeling with me, but directly with the Office Director, a not unreasonable approach because it is the Office Director, not I, who has the final say on the specific words that will be used in the labeling of an NCE.

In my view, Dr. Levin has done a masterful job; I am all the more impressed because he has had to work under circumstances where he was obliged to set aside his personal sentiments concerning the regulatory action being taken.

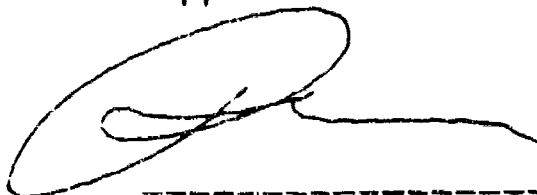
I am mindful that the sponsor has refused to make a commitment to

views of the approvability of the application.

Recommendation:

NDA 20-397 for Zanaflex's use as "a short acting drug for the acute and intermittent management of increased muscle tone associated with spasticity" should be approved provided that Zanaflex is marketed under the version of labeling attached to the approval action letter.

Accordingly, the Office should issue the approval action letter being forwarded by the Division.



Paul Leber, M.D.
November 26, 1996

Certificate of Debarment

This is to certify that no debarred individuals as defined and listed in the Federal Register as of October 1993 participated in the development of Zanaflex™ (tizanidine.HCl).

Additionally, no item or section of the NDA# 20-397 was generated, written or reviewed by a debarred individual.

Hana Berger Moran

12-3-93

Hana Berger Moran, Ph.D.
Director, Regulatory Affairs
Athena Neurosciences, Inc.

Date

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-397 Trade (generic) names Zanaflex (tizanidine HCl)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
To be addressed at time of Approval
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

Final Printed Labeling

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

**DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE
ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE
PUBLIC.**

Medical Officers Review

COMPLETED

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S CONSULT REVIEW

NOV 4 3 1994

NDA: 20-397
Sponsor: Athena Neurosciences, Inc.
Date Received at HFD-180: August 24, 1994
Drug: ZANAFLEX™ (Tizanidine • HCl)
Pharmacological Category: Antispastic
Material Reviewed: a) 2 volumes containing what the sponsor considers relevant information on liver function tests. This material is supposedly similar to what the sponsor provided to the Athena consultant.
b) MOR of four month Safety Update 4-4-94
c) E-Mail message from V. Tamara to HFD-180 CSO.

I. BACKGROUND

TIZ is an agonist at α_2 -adrenergic receptor sites within the CNS at supra-spinal and spinal levels. The sponsor is seeking approval for the marketing of TIZ for the treatment of spasticity of spinal cord origin. TIZ has been launched in 38 and approved in 44 countries, including Germany and Japan. After oral dosage, TIZ is extensively degraded and converted into ca. 15 metabolites, 3 major. Two of the latter are inactive, the activity of the third is not known. Amidation and glucuronidation have been described. The unchanged drug does not accumulate, but the total radioactivity accumulates by a factor of three. There is no information on the effect of liver impairment on drug disposition but impaired renal function resulted in 7-fold increase in half-life and a corresponding $\downarrow$ in clearance. Gender has no effect on the disposition of the drug but elderly subjects clear the drug four times slower than younger subjects. No data are provided as to whether the drug is metabolized through the cytochrome P₄₅₀ ENZ system, what are the intended doses and dose duration (supposedly very L-T?), what is the main route of excretion of the compound and whether it undergoes an entero-portal-hepatic-biliary circulation.

As part of Appendix C-2 ("Summary of Effects of TIZ on Liver Function Reported During Clinical Trials") the following information on Animal Pharmacology is provided (this part is reproduced in its entirety below).

"Animal safety studies in rats and dogs suggest that the liver might be the most sensitive target organ for tizanidine toxicity. There were slight and temporary increases in SGPT/ALT levels in the 13-week oral dose studies in rats and dogs and in the one-year dog study. The histopathological changes were restricted to a few animals treated with the highest doses of tizanidine and consisted of focal single cell necrosis (13-week rat), mild inflammatory infiltrates (13-week dog) and increased periacinar eosinophilic hepatocytic hypertrophy (104-week rat). These hepatic changes were considered mild and reversed shortly after cessation of treatment."

COMMENT

With the information so far provided it is not possible to fully characterize the hepatic effects of the drug (in animals). Based on hypertransaminasemia alone, it would seem that the injury is predominantly of the hepatocellular type and this is suggested by the focal single cell necrosis in the 13-week

studies in rats and mild inflammatory infiltrates in the 13-week studies in dogs. But no information is given on liver markers of cholestasis, namely AP and direct bilirubin. Were these normal? Was LDH determined? If so, did it change with treatment? Were electron microscopic examinations done? Were histochemical reactions done?

At the end of the above quoted paragraph the sponsor states that these hepatic changes were considered mild and reversed after cessation of treatment. This is an important statement. If true, it is somewhat reassuring (of the animal findings) but was this reversibility seen after administration of the compound to rats for 104 weeks? All doses? Both biochemical and histological parameter regressed? If there was submicroscopic alteration of organelles did these alterations normalize "shortly after cessation of treatment"?

Additional questions regarding TIZ and liver function in animals:

- Are there data on liver perfusion studies in animals?
(these would show dose-related histopathologic alterations)
- Does the compound or its derivatives have an EPHS circulation?
(This would lead to metabolite accumulation)
- Does it have an effect on bile flow?
(↓ bile flow is one of the earliest signs of toxicity)
- Does it have an effect on membrane permeability in isolated hepatocytes?
(negative results may not exonerate the cpd. as being a hepatotoxin but positive results may add in the characterization of its potential for liver toxicity).

The requester states that the sponsor has concluded that TIZ is associated with a mild, reversible increase in transaminases in roughly 2% of patients. The sponsor states that progression to liver disease is highly unlikely.

It is also stated that post-marketing reports¹ have yielded

- 5 cases of hepatic dysfunction
- 3 reports of hepatitis
- 3 reports of jaundice
- 12 reports of increased liver ENZ
- 1 death. This was reported in a 68 y-old M treated with the drug at the (oral?) dose of 4 mg/day x 2 months. The patient developed "cholestatic jaundice" and died 20 days later of bronchopneumonia.

II. PRESENT SUBMISSION

The materials listed below are the object of the present review. These were submitted by the sponsor on August 23, 1994 and reached HFD-180 on August 24, 1994.

¹ But at this point no information is provided about the source of such data. When was the drug first approved? Is there a rough estimate of the total patient exposure to date? Is this post-marketing information from a reliable source? How complete is it? etc, etc.

A. Appendix C-2² Report "Summary of Effects of TIZ on Liver Function Reported During Clinical Trials".

In the introductory paragraph to Appendix C-2 it is said that it deals primarily, but not exclusively, with changes in serum transaminases (SGPT/ALT and SGOT/AST) reported in the clinical trials with the drug. It is further explained that other tests of liver function were also evaluated, but the focus on transaminases is based on the likelihood that they would be the most sensitive indicators of potential liver toxicity.

- B. Test summaries for patients who D/C due to a related AE (from Integrated Safety Summary - Appendix B-2).
- C. Data listings for the patients discussed in the above report.
- D. F/U data on these patients (from the 120-day Safety Update). The sponsor states that this is more recent information that was not available to the Athena consultant.

The sponsor explained that the above listings were compiled by site with the affected patients listed for each site. The content of each set of listings were provided in the table heading.

III. REVIEWER'S APPROACH

The main focus of the consult appear to be the 2-volumes containing the information of LFTs provided to the Athena consultant. This information will be reviewed first. When available, emphasis is put on individual cases, to document liver toxicity in the individual patient.

The above evaluation will be followed by an overview of the data in an attempt to establish the magnitude of the problem in the entire patient population.

III. CLINICAL DATA IN APPENDIX C-2

The data reviewed here were derived from the three critical efficacy trials (DSO 502, 021-001 and 021-003), open-label trial AN 021-002 and additional data from post-marketing experience.

A. Study DS-0502

A summary of the design and execution of this study is not given. Specifically, what doses of compound were tested, under what regimen and for how long?

This appears to be a multicenter, PL-controlled, 2-arm (?), single or double-blinded?, U.K. trial in 187 MS patients (PL=93; TIZ=94). Of these, 23 patients had elevated transaminases at some time (PL=11, TIZ=12).

Of the 12 TIZ-Tx patients:

- 5 had abnormalities at BL; 1 had no BL values. The consultant proposes to drop these patients for further consideration. The comment is made

² This Appendix contained also a short summary of the clinical pharmacology data in animals referred above, under I. BACKGROUND.

that there were 6 pts. with abnormal BL values in the PL group and that overall, 5.9% of patients had elevated BL values.

COMMENT

The information presented above can be summarized as follows:

Study DS-0502
Pts. Developing † of Serum Transaminases

	PL	TIZ	Total
No. of Pts. Enrolled	93	94	187
Pts. with † transaminases at some time	11 (11.8%)	12 (12.8%)	23
Pts. with † transaminases at BL	6 (6.5%)	5 (5.3%)	12 ^a

a) 1 TIZ Pt. had no BL values

The approach of dropping from consideration patients merely because the BL values are abnormal is not appropriate. In some patients the "abnormalities" consisted of extremely mild elevations of one of the parameters. For example, Pt. #2 (306) had a BL PT of 38 μ mol/l [Normal = 35 μ mol/l] and no other abnormality in any other parameter [γ -GT, AP, BIL. (OT was not done)] at any time. Since this increase is less than 3 x ULN, this reviewer agrees with the approach of dropping this particular patient from further consideration. Everything else being normal, an increase of 3 μ mol/l in PT does not appear to be clinically relevant.

But consider the results in patient #9 (301):

Phase/ Study Day/ Visit	OT 0-37 ^a (U/L)	PT 6-62 ^a (U/L)	γ -GT 0-70 ^a (IU/l)	AP 39-127 ^a (IU/.)	BIL 3-19 ^a (IU/l)
B/-5/1	40	ND	42	80	4
T3/21/4	22	ND	42	70	4
P3/84/7	182	ND	171	102	27

a through e) Normal Ranges.

Only the OT value was slightly abnormal at BL (an † of 3 mmol/l over ULN). All the other three parameters were WNLs (PT was not done). There were no changes after 3 weeks of Tx but, at the end of almost 3 months of Tx, the OT, γ -GT and BIL were all higher than the BL values (x4, x4, x6, respectively) and higher than the ULN. This reviewer's suggestion is that one needs to know more about the clinical Hx of this patient, F/U values, concomitant medications³, alcohol consumption, drug abuse, gallbladder Dz, results of tests for viral hepatitis, etc. Are any of these confounding? Even in the absence of such information, the available data suggest that at the end of

³ In another part of the Consult it is mentioned that this patient was receiving INS for diabetes mellitus and temazepam was recorded as concomitant med. Both could be confounding. Abnormal liver function tests have been reported with benzodiazepines.

month 3, a hepatocellular-cholestatic process, of unknown etiology, is going on. The true severity of the process is unknown because results of histopathological evaluations are not available. But this case needs further evaluation. Incidentally, in this patient, serum concentrations of glucose, slightly higher at BL at 4.9 (Normal=2.2 to 4.4 μ mol/l) are going up (21 days=5.7 and 84 days=12 μ mol/l). Further work up to rule out the status of D.M. in this pt. is needed.

- 6 pts. had elevated transaminases values at only one time interval. The statement is made that 3 of these were "only (elevated) at the final time period".

COMMENT

These 3 patients had no changes in γ -GT, AP or BIL. Whether concomitant changes in OT and PT occurred cannot be said because only one of the two parameters was determined in these three patients. What is certain is that in all 3 patients F/Us are needed because the last transaminase values are abnormal, especially in pts. #8 (208) and #10 (201). Of the three concomitant medications mentioned, aspirin could certainly be confounding. The 1994 PDR does not mention alteration of liver enzyme or AEs related to the liver with the peripheral dilator isosorbide (ISMO[®]); the antidepressant dothiepin is not yet listed.

B. Study ANO21-001

Again, information was not provided on the design and execution of this trial, especially doses of compound tested, dose regimen and length of exposure (3 months?).

This appears to be a multicenter, PL-controlled, 2-arm (?), single or double-blinded?, U.S. trial in 256 patients with MS. Of these, 45 patients developed elevations of serum transaminase concentrations at least once during the study. Pertinent information is summarized below.

Study ANO21-001

Pts. Developing $\uparrow$ of Serum Transaminases

	PL	TIZ	Total
No. of Pts. Enrolled	125	131	256
Pts. developing $\uparrow$ in serum transaminase levels at least once during the study	15 (10%)	30 (23%)	45
Pts. with $\uparrow$ transaminases at BL	5 (4%)	6 (4.6%)	11

- At the end of the trial, 2 of the PL-treated patients and 4 of the TIZ-treated patients ended up with high abnormal values of both OT and PT. Other differences of interest between the 2 groups were:
 - In none of the PL patients the transaminases values were 100 U/L or higher.
 - Pt. #037 (4) ended up with levels of OT of 101 U/L (BL was normal at 49) and levels of PT of 254 U/L (BL was 72, high). F/U values are needed in this patient.

- Findings in TIZ Pt. #163 [14] are addressed below. The following narrative was provided for this Pt..

This pt. was a 46-y-old BF with a 25-y Hx of MS of mild severity marked by periods of remission and relapse. She also had a Hx of urinary urgency, frequency and incontinence, spasms, clonus and decreased sensation on the right side of the body. No concomitant medications were reported for these conditions. On Day 8, at 12 mg/day, the patient experienced dry mouth, dizziness, somnolence and amblyopia and on Day 15 at 12 mg/day, she experienced rhinitis. On Day 29, at 12 mg/day, she experienced abnormal gait and vertigo. Additionally, on Days 33 and 42, both at 12 mg/day, she experienced myasthenia and vomiting, respectively. All these events were considered to be of mild or moderate severity. The dry mouth, dizziness, somnolence, myasthenia and vomiting were considered to be possibly related to study drug and the amblyopia, rhinitis, abnormal gait and vertigo were considered to be not related to test med. The rhinitis resolved by Day 29 and the somnolence and amblyopia resolved by Day 63, whereas the dry mouth, dizziness, abnormal gait, myasthenia, vomiting and vertigo were ongoing. On Day 63, at 12 mg/day the patient reported headache, nausea and dyskinesia. Elevated liver enzymes were also determined. The headache, nausea and dyskinesia were considered to be of mild severity and possibly related to test med. The elevated liver enzymes were considered to be of moderate severity and related to test med. These resulted in her dismissal from the trial (On Day 69, at 12 mg/day). This information is summarized below:

Events in Pt. #163 [14], resulting in her premature
D/C from trial AN021-001

	BL	Day 63 ^a	Day 69 ^b	Day 85 ^c
AP (U/L)	94 (↑)	237 (↑)	W/D from trial	154 (↑)
OT (U/L)	21 (WNL)	716 (↑)		43 (↑)
PT (U/L)	22 (WNL)	1392 (↑)		92 (↑)

- Pt. had frank jaundice on Day 64.
- The ↑ on ENZ were considered to be a SAE. In this pt., vomiting resolved by Day 72 and nausea, dyskinesia and myasthenia resolved by Day 85.
- On Day 85, the pt. also reported a 5 pound weight loss and complained of LUQ pain of moderate severity. The pain worsened and became severe in nature occurring two to three times a day. P.E. revealed a non-tender 7 cm smooth liver.

Numerous tests for viral hepatitis were all negative. On Day 85, the patient also experienced moderate thrombocytopenia with a platelet level of $135 \times 10^9/L$ and lymphocytosis with a lymphocyte level of 37%. Both events were considered to be related to test medication. The liver enzyme values returned to WNLs on Day 106 at which time the abdominal pain and thrombocytopenia also resolved. The lymphocyte value returned to within normal levels on Day 120 whereas the dry mouth, dizziness, abnormal gait, vertigo and headache were ongoing at the last visit.

COMMENT

This case of jaundice occurred in apparent temporal relationship with the adm. of TIZ. Note that on Day 85 all parameters of LF that were evaluated (γ -GT was not done) were still elevated, although only AP had been elevated at BL. It is worth mentioning that at Day 85 serum BIL concentration was not flagged but the value at this time (1.30 mg/dl) was > x3 the value of 0.30 mg/dl at BL. There were no concomitant medications. Tests for viral hepatitis were all negative. This case of hepatocellular cholestasis, in a patient with some kind of liver abnormality at BL, was almost certainly due to TIZ.

- 17 of the 24 remaining TIZ-Tx pts. had single ENZ elevations
 - in 10 of these the final value was elevated and in the other 7 the single elevations occurred in mid-study and were followed by ↓ to normal values.

- In 2 cases the consultant/sponsor proposes that spurious results may have been due to lysis of BCs as a consequence of leaving the specimens standing O/N.

Of note, on page 380 of this report, Pt. #151 [Center 2] is listed among this group of pts. But according to the Clinical Statistical Report provided, Center No. 2 did not have a Pt. #151 (?).

- 5 of the 8 PL-Tx pts. had a single transaminase value at the time of their final lab. testing and in 1 pt. OT elevation was mild, occurred at mid-study and was followed by a normal value. Again, it is worth noting that the consultant/sponsor listed Pt. #089 [Center 3] as one of the pts. in this group but this reviewer could not locate data for this pt. in the Clinical Statistical Report for Study 021-001.

Also, a narrative was provided for Pt. A085 [Center 8]. Although this is reproduced below in its entirety, the data in the narrative do not seem to match the data on page 11 of the Clinical/Statistical Report, Appendix C. 20.2 for Study 021-001.

Pt. #A085 [Center 8]

This was a 28-y-old WM with a 3-y Hx of MS of moderate severity marked by periods of remission and exacerbation. The patient also had a Hx of spastic bladder, intermittent low back pain and fatigue. Throughout the study, the patient was receiving pemoline magnesium and oxybutynin for Tx of fatigue and spastic bladder, respectively. On Day 15, at 24 mg/day, the patient experienced dry mouth and asthenia each lasting for 7 days. Both events were of moderate severity and considered to be related to test med. On Day 22, at 32 mg/day, the patient experienced dry mouth, taste loss and asthenia each lasting for 22 days. These events were considered to be severe and related to test med. On Day 61, at 24 mg/day, the patient experienced severe arthrosis (polyarticular joint effusions) and severe rash. On Day 63, at 24 mg/day, the symptoms worsened and the patient was consequently hospitalized. On admission, the patient presented with a severe erythematous rash over his face, chest and back and a temperature of 100.7 F. At this time, the patient was D/C from the study and received antiinflammatory medication for joint pain and the left knee was tapped for excessive fluid. In addition, laboratory tests revealed severely elevated OT (716 U/L) and PT (1392 U/L) values. The consulting rheumatologist considered the event to be severe serum sickness related to the study drug. By Day 65, at 24 mg/day, the joint effusion, rash and fever had resolved and the elevated transaminase values had returned to near normal levels (SGOT/AST: 43 U/L; SGPT/ALT: 92 U/L). F/U examination on Day 77 at 24 mg/day revealed no abnormalities. Hospitalization due to macular rash and polyarticular joint effusion fulfilled the sponsor defined criteria as a SAE. It is stated that this event was reported to the FDA (by Athena Neurosciences, Inc.) as a 10 day safety report.

NOTE: This Clinical Summary seems to belong to a patient other than , #085 [Center 8]. The sponsor needs to explain this important discrepancy.

- In 9 pts. (PL=2; TIZ=7) the transaminases were elevated at two or more times, including the final visit. Events in Pt. #131 [Center 11], briefly summarized below, are worth mentioning.

In this pt. (S.E.M.) BL for all 6 parameters were WNL. Both OT (206 U/L) and PT (552 U/L) peaked by Day 102. Both were going down by the last observation at Day 116 (82 and 205 U/L, respectively) but had not normalized quite yet. Although neither AP nor BIL showed significant changes, serum BIL was not assessed at Day 116.

COMMENT

The sponsor's consultant notes that this study suggests that TIZ is associated with mild to moderate elevations in serum transaminase levels and that serious liver problems are possible but quite infrequent. These conclusions are based on the increased number of elevated transaminase levels in the TIZ group as opposed to the PL control group and the fact that many of the elevations

occurred following prolonged exposure to TIZ (elevated values at the time of the final laboratory testing).

At this point, this reviewer believes that serious liver problems with TIZ are possible but does not yet have a feeling for their frequency because one does not know the total number of patients exposed. Since at least one patient developed jaundice, the problem is not just elevations of ENZs. AP was elevated at some time in three (3) patients only. So, the manifestations of liver injury seem to be more hepatocellular than cholestatic. But in the present trial, no determinations of γ -GT were carried out.

Controlled trials will be put together and analyzed in order to get an idea of the magnitude of the problem.

C. Study ANO21-003

This is another PL-controlled U.S. study in 118 spinal cord injury patients. Elevated OT or PT were reported in 23 patients. Pertinent information is summarized below.

Study ANO21-003

Pts. Developing ↑ of Serum Transaminases

	PL	TIZ	Total
No. of Pts. Enrolled	59	59	118
Pts. with ↑ transaminases	5 (8.5%)	18 ^a (30.5%)	23
Pts. with transaminase abnormalities at BL	2 (3.4%)	8 (13.6%)	10

a) 10 pts. developing elevated transaminases while on TIZ had had normal BL values.

- None of the pts. developing ↑ in serum transaminase concentrations developed significant (clinically manifested) liver disease.
 - In 2, the ↑s were considered by the investigator to be possibly due to TIZ. Events in one of these pts. are summarized below.

Pt. #036 [Center 2]

a 44-y-old WM, had a 9-y Hx of spinal cord injury to C5-C6 and entered the study with a Frankel rating of C. The patient presented with mild dysphagia and healed PU and a Hx of contact dermatitis. He did not receive any concomitant medication. Six days prior to the start of D-B Tx (Day -6), during the S-B PL BL Phase, the patient experienced asthenia (fatigability), dyspnea (shortness of breath) and dizziness (lightheadedness), all of which resolved by Day 67. Pertinent information is summarized below.

Events in Pt. #036 [Center 2] resulting in his premature D/C from trial ANO21-003

	BL	Day 43 ^a	Day 44	Day 46	Day 51	Day 61
OT (Normal=13-36 U/L)	18	122	W/D from Study	76	49	"Resolved" ^b
PT (Normal=6-43 U/L)	21	399		290	184	"Resolved" ^b

a) Dosed at 10 mg/day

b,c) According to the investigator, these events were resolved but no lab. values were recorded.

All of these events were considered by the investigator to be of mild severity and possibly related to test med. On Day 44, at 4 mg/day, the patient was prematurely D/C from the study due to the abnormal LFTs. There were no F/U data.

COMMENT

The statement that "all of these events (meaning elevations of ENZs on Day 43) were considered by the investigator to be of mild severity" seems incongruent with the patient's W/D on the next day due to abnormal LFTs. In reality, on Day 46 both transaminases were still elevated. Neither AP nor LDH changed. No results of serum BIL concentrations were listed. The comment (from Appendix C.21, Listing of AEs) on Day 43 is "elevated LFTs to high panic level" which is probably what originated the patient's W/D from the trial.

Pt. #097 (Center 5)

This pt. had normal values until the TIZ was tapered. At that time, the OT was reported to be 368 and the PT/ALT 819 units, and were associated with elevated AP and LDH. According to the clinical summary, final values were normal for all tests. Concomitant medications included baclofen and ciprofloxacin. It is stated that the sudden elevation of all LFTs from one single sample with rapid return to normal suggests the possibility of a laboratory error or mishandling of the patients blood/serum specimen. Further, the patient continued TIZ Tx without additional transaminase elevations, suggesting that the event was not related to TIZ.

COMMENT

This reviewer should like to offer another interpretation of the above results. Although the levels for both transaminases had reverted to normal, the level of AP (143) was still almost twice the levels of 48, 46 and 46 in the three preceding determinations [to that showing elevation]. One cannot really say that values were normal for all tests because LDH levels were simply not determined. The elevation of LFTs were not sudden because there were 7 days between the day the elevations were shown and the previous test. Furthermore, the normalization was not rapid because 14 days elapsed between the high and the normal values of transaminases. On the other hand, it is indeed possible that, in some patients and for reasons still unknown, TIZ-induced elevations of serum concentrations of ENZ may normalize even under conditions of continuous use of the drug. But the F/U is too short to determine L-T effects.

- 8 TIZ-treated pts. developed either a) mild isolated single elevations [(N=4); 2 PL pts. had similar data] of doubtful clinical significance or b) more sustained elevations [(2 or more elevated values) (N=4); 1 PL pt. had similar data]. In two of the TIZ-Tx pts. the elevations of transaminases were accompanied by elevations in LDH (in one, AP was also high); but these changes were not seen among the PL-Tx patients. This reviewer agrees that, in most of these patients, concomitant medications confound the interpretation of results.
- 8 pts. (PL=2; TIZ=6) had elevated transaminase values at the final period and for these, additional F/U is needed.
- Pt. #006 (Center 2) received an accidental overdose of TIZ. The pt. developed stupor and increase serum BIL (2.3 mg/l). Transaminases and other LFTs remained in the normal range. The serum BIL returned to normal in ca. 1 week after D/C of TIZ.

COMMENT

"Overdose" is not defined but this case is of special interest because it shows effects of the drug that can be characterized as being predominantly or nearly exclusively of cholestatic nature in apparent absence of gross

hepatocellular damage. This, together with the many instances of hepatocellular injury demonstrated above - after L-T exposure to the drug - strongly suggest that adverse hepatic reactions associated with TIZ are heterogenous in nature.

D. Open-label Data (Study AN 021-002)

According to the report (page 385) LFTs in this trial suggest that a number of pts. entering the study with BL abnormalities had these values decrease or return to normal while taking open-label drug. The statement is made that there were no patients who had a deterioration of liver function that could be specifically related to TIZ Tx.

COMMENT

These open-label data appear to contradict, to some extent, some of the data from controlled trials reviewed here. In some TIZ-Tx pts., that had abnormal LFTs pre-drug, the parameters worsened. Neither tests of global liver function (serum bile acids, BSP-like evaluations, etc.) or liver Bxs have been done. It seems premature to state that no deterioration of LF, that could be related to TIZ, occurs in pts. that have liver function abnormalities pre-TIZ.

E. Other Data⁴

This information is taken from page 386 of the August 23, 1994 submission.

- In 44 studies involving 765 patients treated with TIZ, 14 (2%) were reported to have a clinically significant increase⁵ in OT, PT or γ -GT.
 - In 7 of these pts. the abnormality resolved with either continuing TIZ Tx or D/C.
 - 3 additional pts. were reported to be taking concomitant medications that may have been contributory.
- From spontaneously reported post-marketing AEs (Table 70) there were
 - 5 reports of hepatic dysfunction,
 - 3 reports of hepatitis,
 - 3 reports of jaundice and
 - 12 reports of $\uparrow$ liver enzymes.
 - The number of pts. treated is uncertain, but based on sales figures and estimates of dose and duration of Tx could be as high as 6 million to 15 million, primarily in Japan with Germany second.
- One death has been reported in a 66-year old M Tx with TIZ 4 mg/day for 2 months.
 - He developed "cholestatic jaundice".
 - TIZ and concomitant carbamazepine were stopped, but the patient died 20-days later of bronchopneumonia (Section 8.0).

⁴ Information from a review of the Sanduz clinical trials and post-marketing experience.

⁵ Defined as a 3-fold or greater increase from BL or a 2-fold or greater increase above the upper limit of the normal range.

- A cumulative frequency of adverse events reported in 130 clinical publications, 6895 (Section 8.0) patients provides the following data: hepatic enzymes increased 18 (0.26%), hepatic function abnormal 2 (0.03%).

COMMENT

- The reviewer has some questions about the pt. that died. Although he died of bronchopneumonia did the pt. also have liver failure? Was the death the result of drug hepatotoxicity = due to TIZ alone or in some kind of drug-drug interaction with carbamazepine or was the latter the culprit?
- The very small number (12) of reports of ↑ of liver ENZ, suggests a) considerable under reporting of these events or b) too liberal definition of ↑. The reviewer makes this statement on the basis of the data reviewed here: 12 reports among 94 pts. treated in Study DS-0502, 30 reports among the 131 patients treated in Study AN 021-001 and 18 among the 59 patients treated in Study AN 021-003. These equate to 13, 23 and 3% of the total number of patients enrolled in each trial, respectively.
- It is also possible that only the very serious events are being reported but this needs to be clarified.

V. SOME PUBLICATIONS OF INTEREST

Results from three pertinent literature publications are briefly summarized below.

- In the first [Y. Lapierre et al. (Montreal), Can. J. Neurol. Sci. 14:513-517 (1987)] results of a double-blind PL-controlled, 8-week trial in 66 MS pts. are described. The TIZ dose was up to 32 mg per day. Side effects most frequently cited included dry mouth and drowsiness. There were 2 treated pts. (ONLY) where "significant" (not defined) QT and PT elevations occurred that resolved to normal after reduction or W/D of the drug.
- In another [A.E. Lang and D.E. Riley (Toronto), Clin. Neuropharmacol. 15:142-147 (1992)] 10 pts. with cranial dystonia were enrolled in open-label evaluations with a single-blind PL wash-in; 8 pts. tolerated doses of between 28 to 36 mg per day (12 mg t.i.d.). Tx duration was 6 weeks. Two patients developed abnormal LFTs (not specified what parameters became abnormal). One of these 2 pts. developed a pruritic erythematous, maculopapular rash as well as abnormalities of LFTs while taking 34 mg TIZ. The reporters indicate that this patient's son "may have had a similar illness 1 to 2 weeks earlier, and, therefore, it is not certain that the drug was causative".
- A study from Japan [N. Ogawa et al., J. Internat. Med. Res. 20:78-86 (1992)] evaluated the effects of TIZ⁶ in 30 patients with sequelae of cerebrovascular Dz. Safety assessments included LFTs (not specified). No abnormal values after TIZ administration were reported.

⁶ (3 mg/day x 14 days or more; the dose was then increased to 6 to 9 mg/day if the lower dose proved ineffective).

COMMENT

The incidence of LF abnormalities reported in two of these three literature publications is much lower than the incidence in the randomized clinical trials here reviewed. This discrepancy may be due to several factors including the TIZ dose, daily regimen, dose duration, concomitant medications, underlying liver conditions (viral Dz, alcohol or drug abuse, cholelithiasis), etc. Could the underlying disease play a role in explaining these discrepancies (some clinical conditions may be associated with liver dysfunction; others not).

VI. MAGNITUDE OF PROBLEM/SUMMARY OF FINDINGS

- The total number of pts. exposed to TIZ can be summarized as follows:

LENGTH OF EXPOSURE	NO. OF PTS./SUBJECTS
Cumulative Total exposed to TIZ-Tx in clinical trials	2327
S-T Tx up to 1 month up to 2 months	1054 667
Medium-Term Tx up to 6 months	400
L-T up to 12 months up to 36 months	142 23

- The firm estimates 15 million exposures in post-marketing experience.
- For the three primary efficacy trials reviewed here (DSO-502, 021-001 and -003) pooled, which include 525 pts. (PL=261; TIZ=264), the mean duration of Tx, including titration and taper was 71 days in the PL group and 70 days in the TIZ group. According to the information on page 4 of the MOR of SU, the most common duration of stable dose of test medication (plateau phase) was >9 weeks (n=124) for patients in the TIZ group. During this period, 32 TIZ patients received an average daily dose up to 19 mg, 32 patients received an average daily dose between 19 and 28 mg, 20 patients received between 28 and 35 mg and 40 received an average daily dose >35 mg. Of the patients who had a plateau phase >9 weeks, a higher proportion of PL-Tx patients (88, 64%) were titrated to a daily dose >35 mg compared to TIZ-Tx patients (40, 32%).
 - The mean maintenance dose of TIZ across all supportive PL- and active-controlled trials (excluding studies involving modified release formulation) was ca. 18 mg/day, typically administered in 2 or 3 daily doses. The maximum permissible daily dose of TIZ in these supportive studies ranged from 16 to 36 mg/day, with 4 trials allowing the dose to be adjusted to 36 mg/day given t.i.d. In 3 of the L-T trials, the average daily dose of TIZ was 7.6 mg/day (range: 5 to 9 mg/day) while in the remaining 5 trials it was 16.7 mg/day (range: 15 to 20 mg/day). In all but one of the clinical pharmacology studies, doses of TIZ ranged from 3 to 8 mg/day; in the remaining study (S-63), the average maintenance dose of TIZ was 24.8 mg/day.

From the above, the percentages of pts. with elevated serum transaminases were reported as AEs:

	<u>PL</u>	<u>TIZ</u>	<u>p-value</u> ^a
Pts. with ↑ AST (OT)	0%	2%	0.030
Pts. with ↑ ALT (PT)	1%	3%	0.068

a) Details of statistics not given

- Computation of Tx-emergent LFT abnormalities in critical clinical trials (p. 12-13 of MOR of SU):

Parameter (Units)	<u>PL</u> N/(%)	<u>TIZ</u> N/(%) ^a	p value ^b
AST (OT) ^c (U/L)	0/214 (0%)	5/208 (2.4%)	0.003
ALT (PT) ^c (U/L)	1/231 (0.4%)	11/227 (4.8%)	0.028
AP ^c (U/L)	0/248 (0%)	1/249 (0.4%)	N.S.

a, b) 3 x the UNR or 2 x BL if value was >UNR at BL

c) 2 x UNR or 2 x BL if value was >UNR at BL

d) Percentages are based on the # of pts. with any post-BL value for given parameter

e) Two-tailed Fisher's exact test, no correction for multiple comparisons

- Summary of incidence of elevated transaminases in clinical trials reviewed here.

	<u>PL</u>	<u>TIZ</u>
<u>I. Randomized, Controlled Studies</u>		
A. <u>Study DS-0502</u>	11/93 (12%)	12/94 (13%)
B. <u>Study ANO21-001</u>	13/125 (10%)	30/131 (23%)
C. <u>Study ANO21-003</u>	5/59 (8%)	18/59 (31%)
<u>II. Open-label Studies</u>		
D. <u>Study ANO21-002</u> ^a	N/A	23/161 (14%)

III. Supportive Clinical Trials

E. 44 Studies ^b	N/A	14/765 (2%)
F. 130 clinical publications ^c		18/6895 (0.26%) ^d
- <u>Abnormal Hepatic Function</u>		2/6895 (0.03%)

- a) This is an open-label extension of Study -001.
- b) From a review of the Sandoz clinical trials and post-marketing experience.
- c) Exposure data estimated to be 6 million to 15 million, primarily in Japan and Germany.
- d) Represents cumulative frequency of AEs reported in these 130 publications involving a total of 6895 pts.

COMMENTS/STATISTICS

For TIZ, the incidence of elevated transaminases in randomized, controlled trials is considerably higher (13% to 31%) than in the so-called supportive clinical trials (2%). These differences could be due to a number of factors, including dose, dose duration, age, gender, race, liver function, kidney function, definition of elevation, and underreporting (foreign data) etc., etc. A review of the reasons to explain these differences is beyond the realm of the present review.

From the practical viewpoint, it is seen that the incidence in the supportive clinical trials is even lower than that observed among PL-Tx pts. in the randomized, controlled studies. The PL response in the latter trials was consistent (8% to 12%). In the absence of medications, this finding suggests that, under pre-drug conditions, the underlying Dz is associated with LFT abnormalities. Although the open-label studies are less reliable data because they do not have a concurrent control, the 14% observed in these trials lies within the 13% to 31% in the randomized, controlled studies, the most reliable data. Based on this observation, this reviewer has carried out a meta-analysis of the incidence of elevated transaminases in the randomized, controlled studies. The results can be summarized as follows:

Statistics^a

<u>Study</u>	<u>PL</u>	<u>TIZ</u>	<u>95% CI</u>	<u>p-value^c</u>
DS-0502	12%	13%	-10.4, 8.5	N.S. ^b
AN021-001	10%	23%	-21.5, -3.5	<0.05
AN021-003	8%	31%	-35.8, -8.3	<0.05

- a) Statistical evaluations were carried out by Dr. M. Nuque (Biometrics).
- b) N.S. because the CIs include 0.
- c) Overall comparisons based on Odds Ratio (Peto Method):
OR=0.45 (0.29, 0.71) [These values do not include 1.0].
Z-value= -3.452
p<0.001

- The reviewer's conclusion, from the above evaluations, is that TIZ is associated with a statistically significantly higher incidence of elevated transaminases than PL (on the average, 20% vs 10%, respectively). If one were to include the open-label data the corresponding percentages would be 18% vs 10%.
- The rates in the 44 studies (2%) and the 132 publications (1%) are so low that this suggests a) transaminase levels were not observed with sufficient frequency to detect most elevations; or b) gross BL disease state and severity differences. Either of these implies that pooling of these data with those from randomized, controlled trials would be inappropriate.

VII. REVIEWER'S CONCLUSIONS

From the available data provided, this reviewer concludes that orally administered TIZ is associated with liver injury in animals and man.

No information on liver markers of cholestasis (AP, direct BIL) or LDH was given but it appears that, in animals, the liver injury is predominantly of the hepatocellular type. Since EM assessments of mitochondria, microsomes and other organelles was not done, it is not known if the lesions in animals were completely reversible.

An attempt was made to fully characterize the liver adverse reactions in association with TIZ in humans. Included in the present review were data from three PL-controlled trials, open-label studies, post-marketing (mostly Japanese and German) information and a few pertinent publications. The approach consisted of reviewing data from individual clinical studies first followed by assessment of overall incidence. The observed ARs included both patients without apparent liver abnormalities as well as patients with alterations of LFTs pre-drug. No mention is made as to whether the latter type of patients had biopsy-proven chronic liver Dz such as liver cirrhosis but some appeared to have a Hx of alcohol intake so they may have had alcoholic liver Dz at BL. The underlying conditions for which TIZ was being tested or prescribed included primarily MS, but patients with spinal cord injuries, cranial dystonia, and those with sequelae of cerebrovascular Dz were also included. Although liver viral Dz and concomitant medications were confounding some of the cases, in others, the liver injury developed after administration of TIZ as the only medication the patient was taking. In many instances positive dechallenges are suggested because biochemical parameters of hepatic injury occurred during TIZ therapy but resolved upon D/C of the drug. From the data at hand it is concluded that the relationship of liver ARs to TIZ is uncertain in some cases but probably in some. Also, the information is not clear as to whether these episodes compatible with hepatotoxicity occurred only in patients who had not previously received TIZ as well as those who had previously been exposed to the drug. Information on positive rechallenges is not presented.

Although the clinical picture of liver ARs apparently related to TIZ is yet to be fully characterized it appears heterogeneous. Both hepatocellular and cholestatic manifestations of liver injury have been reported. More data are needed to establish with certainty whether these abnormalities are reversible (as the sponsor proposes) get worse or stay the same over time. How does one go about this (before or after NDA approval) depends - of course - of the risk/benefit assessment and this is up to HFD-120.

The Athena consultant concluded that TIZ treatment appeared to be associated with a mild, reversible increase in transaminase test results in a modest number of patients, estimated at about 2% and that progression to more serious liver disease is highly unlikely based on the present data. This reviewer believes that the incidence of increased transaminases is higher than 2% and that a more comprehensive description of the human data should be included in the labeling.

VIII. RECOMMENDATIONS FOR REGULATORY ACTION

1. To better characterize the effects of the drug on liver function, follow-up studies are needed to determine the long-term (>3 months) effects of the drug. These studies should differentiate between patients in whom liver function is normal vs those with biopsy-proven liver cirrhosis, alcoholic liver disease, or those with gallstone disease, viral hepatitis, those being treated with known hepatotoxins, etc. These evaluations should include:
 - a) Routine evaluations of Bil, OT, PT, AP, γ -GT and LDH as a function of time. Determination of serum concentration of only OT and/or PT is inadequate.
 - b) Test of global liver function before drug administration and at the end of 3, 6, 12 months, etc. The aim of these dynamic evaluations is to demonstrate mild to moderate degrees of liver injury that could be missed with biochemical parameters, especially if - as proposed by the sponsor - the latter are to be used alone.

These tests should include serum bile acid concentrations and BSP-like tests (MEGX, galactose/ICG clearance/excretion, a test of hepatic microsomal metabolism/activity (aminopyrine/caffeine excretion) and a test to assess changes in liver blood flow. It is up to the sponsor to establish a priori the quantitative assessment of results from these tests of global liver function.
 - c) The confirmatory diagnosis of the liver injury induced by TIZ in man should be based on liver biopsy.
2. Although the clinical data are the most important, studies to determine the potential of the drug to induce liver injury should also be considered. These include evaluations in isolated perfused rat liver to assess effects on function, including bile flow and bile acid secretion/composition. Also included should be studies in isolated hepatocytes to assess effects on permeability of plasma membranes to ions and effects on bile acid uptake and release.
3. Since it appears that important ADME studies of the drug in man are yet to be performed, the following is recommended:
 - a) Studies to establish if there is an enterohepatic circulation of the drug/metabolites and the extent of such an EHC (in man).
 - b) What effects do hepatic function (example Child A vs B vs C patients) have in the handling of the drug by the body?

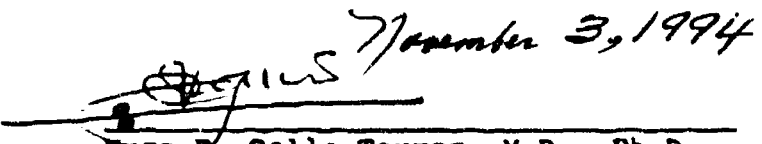
The studies listed under 1. through 3. above should preferably be conducted before approval of the drug. Alternatively, a commitment to carry out these evaluations, as a condition of approval, may be acceptable.

4. The labeling should be comprehensive. Based on the available information the following is proposed.

AR Section

Hepatic: Mild to moderate and, rarely, marked elevations of markers of liver function (SGPT (ALT), SGOT (AST), alkaline phosphatase, γ -glutamyl transpeptidase, LDH and bilirubin (jaundice)). The overall incidence of increased transaminases in randomized, controlled clinical trials is 18% to 20% (PL=10%). Progress to overt and/or serious liver disease is infrequent. Hepatocellular, cholestatic (in one case leading to death) and mixed hepatitis has occurred.

Since there are presently insufficient data to clearly establish that a relationship existed between the serious AEs (including death) and TIZ a disclaimer at the beginning of the AR Section listing the rare ADRs is needed. This could be worded as ...In many instances, the relationship to tizanidine was unclear.

Hugo B. Gallo-Torres November 3, 1994


Hugo B. Gallo-Torres, M.D., Ph.D.

cc:
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-180/CSO Consult File
r/d 9/7/94, 11/2/94 jgw
f/t 11/3/94 jgw
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11/3/94
Concur
[Signature]

MEMORANDUM OF CONSULTATION

Date: February 2, 1995

Between: Randy Levin, M.D. and Janeth Rouzer-Kammeyer, M.D. (HFD-120)
and
Joy D. Mele, M.S. (HFD-713)

Subject: Blinding in efficacy studies of Tizanidine (NDA# 20-397)

The sponsor, Athena Neurosciences, submitted the results of 3 double-blind, randomized, parallel studies (Studies DS-502, 021-001 and 021-003) which were reviewed by this statistician in a document dated 12/23/94. An overview of these studies is shown below.

Table 1. SUMMARY OF 3 MAIN PLACEBO-CONTROLLED TRIALS

Study Number	# of Centers	# of Placebo Patients	# of Tizanidine Patients	Patient Population	Duration of Treatment	Placebo Ashworth	Tizanidine Ashworth	P-value
DS-0502	16	93	94	MS	13 weeks	-1.5	-3.9	.008
021-001								
With Center 4	15	125	131	MS	13 weeks	-2.8	-1.7	.46
Without Center 4	14	109	112			-3.8	-3.2	.99
021-003	14	59	59	spinal cord injury	7 weeks	-0.4	-4.4	.0001

Questions regarding the maintenance of the blind in each study were raised for the following reasons.

1. Statements by study investigators in a publication sent to the Division of Neuropharmacological Drug Products (HFD-120) in November, 1994¹ indicated that it was easy to ascertain whether the patient was on active drug from the side effects.
2. The choice of the person performing the efficacy assessments differed among the 3 studies. For Study 021-001 (a negative study), two physicians were involved with patient evaluation; an assessor who performed the efficacy measures and a prescriber who managed the dose titration and patient care. Study 021-003 (a positive study) used a similar

¹ Neurology November 1994, Volume 44 Supplement 9 titled "Role of tizanidine in the treatment of spasticity"

design except the assessor was a physical therapist not a physician. For Study DS-502 (a positive study), a single physician acted as both assessor and prescriber. Based on design, it appeared that the blinding would be best maintained in Study O21-001, the negative study.

3. There were no explanations for the negative results of Study O21-001. Even though negative or failed studies are not unexpected in NDA submissions, this study seemed particularly unusual due to the size of the trial (twice the size of O21-003 and about 30% larger than DS-502) and the reversal of the observed effects. There were concerns that the lack of effect in O21-001 may be due to maintenance of the blind (implying that the drug is ineffective).

The most common side effects of tizanidine were somnolence, asthenia and dry mouth. About ¼ of the placebo patients and about ¾'s of the tizanidine patients exhibited one of these side effects. The number of patients with each side effect is shown in Table 2.

Table 2. Number of Patients with Each Common Side Effect

Side Effect	Placebo n (%)	Tizanidine n (%)
Asthenia		
DS-502	9 (10%)	32 (34%)
O21-001	20 (18%)	53 (48%)
O21-003	8 (14%)	18 (31%)
Dry Mouth		
DS-502	6 (6%)	43 (46%)
O21-001	16 (15%)	63 (57%)
O21-003	4 (7%)	23 (39%)
Somnolence		
DS-502	17 (18%)	50 (53%)
O21-001	3 (3%)	53 (48%)
O21-003	4 (7%)	23 (39%)

Note that some patients may be counted more than once.

To see if the data suggested a relationship between the presence of a side effect and a decrease in the Ashworth score, descriptive statistics of the Ashworth score were tabulated for patients with and without side effects (Table 3). Since the data was not readily available in electronic form, we began our examination with just the placebo patients. We also thought that in the placebo group, a larger change for patients with side effects may be indicative of unblinding, while in the tizanidine group such changes may be due to effective doses causing more side effects. If a difference between the placebo patients with and without side effects was seen, we looked at the tizanidine patients. Note that the results in Studies 021-001 and 021-003 were consistent across groups while in Study DS-502, the magnitude of the results in the patients with side effects is larger than those without side effects in each treatment group.

Table 3. Ashworth Scores for Patients with and without Common Side Effects

	N	Baseline	Endpoint Change
DS-502			
Placebo Patients			
With Side Effects	26	15.6 (8.7)	-2.4 (4.6)
Without Side Effects	67	17.3 (12)	-1.2 (5.7)
All Tizanidine Patients	94	18.5	-3.9 (5.0)
With Side Effects	74	18.3 (8.9)	-4.2 (5.4)
Without Side Effects	20	19.0 (11.1)	-2.7 (4.9)
001 with Center 4			
Placebo Patients			
With Side Effects	37	15.0 (9.3)	-4.1 (9.0)
Without Side Effects	83	18.9 (14.1)	-3.7 (9.7)
All Tizanidine Patients	125	15.6	-3.2 (9.3)
001 without Center 4			
Placebo Patients			
With Side Effects	31	13.1 (7.7)	-2.3 (7.1)
Without Side Effects	73	15.7 (10.3)	-3.1 (7.2)
All Tizanidine Patients	112	13.0	-1.7 (7.2)
003			
Placebo Patients			
With Side Effects	12	10.2 (3.9)	+0.7 (5.1)
Without Side Effects	43	10.9 (4.9)	-0.7 (3.0)
All Tizanidine Patients	49	11.9 (4.5)	-4.4 (4.0)
With Side Effects	36	12.0 (4.6)	-4.4 (3.8)
Without Side Effects	13	11.5 (4.6)	-4.5 (4.7)

Since dry mouth may be the most readily recognized side effect, we looked at the responses of patients with dry mouth separately (Table 4).

Table 4. Ashworth Scores for Patients with Dry Mouth

	N	Baseline	Endpoint Change
DS-502			
Placebo	6	16.0 (7.8)	-3.5 (5.6)
Tizanidine	42	19.7 (9.9)	-4.6 (5.0) ¹
001 with Center 4			
Placebo	16	12.4 (6.1)	-1.3 (5.4)
001 without Center 4			
Placebo	15	12.0 (6.1)	-1.5 (5.6)
003			
Placebo	3	8.8 (4.6)	-1.0 (3.0)
Tizanidine	20	12.3 (4.4)	-4.4 (4.4)

In Study DS-502, the subset of patients with dry mouth had a slightly higher response (Table 4) than the patients with and without side effects (Table 3).

¹22 of the 42 patients had dry mouth associated with asthenia. The mean change for asthenia was -4.6 also.

We looked at the number (percentage) of patients who showed any decrease on the Ashworth scale at endpoint by treatment group and the presence of common side effects (Table 5). Again in DS-502, a higher response is observed in the patients with side effects compared to those without side effects.

Table 5. Patients Showing a Decrease on Ashworth at Endpoint

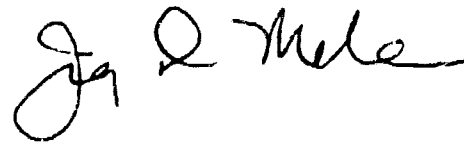
DS-502	
Placebo	
With side effects	16/26 (62%)
Without side effects	30/67 (45%)
Tizanidine	
All	67/94 (71%)
With side effects	57/74 (76%)
Without side effects	11/20 (55%)
001 with Center 4	
Placebo	
With side effects	25/37 (68%)
Without side effects	50/83 (60%)
Tizanidine	
All	79/125 (63%)
001 without Center 4	
Placebo	
With side effects	20/31 (65%)
Without side effects	45/73 (62%)
Tizanidine	
All	64/105 (61%)
003*	
Placebo	
With side effects	4/12 (33%)*
Without side effects	23/43 (53%)*
Tizanidine	
All	40/49 (82%)*
With side effects	29/36 (81%)
Without side effects	11/13 (85%)

* The denominator includes only patients with endpoint data. If one includes all patients randomized the values are 4/14 (29%), 23/45 (51%) and 40/59 (68%) respectively.

The data in Tables 3 to 5 suggests differential effects in Study DS-502 due to presence of side effects; however the number of patients are small in the subgroups. Tests for interaction (treatment by side effect) yielded nonsignificant results ($p > .50$).

Overall Comments

These analyses are exploratory and do not yield any definitive results but could be helpful for suggesting where a problem with blinding may have existed such as for Study DS-502, particularly in light of other information known about the trials. However one should recognize that forming subgroups based on variables measured after randomization can be problematic¹ since assignment to subgroups may be treatment-related as it is here. That is, in the tizanidine group, one might not be surprised to find a larger effect in patients with side effects since the presence of side effects may be indicative of therapeutic dosing. So by definition of the subgroup, a favorable outcome is predictable. (It is interesting to note, however, that this was clearly not the case in Study O21-003 where responses in both tizanidine subgroups were the same.)



Joy D. Mele, M.S.
Mathematical Statistician

cc:
Orig. NDA 20-397
HFD-120
HFD-120/Drs. Leber, Katz, Rouzer-Kammeyer and Levin
HFD-120/Ms. Higgins
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-713/Ms. Mele

Mele/x45478/SERB/WordPerfect Windows-tizblind.rev/Feb. 2, 1995

¹ Yusif, et al . Analysis and Interpretation of Treatment Effects in Subgroups of Patients in Randomized Clinical Trials. *JAMA* 1991;266:93-98.

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:----- 20-397
SPONSOR:----- Athena
DRUG:----- Tizanidine
INDICATION:----- Spasticity
MATERIAL SUBMITTED:--- Response to Not Approval letter
CORRESPONDENCE DATE:- 9/8/95
DATE RECEIVED:----- 9/11/95
DATE REVIEWED:----- 1/7/96

Introduction:

The sponsor received a Not Approvable letter from the Agency on 3/6/95. A meeting between the sponsor and members of the division and ODE-1 was held on 7/27/95. As a result of the meeting, the sponsor has submitted a response to the Not Approval letter. In this response, aside from restating their previous positions, the sponsor has submitted the following new clinical information:

- (1) A reanalysis of the global assessment in study 502, a secondary outcome measure showed a significant improvement in global assessment for tizanidine.
- (2) A reanalysis of the spasm and clonus data from study 003 using LOCF data which did not include the period of use following taper which was included in the initial analysis which shows a statistically significant difference for spasm and clonus at endpoint.
- (3) Results of study 005, a single dose study in patients with MS, which shows a statistically significant reduction in muscle tone in patients receiving a single dose of 8 or 16 mg of tizanidine.
- (4) Additional safety information from long term, open label, safety extension trials of study 001, 003 and 005.
- (5) An analysis of the dose at which patients who responded to treatment with a reduction in spasms or muscle tone had their initial response to treatment.

I have reviewed the clinical portions of the sponsor's response, re reviewed portions of the original NDA and safety updates as well as the original reviews of

these submissions, and reviewed the sponsor's revised labeling which was submitted in a separately on 11/30/95 for my response to the sponsor's submission. Additional reviews were also performed by the division's statistical consultant, J. Mele. Dr. Atrakchi has reviewed the preclinical information and Dr. Guzewska has reviewed the chemistry information.

Study AN021-005:

Protocol:

Design: MS patients with spasticity severe enough to cause disability were withdrawn from their anti spasticity medication over a 2 weeks period. They were then randomized to receive a single dose of either 8 or 16 mg of tizanidine or placebo after a 1 week placebo run in.

Efficacy outcome: Antispasticity efficacy was assess at 0, 1, 2, 3 and 6 hours after dosing in the placebo run in and double blind phase with the Ashworth scale and Pendulum test. The patients counted spasms hourly. For the Ashworth score, tone was assessed in the hip adductors, knee flexors and extensors and plantar flexors. To enter the study, the Ashworth score for one of the muscles must reach a minimum score of 2 with the total Ashworth for the extremity ≥ 4 . The Pendulum test was assessed with the change in angle on the best of three swings of the leg which had satisfied the Ashworth entry criteria.

Safety outcome: Vital signs (reclining and immediately upon standing (preferred) or sitting) was assessed at 0, 1, 2, 3, 4, 5 and 6 hours after administration.

PK: Plasma levels was checked at 0, 0.5, 1, 1.5, 2, 3, 4 and 6 hours after administration.

Analysis: The primary endpoint was the actual differences between the assessments of the Ashworth and Pendulum score 1 hour after the first dose of the single blind placebo run in and 1 hour after the dose in the double blind phase. Between treatment comparisons of tizanidine and placebo was made with ANOVA with center and treatment effects. A dose response analysis used plasma levels. Repeated measures were used to assess the changes over time.

Endpoints include in the order listed in the final protocol: the total Ashworth score of all muscles in the leg used to meet the entry criteria, the angle of displacement on the best of three swings of the leg used to meet the entry criteria, the Ashworth score for the most spastic muscle on the limb used to meet the entry

criteria, and spasms counts.

Results:

Disposition: A total of 142 patients were enrolled. One patient withdrew for personal reasons from the 8 mg group and one withdrew from the 16 mg group for hypotension. The disposition is summarized in the following table.

Disposition	Plb	8 mg	16 mg
Randomized	48	45	49
Withdrew	0	1	1
Not evaluable	2	1	6
No 2 hr Ashworth	0	0	2
Ashworth not ≥ 2 at single blind	2	0	3
Ashworth not ≥ 2 at double blind	1	1	2
Total Ashworth not < 4 at double blind ^d	0	0	1

Demographics: The demographics were similar except that equal numbers of males and females were in the 8 mg group while the placebo and 16 mg group had 2/3 females. The weight in the 8 mg group was higher (73.3 kg) compared to placebo (66.8 kg).

Efficacy: Analyses of the Ashworth score, Pendulum test and spasms counts are included in J.Mele's review. For the Pendulum test, a comparison of both the 8 and 16 mg groups with placebo showed a statistically significant difference between groups at 1 and 2 hours. At 3 hours, there was a statistically significant difference between the 16 mg group and placebo. The difference between the 8 mg group and placebo was of borderline significance ($p=0.05$). No difference between either the 8 or 16 mg groups was found at 6 hours. There was no statistical difference between either the 8 or 16 mg groups and placebo for the spasm counts. For the Ashworth score, a comparison of both the 8 and 16 mg groups with placebo showed a statistically significant difference between groups at 1, 2 and 3 hours. No difference between groups was found at 6 hours. The total Ashworth score of all muscles in the leg used to meet the entry criteria are summarized in the following table:

Total Ashworth score for the muscles in the leg used to meet the entry criteria			
Hours post dose	plb	8 mg	16 mg
0 hr	8.8	8.9	8.4
1 hr	8.7	6.3	4.9
2 hr	8.4	6.3	4.2
3 hr	8.0	6.7	4.5
6 hr	8.6	8.2	7.5

Safety:

Treatment emergent AEs: The most common AEs were drowsiness, dry mouth, tiredness and dizziness. These events started to be evident as early as 30 minutes in the 16 mg group and 1 hour in the 8 mg group. The effects appeared to peak between 1 and 2 hours for the 16 mg group and 1 to 3 hours for the 8 mg group. The sponsor noted that AEs lasted 3 to 4 hours for the 8 mg group. The AEs were still apparent at 6 hours for the 16 mg group. In regards to hypotension, two episodes were considered to be serious. Patient 113 was a 38 year old female who received 8 mg. 75 minutes after dosing the patient was hypotensive and found to have a sitting BP as low as 54/46. The hypotension lasted over 5 hours before resolving. One hour and 45 minutes after dosing, the patient also had bradycardia with a rate as low as 52. This resolved after 3 hours. Patient 38 was a 63 year old female who had a history of hypertension and was treated with enalapril. One hour after treatment, the patient was hypotensive with a BP of 92/70. The patient was treated with fluids and epinephrine and steroids. She was transferred to the ICU and treated with low dose dopamine drip. The patient was withdrawn from the study. The problems resolved by the next day. The summary of the frequency of treatment emergent AEs are in the following table.

Treatment emergent AEs			
	Plb	8 mg	16 mg
Drowsiness	31%	78%	92%
Dizziness	4%	22%	45%
Dry mouth	35%	76%	88%
Tiredness	40%	67%	78%
Hypotension	0	16%	33%
Bradycardia	0	2%	10%
Syncope	0	0	2%

Vital signs: The systolic and diastolic BP decreased in both the 8 and 16 mg treatment groups. The greatest changes occurred at 2 hours with the exception of the diastolic BP which was greatest at 3 hours. The changes are summarized in the following table.

Vital signs						
	0 hr	1 hr	2 hr	3 hr	4 hr	6 hr
PLB mean BP	120/74	119/75	117/74	122/74	120/73	120/73
mean heart rate	76	70	71	71	74	74
Orthostatic change BP	118/74	120/74	120/75	123/77	121/72	121/74
HR	78	73	74	75	76	77
8 mg mean BP	120/75	106/69	103/69	108/68	111/68	115/70
mean heart rate	74	68	66	68	70	71
Orthostatic change BP	120/77	101/66	100/65	106/68	109/68	116/71
HR	77	75	70	72	73	74
16 mg mean BP	122/75	102/66	96/61	101/66	106/64	115/70
mean heart rate	72	66	61	63	67	69
Orthostatic change BP	121/76	97/64	92/57	97/64	103/64	113/71
HR	74	68	68	68	70	70

The sponsor defined clinically significant BP changes for patients with a baseline systolic BP > 80 as decreases $\geq 20\%$ in either the supine systolic or diastolic BP. For patients with a baseline BP of ≤ 80 , a change of 10% was significant. The percent of patients with clinically significant changes in BP are summarized in the following table:

Percent of patients with clinically significant reduction in BP						
	1 hr	2 hr	3 hr	4 hr	6 hr	Anytime
Placebo (N=48)	2%	6%	4%	8%	10%	17%
8 mg (N=45)	36%	47%	31%	20%	22%	67%
16 mg (N=49)	47%	57%	43%	41%	22%	71%

Other safety: Labs and PE were evaluated at screening and at follow up. There were no changes noted.

Plasma levels: The sponsor concluded that the AE and efficacy effects lag behind the plasma levels. The plasma concentrations varied and a subset of patients did not respond with plasma levels that were effective for others.

Overview of safety data from the NDA and safety update:

As with efficacy data, study 005 has provided a time course of acute adverse events associated with a single dose of tizanidine. It does not provide evidence for the safety of multiple doses of tizanidine. I have included an overview of safety information presented in the submissions and reviews of the original NDA and safety updates for tizanidine including a discussion of the size of the safety database, deaths, discontinuations, serious AEs and other common AEs.

Size of the safety database:

Information about the safety of tizanidine comes from: (1) controlled clinical trials and open label, long term studies in patients with spasticity in which over 1000 patients were exposed to tizanidine, (2) controlled clinical trials in patients with muscle spasms in which 736 patients were exposed to tizanidine, (3) clinical pharmacology trials in which 474 healthy subjects were exposed to tizanidine, and (4) post marketing surveillance.

A break down of patients in the clinical trials is summarized in the following table:

Number of subjects in clinical trials conducted by Athena and Sandoz		
	Tizanidine	Placebo
Athena studies		
Study 001 - Multiple Sclerosis	111	109
Long term extension study 002	88 ^a	
Study 003 - Spinal cord lesion	59	59
Long term extension study 004	42 ^a	
Study 005 - Multiple Sclerosis	94	48
Long term extension study 002	9 ^a	
Sandoz studies - spasticity		
Study 502 - Multiple Sclerosis	94	93
Clinical Pharmacology-MS/spinal cord	62	29
Sandoz studies placebo controlled -MS	65	64
Active controlled -various conditions including stroke	411	
Open label -various conditions	127	
Total patients with spasticity	1097	402
Sandoz studies -Spasm	736	240
Sandoz studies -Healthy subjects	474	123
Total subjects in safety database (including safety update)	2307	765

^a Only includes patients who were previously on placebo

In study 001, the sponsor discovered that some of the patients randomized to placebo were receiving tizanidine. This was discovered when patients in the placebo group were found to have AEs of similar severity and type to those seen in patients on tizanidine. This led to the elimination of center 4 from the safety

and efficacy data base.

An additional 786 patients with spasticity and 790 patients with painful spasms have been treated in Asia. These patients received low doses (one mg doses were used) and only summary information is available.

The drug is also marketed in 48 countries with many exposures.

Dose and duration of exposure:

Muscle Spasm (736 patients): In the trials involving patients with muscle spasm, tizanidine was given in doses of 6 to 12 mg/day. 84% of the patients were treated for ≤ 7 days. The maximum duration of treatment was 14 days.

Healthy subjects (474 patients): The studies involving healthy subjects were PK studies evaluating a single dose of tizanidine in about 80% of exposures. The greatest exposure was in 33 subjects on doses of 12 to 16 mg/day for 6 weeks.

Post marketing: The exposure from post marketing is not known. The sponsor notes that millions of doses have been prescribed. While the drug is marketed for the treatment of spasticity with recommended doses of 12 to 24 mg/day and a maximum dose of 36 mg/day, the sponsor noted in the NDA that 80% of the use of tizanidine is for the short term treatment of muscle spasm. These numbers are consistent with the use in the spontaneous post marketing AEs reported by Sandoz in 1993. In these reports, 22% of the patients were being treated for spastic paralysis (the exact etiology of the spasticity was not noted). The average dose in these patients was 7.5 mg/day, not 12 to 24 mg/day as recommended in labeling.

Spasticity (1097 patients): The doses used in the clinical studies for patients with spasticity varied from 2 mg/day to 36 mg/day. The duration of exposure ranged from a single dose to treatment for over 1 year.

The sponsor notes that dosing information is available for only a subset of several hundred patients in the Sandoz studies in spasticity. The sponsor incorrectly states that the distribution of dosing of this subset conforms to the dosing in the US studies where 1/3 of patients received doses of 30 to 36 mg/day. The maximum dose in this subset of Sandoz studies, as the sponsor noted in distribution tables, was only 20 mg/day. No patient received a dose of 30 to 36 mg/day.

The number of patients treated at each dose level for study 002, 004 and the Sandoz long term studies where dosing information is available are summarized

in the following table:

Cumulative distribution of the total daily dose in patients in studies 002 and 004 and long term Sandoz studies with dosing information				
Duration of treatment	Any dose	≥8 mg/day	≥16 mg/day	≥24 mg/day
One dose or more	738	678	541	334
More than 3 months	337	319	271	167
More than 6 months	237	226	191	120
More than 12 months	105	101	94	63

Adverse Events:

Deaths:

There were two deaths reported in the NDA data base, two in the 4 month safety update and 6 in post marketing for patients on tizanidine. The sponsor has provided very little information regarding these deaths. The information is summarized in the following table:

Deaths on Tizanidine				
Study/Pt ID	age/sex/dx	Dose	Duration	Cause of death
	55/m/sci	24 mg	69 days	CHF started on day 69 leading to death on day 79
	44/f/ms	24 mg	6 years	Complications of MS
	36/m/sci	36 mg	4 months	unknown
	?	?	46 weeks	Not provided
	64/f /spasticity	9 mg	?	Increase in blood sugar
	50/m/CBS#	3 mg	?	CHF 4 days after discontinuation
	68/m/	4 mg	2 months	Cholestatic jaundice (patient also on carbamazepine)
	70/f /spasticity	2 mg	?	Exacerbation of underlying CHF
	m/spasticity	?	?	Respiratory failure
	?	?	?	?

#CBS=cervico brachial syndrome

Discontinuations:

45 of 264 (17%) patients receiving tizanidine and 13 of 261 (5%) patients receiving placebo in the controlled clinical trials, 502, 001 and 003, discontinued for AEs. 32 of the 161 (20%) patients in the long term extensions 002 and 004 also discontinued for AEs. When patients discontinued from the study, they frequently had more than one reason for discontinuing. The number of patients with an AE that was involved in the decision to discontinue treatment are summarized in the following table:

Number of patients with an AE associated with discontinuation		
	Placebo (N=261)	Tizanidine (N=264)
Number of patients with AEs associated with discontinuations	13	45
Asthenia	2	8
Somnolence	0	8
Dry mouth	2	7
Increased spasm/tone	2	6
Dizziness	0	5

Serious AEs:

Hallucinations:

The sponsor reported hallucinations occurring in 5 of 170 patients on drug in studies 001 and 003. No patients on placebo reported hallucinations. 5 of 117 patients in study 002 and 3 of the 62 patients in study 004 reported hallucinations. In the NDA, the sponsor discussed the first 11 cases. In 4 of the 11 cases the hallucinations led to discontinuation of the drug. In 3 of the 11 patients, the dose was reduced and in 4 the drug was continued at the same dose. The sponsor noted that 3 of the 11 patients were on other medications that list hallucinations as AEs. Patients had been on tizanidine from 12 days to more than 5 months prior to the hallucinations. The hallucinations disappeared in all but 2 patients. One patient continued to have hallucinations 2 weeks after the drug was discontinued. One patient (88), in study 003 had hallucinations associated with depersonalization, delusions and somatic pain beginning on day 23 at a dose of 36 mg/day. The patient was hospitalized. The symptoms did not resolve with tapering and the drug was discontinued on day 25. The hallucinations resolved but the patient continued to have paranoid ideation and was receiving psychiatric care at the last follow up report.

In Appendix A-1 in volume 165 of 214, the sponsor reports that no hallucinations were reported in study DS-0502 though in Appendix C.20 in the study report for study DS 0502, patient 8-307-Y was reported to have hallucinations.

Corneal Opacities:

Because of the finding of corneal opacities in the animal studies, ophthalmologic examinations were performed in study 001 and 003 and the long term extensions 002 and 004. The sponsor did not find evidence for an increase severity of findings. An ophthalmology consultation from Dr. Carerras noted that while there were no reports of corneal opacities reported in any of the studies, there were "too many inconsistencies in the reported data to assume that the examinations were properly performed" and the data as reported did not allow for quantitative evaluation or sound scientific conclusions".

Hypotension:

In study 005 and S-87, BP was closely monitored following a single dose of tizanidine. Study S-87 was a crossover study evaluating 0, 2, 4 and 8 mg of tizanidine in 16 patients. The results from study S-87 are summarized in the following table:

Study S-87 Mean BP following single doses in patients with spasticity				
	2 mg	4 mg	8 mg	Placebo
Baseline	113/79	117/81	120/82	117/81
1 hour	113/79	107*/75*	107*/74*	118/80
2 hours	108*/77	108*/73*	101*/69	117/80
3 hours	112/80	112/77	108/77	112/79
4 hours	115/78	117/76	110*/74*	117/79
6 hours	115/78	116/79	119/79	120/80

* Statistically different from the corresponding mean placebo value (Dunnet's $p \leq 0.05$)

In other studies, BP was not monitored closely as in study 005. In study 003, when patients came for an evaluation, BP was checked soon after dosing, prior to the peak effects that were seen in study 005. The incidence of clinically relevant decreases in supine BP discussed in the integrated safety summary included BP taken while the patient was lying or sitting. In the long term safety study, 002, which involved patients with MS, 11 of 117 (9%) patients treated were noted to have clinically relevant changes in supine systolic and/or diastolic BP. In study

004, the long term extension of study 003, 28 of 58 (47%) patients were noted to have clinically relevant changes in supine systolic and/or diastolic BP.

The sponsor had defined clinically significant BP changes as reductions from baseline of $\geq 20\%$ for either the systolic or diastolic BP. In study 005, over 2/3 of the patients receiving 8 mg or 16 mg had a clinically significant reduction in BP at some time during the 6 hours after receiving tizanidine. It is possible that these patients were symptomatic with complaints of dizziness.

Dizziness, a frequently reported AE in patients on tizanidine, may result from drug induced hypotension. Since most patients did not have BP evaluations at the time of the complaints of dizziness, one cannot assure that dizziness is always related to a decrease in BP. With this in mind, dizziness occurs in about 15% of the patients on drug in the controlled clinical trials. Equal number of patients reported this symptom in week 1, week 1 to 3, week 3 to 6 and $\geq$ week 6 of treatment. Dizziness was a rare complaint in placebo patients.

To determine if patients with clinically significant hypotension had associated clinical symptoms, I evaluated the BP status of patients with AEs of dizziness, lightheadedness and/or hypotension. AEs include those elicited or reported spontaneously. Dizziness is a nonspecific complaint and may be a symptom of many drug effects. For this drug, it may be an indication of hypotension. While none of the placebo patients had dizziness associated with clinically significant hypotension, 78% of the 8 mg and 78% of the 16 mg patients with dizziness also had clinically significant hypotension. The symptom of dizziness is not necessarily a sensitive marker as only 34% of patients with clinically significant hypotension had symptoms of dizziness. The results are summarized in the following table:

Association of AEs dizziness and hypotension with clinically significant P changes (% of patients)			
	Placebo (N=48)	8 mg (N=45)	16 mg (N=49)
No dizziness or clinically significant hypotension	39	13	9
Dizziness without clinically significant hypotension	1	2	5
Dizziness with clinically significant hypotension	0	7	18
No dizziness with clinically significant hypotension	8	23	17
No AE of dizziness/hypotension or clinically significant hypotension	39	13	9
AE of dizziness/hypotension without clinically significant hypotension	1	2	5
AE of dizziness/hypotension with clinically significant hypotension	0	11	22
No AE of dizziness/hypotension with clinically significant hypotension	8	19	13

Clinical events which may have been related to hypotension were noted in the clinical trials. In the controlled clinical trials, 16% of the drug group and 4% of the placebo group had complaints of dizziness. In the controlled clinical trials, the following patients were discontinued for events or had serious AEs that may have been related to hypotension:

a 47 year old male with moderate MS in study 001 was on 32 mg/day (12, 8 and 12 mg over the day) on day 28 when he developed lightheadedness and wobbliness.

a 47 year old female with severe MS, developed hypotension with slurred speech and decreased alertness on day 14 at a dose of 24 mg/day (8 mg tid). Patient 138 in study 003 was a 19 year old male with C6 cord injury who had syncope on day 13 and 15 at 24 and 28 mg/day. The patient continued on treatment.

Study S-003 was a RCT in patients with MS. 50 patients were randomized to tizanidine with doses ranging from 6 to 24 mg/day. Patients were treated for 6

weeks. In this trial, three patients were discontinued from the study for hypotension or orthostatic hypotension.

 was discontinued on day 36 while on 24 mg/day with orthostatic hypotension.

 was discontinued on day 13 while on 12 mg/day with orthostatic hypotension and bradycardia with prolongation of the PR interval.

Four additional patients were found to have orthostatic hypotension but did not withdraw from the study. The onset of symptoms was within the first 2 weeks of treatment.

In study S-60, 12 patients received a single 6 mg dose of tizanidine.

A single patient developed hypotension 45 minutes after dosing. The patient was hypotensive and was treated with methyl-dopa.

In study S-54, 20 healthy subjects received a single dose of tizanidine ranging from 4 to 14 mg. 4 patients were discontinued.

Two patients who received 12 mg were discontinued for bradycardia. One patient had syncope.

A patient on 10 mg was discontinued for hypotension with dizziness and weakness.

A patient on 6 mg was discontinued for orthostatic hypotension.

In study S-47, One out of 12 patients receiving a single dose of modified release tizanidine was discontinued with hypotension and dizziness.

The subject was on 18 mg of the modified release preparation. .

In study S-64, all 8 subjects receiving doses of the modified release tizanidine had clinically significant reduction in BP.

In study S-88, all 15 patients receiving a single dose of 4 mg had a reduction in the systolic or diastolic BP of at least 15 mm Hg. The reduction in BP was seen within the first 4 hours and returned to baseline within 12 to 24 hours.

NDA-020397

FIRM: ATHENA NEUROSCIENCES

2 OF 7

TRADE NAME: ZANAFLEX ORAL TABS. 4MG

GENERIC NAME: TIZANIDINE HCL

In spontaneous post marketing reports for 1993, 8 of 63 reports were for hypotension at times associated with bradycardia and/or and dizziness. The average dose was 3.9 mg/day.

Bradycardia:

The sponsor noted that there were significant decreases in pulse noted in the tizanidine group when compared to placebo. For the 8 mg group, the maximum changes occurred at 2 hours for the sitting pulse and 1 hour for the supine pulse.

Hepatotoxicity:

Temporary increases in ALT levels were noted in the 13 week rat and dog study and the 1 year dog study. The histopathological changes consisted of focal cell necrosis, inflammatory infiltrates and periacinar eosinophilic hepatocyte hypertrophy.

The sponsor defined a treatment emergent, clinically significant relevant change in the LFT as an increase of 3 times the ULN or 2 times an abnormally elevated baseline value. 12 of 227 (4.8%) patient exposed to tizanidine with post baseline data had clinically relevant changes in the ALT and/or AST while only 1 of 221 (0.4%) patients on placebo had an elevation.

On review of Appendix A-5 of the integrated safety summary, (volume 1.165), there are inconsistencies in the doses received by patients and the duration of treatment. All of the charts have timelines for 15 weeks and 4 days while the studies lasted from 9 to 13 weeks. The doses received by an individual patient vary by page. See Patient B068 in study 001 for an example.

in study 001 had an elevation of the ALT noted on day 63 to a level of 1392 (baseline 22) at a dose of 12 mg/day. The elevation was associated with nausea and vomiting, anorexia, weight loss, abdominal pain, mild thrombocytopenia (135,000) and jaundice. Tests for viral hepatitis were negative. The drug was discontinued on day 69 and the signs, symptoms and LFTs resolved by day 120.

in study 001 was listed as being on placebo though in Dr. Rouzers review, the patient, a 28 year old female was noted to be on drug. On day 61, at a dose of 24 mg/day, the patient developed polyarticular joint effusions and rash with a low grade fever. ALT was 1392. A

rheumatologist related the events to serum sickness from the study treatment. The problems resolved off treatment. The sponsor had already noted that some patients randomized to placebo received tizanidine at center 4. This was discovered after the sponsor noted that patients on placebo were having AEs to the severity found in patients on tizanidine. This patient had complained of moderately severe dry mouth and asthenia.

in study 003 was a 44 year old male developed elevation of the ALT to 399 on day 43 (baseline ALT was 21). On day 44, at a dose of 4 mg/day, the drug was discontinued. The investigator noted that the events resolved by day 61 though no lab values were reported.

in study 003, was a 37 year old male was noted to have an elevation of the ALT to 818 on Day 57 which was at the end of the study taper and beginning of the open label titration. The drug was discontinued and by day 71, the elevation had resolved. The patient went back on drug without further abnormalities.

in study 004 had an elevation of the ALT to 227 (baseline ALT was 11) during the plateau phase which resolved with discontinuation of the drug.

in study 004 had an elevation of the ALT to 1152 (baseline ALT was 29) which was reduced with medication reduction.

In post marketing reports, there was a 68 year old male treated with 4 mg/day who developed cholestatic jaundice after 2 months of treatment. The patient was also on carbamazepine. Both drugs were withdrawn and the patient died 20 days later of pneumonia.

In another post marketing case, a 49 year old male with ALS and post cholecystectomy in 1977, was started on tizanidine on 8/12/92 at 4 mg bid. The dose was increased to 6 mg tid on 9/8/92. On 10/15/92, the patient developed jaundice with liver enlargement. Tizanidine was discontinued on 10/19/92. The ALT was 990, PT was 31%, alk phos was normal. ESR and eosinophils were normal. On 10/29/92, the patient died in an hepatic coma. Viral hepatitis, obstructive and hemolytic icterus were excluded. A liver biopsy showed acute hepatitis with multilobular necrosis without eosinophilic infiltration

An FDA consultant reviewed the results of the LFT elevations. He concluded that

Tizanidine was associated with heterogenous liver disease both hepatocellular and cholestatic.

Hematology:

Leukopenia was not noted in the controlled clinical trials. In post marketing reports, granulocytopenia was reported in 1 patient who was also on ticlopidine. In other controlled trials, Patient 8 in study S-17, had a WBC count of 500.

Common treatment emergent AEs:

The most frequent AEs reported in the studies 001 and 003 listed by the investigator as possibly, probably or of unknown relationship to the study drug are compared with the AEs seen in study 005 in the following table:

Treatment emergent AEs in study 001 and 003 compared to study 005					
AE	Study 001 and 003		Study 005		
	Placebo (n=261)	Tizanidine (n=264)	Placebo (n=48)	8 mg (n=45)	16 mg (n=49)
Dry mouth	10	49	35%	76%	88%
Sedation	9	48	31%	78%	92%
Asthenia	14	39	40%	67%	78%
Dizziness	4	15	4%	22%	45%

As with the efficacy findings, study 005 provided information about the course of the effects of tizanidine. The adverse effects are seen within 30 minutes of treatment with most patients experiencing the symptoms within 2 hours of treatment.

Comments:

Efficacy:

Study 005 provides a time course for the efficacy of tizanidine. For patients receiving 8 mg of the drug, the onset of reduced muscle tone began within 1 hour of treatment, peaked by 2 hours. By three hours, the treatment effects for the pendulum were not statistically significant difference from placebo. The

Ashworth scale score was significant at 3 hours but not at 6 hours. For patients receiving 16 mg, the effects were statistically greater than seen in patients receiving 8 mg and were of longer duration. Both the pendulum and the Ashworth were statistically different at 3 hours. As with 8 mg, the differences were not statistically significant at 6 hours.

The findings of study 003 supports the efficacy of tizanidine. In this study, muscle tone was assessed no later than 2 and one half hours after receiving the morning or afternoon dose of tizanidine. After titration, most patients were receiving 8 mg for the morning and afternoon doses with 16 mg given at night. The time course and duration of the effect were not assessed.

The sponsor argues that evidence from previous studies suggest that patients respond at doses lower than 36 mg/day. They state that for patients who were found to have responded to treatment at endpoint had their initial improvement at doses of 13 to 16 mg/day. For study 003, there is no way that the sponsor could determine the dose when patient with a reduction in muscle tone initially began to respond since muscle tone was not assessed during dose titration. Muscle tone was only assessed at the end of titration and during the maintenance phase.

These studies do provide definitive evidence for efficacy for the following claims: (1) 8 and 16 mg of tizanidine reduce muscle tone due to spasticity (as measured by the Ashworth scale and the Pendulum swing test) in patients with MS or spinal cord injury. (2) The onset of the effect is within one hour of dosing. (3) The duration of the effect is more than 2 hours but less than 6 hours. (4) The effects do not disappear with three times a day, chronic dosing. (5) The effects are present following dose titration to 8 mg.

The studies do not provide evidence for the following claims: (1) Tizanidine leads to improvement in spasm frequency, ADL or other measures of function. (2) Reduction in spasticity is equivalent to baclofen and diazepam. (3) Muscle strength is less effect by tizanidine as compared to baclofen. (4) There is no reduction in the antispastic effect in responsive patients over time. (5) Patients can achieve a constant level of reduced muscle tone with tizanidine over the course of a day.

Therefore, the efficacy data provides evidence for the following: Tizanidine is indicated for temporary reduction of muscle tone due to spasticity from spinal cord injury or multiple sclerosis.

Safety:

From the clinical trials, the following safety problems with tizanidine have been identified which may interfere with the use of tizanidine: hypotension, bradycardia, hepatotoxicity and CNS toxicity.

I have two major reservations about the safety of tizanidine. One is the hypotension associated with the drug and two is the lack of experience with the drug at the dose and duration to be used to treat chronic spasticity.

Hypotension:

Information from the clinical trials suggest: (1) Treatment with tizanidine from single doses of 2 to 16 mg can lead to transient, clinically significant, reduction in blood pressure. (2) The effect is dose related. (3) The onset of the hypotension is 1 to 2 hours following a single dose. (4) The effect lasts from 2 to 6 hours. (5) The reduction is associated with a reduction in pulse.

From the results of study 005, about two-thirds of the patients have a clinically significant decrease in either systolic and/or diastolic BP. The full extent of this problem has not been evaluated and questions remain as to the clinical importance tizanidine induced hypotension.

(1) Does the hypotension worsen with changes in positions? This question was addressed in study 005 and patients were checked for orthostatic hypotension. The evaluation was not adequate as BP was only evaluated immediately after achieving the sitting position. Significant changes in blood pressure may only be noted after a patient has been in the upright position for a few minutes. This was not assessed in study 005. In study 003, orthostatic BP was not evaluated. Though most of these patients were tetraplegic, they may spend time in an upright position (for example, in a wheelchair) and orthostatic BP changes can be a significant clinical problem.

(2) If hypotension is a significant clinical problem, why have there not been more serious effects reported in the clinical trials? Information from the studies has suggested symptoms of dizziness/lightheadedness and rarely syncope may be associated with the hypotension. Hypotension can result in many serious problems and the symptomatic representation of hypotension depends on many factors including the underlying disease state, integrity of the autonomic system, level of activity, time spent in a sitting or standing position within the first few hours following dosing. The incidence of AEs from hypotension and bradycardia

may be different in patients with autonomic system abnormalities such as seen in patients with spinal cord dysfunction than in patients with multiple sclerosis or in patients with normal autonomic function such as patients with back spasms. This is supported by the finding of a higher rate of patients with clinically relevant hypotension (≥ 20 point decrease in systolic and/or diastolic BP) seen the long term extension trial in patients with spinal cord injury (about 50%) when compared to the patients with MS (about 10%).

While serious problems possibly related to hypotension, such as syncope, were rarely seen in the clinical trials, it is possible that the symptomatic presentation of hypotension was averted by the patient staying in a supine position. Problems with hypotension are going to be reduced if the patient remains in bed. This may explain why few serious problems were noted in the patients with spinal cord injury in study 003. In study 003, the highest dose was reserved for the nighttime dose when the patient would be asleep. If patients noted lightheadedness or increased tiredness because of the hypotension, they would be less likely to get out of bed into a wheelchair or a more upright position. If they waited a few hours until getting into the upright position, they would avoid the potentially serious problems that occur with hypotension.

(3) What is the relationship of hypotension to the clinical efficacy of the drug? While both hypotension and a reduction in muscle tone are dose related effects, not all patients who were noted to have a decrease in muscle tone were noted to have a reduction in blood pressure. While BP changes may not directly be associated with efficacy, it may effect efficacy indirectly. If patients are unable to get into an upright position because of drug induced hypotension, then the patients will not be able to take advantage of the benefits of the drug. For example, patients who are using tizanidine to help with spasticity so that they can transfer more effectively or be able to move from the bed to wheelchair may not benefit from the transient reduction in muscle tone because to the problems with have forced them to remain supine.

(4) Are there ways to avoid the hypotensive problems? The sponsor has claimed that hypotension was not a problem in other studies and that the effect is minimized by slow titration. The sponsor has not provided any evidence to support these claims. Besides study S-87, the BP was not monitored closely in other clinical trials. For example, the incidence of hypotension in study 003 cannot be determined because at the follow up visits, the BP was measured to soon after dosing to see the reductions recorded in study 005. If dizziness is related to hypotension, then the incidence in the clinical studies may be similar to that seen in study 005.

Size of the safety database:

Serious adverse events have been noted with the use of tizanidine including hepatotoxicity, CNS toxicity, hypotension and bradycardia. The sponsor states that the safety profile of tizanidine has been adequately evaluated in the many studies in over 3,000 patients performed by Sandoz and Athena. This along with the postmarketing experience in >30 countries provides sufficient information for the safe use of tizanidine in patients with spasticity. At this time, the dose and duration of treatment in most of the clinical trial experience with tizanidine is much less than to be expected in patients with chronic spasticity. For spasticity, the lowest single dose found effective has been 8 mg. Safety information regarding 8 mg doses from the safety trials comes from patients who received a daily dose of ≥ 24 mg/day except in study 003. Since patients in study 003 were given unequal doses, with the highest dose at night, a daily dose of ≥ 32 mg/day would include an 8 mg dose being given during the waking hours. This equates to >24 mg/day if the dose is given in 3 unequal doses with the largest dose given in the evening as recommended by the sponsor. From the clinical trials, 167 patients have received ≥ 24 mg/day for more than 3 months. 120 of the those patients have received ≥ 24 mg/day for more than 6 months and 63 have received ≥ 24 mg for more than a year.

This does not provide a substantial basis for informing prescribers and patients on the safety profile of the drug including reassurance that potentially serious safety problems have either been identified or are unlikely.

Recommendation:

I recommend that tizanidine not be approved for the treatment of spasticity. The evaluation of this drug for the treatment of spasticity is incomplete. Not only has the sponsor not found an adequate dosing regimen to effectively treat spasticity, they have not provided adequate safety experience to justify chronic use of the drug.

Spasticity as a result of multiple sclerosis or spinal cord injury is a chronic condition that can result in disability and discomfort. An antispasticity medication should reduce these problems. Although the sponsor has demonstrated that tizanidine has the potential to treat problems associated with increased muscle tone, they have failed to define the effective dose range and dosing regimen that will lead to a consistent reduction in muscle tone over the course of a day.

The sponsor's recommendations in labeling that the therapeutic dose is between 12 and 24 mg/day and that tizanidine is dosed in three unequally divided doses with the largest dose given in the evening to avoid undesirable daytime side effects is not based on results from the efficacy clinical trials. Why is the daily dose divided into three doses? The three divided doses are not to achieve a consistent level of muscle tone reduction. Study 005 showed that the reduction in muscle tone is completely gone by 6 hours post dosing. To maintain a consistent level of muscle tone reduction, the results from study 005 suggest that the interval between doses must be less than 6 hours. Why does the sponsor recommend a daily dose of 12 to 24 mg/day with the largest dose given at night? If patients follow the sponsor's recommended dosing regimen, during the day, the patients will not even receive a dose shown to be effective (≥ 8 mg/day).

From the current efficacy evidence, the drug could only be recommended for the acute or temporary treatment of spasticity. For example, if a patient's spasticity prevented them from transferring from bed to wheelchair, or for receiving effective personal hygiene or physical therapy, then tizanidine may be helpful to reduce muscle tone long enough to complete the task. The sponsor and their experts have contented that a drug that would even temporarily reduce muscle tone would be an important addition to the treatment options available for patients with spasticity. If the drug is to be recommended for temporary treatment of spasticity, the sponsor would need to amend labeled indication and dosing recommendations accordingly.

The sponsor should evaluate the drug more completely so that prescribers and patients can receive reliable instructions on the most efficient use of the drug. The sponsor should conduct a dose ranging study, similar to study 005 to define the lowest effective dose. They should use the results from the dose ranging study to design an efficacy study like study 003 to define the dosing regimen that would provide for consistent reduction in muscle tone. The outcome measures should be evaluated prior to dosing to show that the reduction in muscle tone persists for the interval between doses

If an 8 mg dose of the drug is effective in reducing muscle tone, even temporarily, could it be used safely? From study 005, 2/3 of patients dosed with a single dose of 8 mg had a clinically significant reduction in either the systolic or diastolic BP after dosing. The sponsor did not adequately describe the clinical effects of this change in BP. Were patients able to tolerate the change in BP? If a patient was upright for extended lengths of time, would they have signs or symptoms of hypotension? Almost 80% of patients given a single dose of 8 mg complained of sedation, mostly of mild to moderate severity. Was this sedation

severe enough to interfere with activities such as transfers and physical therapy that would counter the benefits of the drug?

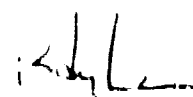
The sponsor should assess patients for evidence of hypotension when they are in the upright position. For patients with spinal cord injury, this means checking BP while patients remain in a wheelchair. They should also try to determine if the more common side effects such as sedation are interfering with the functioning of the patients. The possibility that hypotension, sedation and other AEs would interfere with the beneficial effects of the drug need to be assessed with multiple day time doses.

If it is determined that tizanidine reduces muscle tone and that the more common side effects do not interfere with patients being able to benefit from the reduction in muscle tone, then the prescriber and patient should be informed of any potential serious risk of the drug. This would require that sufficient numbers of patients be exposed to the drug under controlled conditions at doses and durations recommended in labeling to be reasonably certain that drug induced serious AEs have been identified.

The sponsor contends that the large number of patients evaluated in the clinical trials and the large number of patients exposed to the drug post marketing already provides a reasonable risk assessment for the drug. How many patients have been evaluated as recommended in the labeling? In order for a patient to have been exposed to multiple doses of 8 mg a day, the daily dose would have to be ≥ 24 mg. At this time, the number of patients exposed to single doses of 8 mg over 3 or 6 months is between 120 and 170 patients, a number too small to provide reasonable assurance that the drug induced serious AEs have been identified. The sponsor cannot rely on the long term studies conducted by Sandoz because the maximum doses used in those studies were at most 20 mg/day according to the sponsor's report. They cannot rely on the post marketing surveillance as most of the drug's use appears to be at single doses < 8 mg for durations < 3 months. The sponsor needs to evaluate the safety of patients dosed with the recommended regimen for periods over 6 months so that prescribers and patients may be more reasonably assured that serious adverse events have been identified.

The sponsor has performed an insufficient job evaluating this drug for the treatment of spasticity. The incomplete information provided by the sponsor makes it difficult to inform prescribers and patients accurately on the effective and safe use of this drug. The sponsor's labeling recommendations rely on past habits on the use of the drug as an acute muscle relaxant. They have not based

their treatment recommendations on sound clinical evidence.



Randy Levin, M.D.
Medical Reviewer

cc:

Original IND

HFD-120

HFD-120/Leber/Katz/Levin/Grilley

rl/January 7, 1996

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: 2/2/95
From: Randy Levin, M.D., Medical Reviewer
Subject: NDA 20-397, Zanaflex (tizanidine)
To: File

1. Background:

Athena submitted NDA 20-397 on 12/3/93 for tizanidine, an alpha-2 adrenergic receptor agonist, as a treatment for spasticity of spinal cord origin. The drug has been approved in seven countries for spasticity and rejected in two, the UK and Canada. In this application, Athena has presented three new, randomized, placebo controlled trials as pivotal for providing substantial evidence of efficacy of tizanidine. Two studies involved patients with multiple sclerosis (MS). Study 502, was conducted in the UK and study 001, was conducted in the US. Study 003 was conducted in the US and Canada and involved patients with spinal cord injury. Safety information was from clinical trials involving patients with spasticity and other conditions as well as information from post marketing surveillance. The clinical trials included open, placebo and active controlled studies.

In this overview of NDA 20-397, after briefly summarizing the preclinical and biopharmacology findings, I will outline the design and results of the three pivotal efficacy trials, and then assess these studies in regard to the regulatory requirement for substantial evidence of efficacy. This will be followed by a summary of the safety information on the size of the safety data base, deaths, discontinuations and serious adverse events. Following this summary, I have assessed the safety database in regards to the regulatory requirement of sufficient evidence for safety. Finally, based on these assessments, I have provided recommendations for a regulatory action on NDA 20-397 along with requests for additional information from the sponsor.

The information providing the basis of this overview can be found, in additional detail, in the following documents: The primary clinical review by Janeth Rouzer-Kammeyer, M.D. Her review covers the entire clinical safety and

efficacy data of the NDA as well as a 4 month safety update submitted on 4/4/94. The statistical review, dated 12/23/94, by Joy Mele, MS. A consult, dated 9/94, on the question of corneal opacities from Jose Carreras, M.D. of HFD-540. A consult, dated 11-8/94, on the hepatotoxicity of the drug from Hugo Gallo-Torres, M.D., PhD of HFD-180. A biopharmacology review by Vijay K. Tanimara, PhD. A supervisory pharmacology review by Glenna Fitzgerald, PhD. Information was also obtained from several summary volumes of the NDA and a report of a symposium on tizanidine held on 4/16/94 and published in Neurology on November of 1994 (number 44 suppl 9).

2. Preclinical and Biopharmacology

Tizanidine is an imidazoline derivative, structurally similar to clonidine. The proposed mechanism of action is as an alpha-2 adrenergic receptor agonist acting at the level of the spinal cord. The sponsor suggests that the drug may act presynaptically by modulating the release of excitatory amino acid from the spinal interneurons.

The drug is rapidly and well absorbed with peak plasma levels occurring in 1.5 hours. The bioavailability is low due to an extensive first pass metabolism in the liver. Metabolism studies revealed that unidentified metabolites, which account for about 50% of the breakdown products of the drug, have a long half-life of total radioactivity (43-90 hours). This suggests accumulation of these unidentified species. The major metabolites are 3, 4 and 10. Metabolite 10 has not been characterized because of the inability for the sponsor or Sandoz to synthesize it. Isozymes involved in the metabolic oxidative processes have not yet been determined. The major route of excretion is via the kidneys. The terminal half life is 2.2 hours with little or no accumulation of the parent. The drug displayed linear PK over a dose range of 1 to 20 mg. The drug is 30% protein bound. Food affects the rate but not the extent of absorption. The drug delays the acetaminophen T_{max} by 16 minutes. There was no effect of acetaminophen on the PK of tizanidine. Alcohol resulted in a 20% increase in the AUC and a 15% increase in the C_{max} of tizanidine. Retrospective analysis of a multiple dose study indicated that females taking oral contraceptives concurrently with tizanidine had a 2 fold decrease in their clearance of tizanidine. The clearance is 4 times faster in the young. The sex of the patient does not affect the PK of the drug. Clearance is reduced 7 fold in elderly patients with renal insufficiency. From this information it was predicted that a 2 fold increase in clearance would be experienced by young patients with renal insufficiency. The PK of the drug in patients with hepatic impairment has not been studied.

1 year toxicology studies have been completed in the dog. A 6 month toxicology study in the rat was recently completed and will be submitted to the NDA within the next 30 days. In a 13 week study in the rat and carcinogenicity studies in the rat and mouse, corneal opacities and keratitis were found. A similar finding was seen in the rat for clonidine. This was not found in the dog receiving tizanidine.

Carcinogenicity studies were completed for both the rat and mouse. The adequacy of the carcinogenicity studies were questioned because of the differences in metabolic profiles that exist between species. While the sponsor showed that qualitatively, the mouse plasma contained metabolites 4 and 9 and the rat contained metabolite 10 (plasma) as well as metabolites 3, 4 and 9 (urine), these levels were not quantitative. It is not known if the doses given in the carcinogenicity studies produced adequate levels of these metabolites needed to assess the risk for human carcinogenicity. This issue was addressed by the Carcinogenicity Assessment Committee and the opinion reached by the majority of the committee was that the qualitative similarity of the metabolites is all that may be expected from a sponsor and that they could not require or expect similar plasma exposure to the drug and metabolites across species. One suggestion was that genetic toxicology screens of the metabolites be performed. The sponsor was requested to supply the plasma levels of the major metabolites in the mouse and rat and to perform the genetic toxicology studies for the metabolites. They declined to do the mouse test or the genetic toxicology tests as requested. The sponsor provided an estimation of the metabolite levels from a single dose radiolabeled study. They have collected but not submitted metabolite plasma levels in the 6 month rat toxicology study.

3. Regulatory history:

Tizanidine (Sirdalud and Tirelin) was developed by Sandoz and is licensed by Athena under the name of Zanaflex™. This NDA was submitted for the indication of spasticity of spinal cord origin.

The drug has been marketed in various countries with the first approval coming in 1984. 50% of the drug is used in Japan where it is indicated for spastic paralysis and acute muscle spasm. Only in 6 other countries (Austria, Denmark, Finland, Netherlands, Germany and Switzerland) is the drug promoted for spasticity. In the other countries, the indication is for the treatment of acute muscle spasm which the sponsor notes accounts for about 80% of its use.

Tizanidine was rejected for approval in the UK and Canada. In 1984, the UK turned down the drug for inadequate evidence of efficacy. The UK also noted that

the drug should be contraindicated in women of childbearing potential because of teratogenic effects seen in the rat. They also noted that there was insufficient long term exposure and there was concern about ocular and liver problems. They were concerned with the relevance of the animal PK studies to humans. The UK requested information on postural hypotension and withdrawal effects. In 1989, the Canadian authorities turned down the drug for lacking sufficient evidence for safety and efficacy. One of the efficacy studies was study S-1. None of the pivot studies presented with the current NDA were presented to other regulatory authorities.

4. Summary of the efficacy studies:

4.1. Pivotal and supportive studies submitted:

The sponsor offered three trials as pivotal and two as supportive of the claim of efficacy in the treatment of spasticity of spinal cord origin. These trials are identified as follows:

Efficacy studies submitted in NDA 20-397				
Study	Type	population		Location (initiation)
DS-0502	Definitive	MS		UK (1989)
021-001	Definitive	MS		US (1992)
021-003	Definitive	Spinal cord injury		US/Canada (1993)
DS-2N-S-1	Supportive	MS		Canada (1987)
DS103-282	Supportive	MS/chronic myelopathy		Finland (1980)

In addition, there are 15 active controlled trials comparing the effects of baclofen and tizanidine and 6 trials comparing diazepam and tizanidine.

4.2. Study design of the pivotal studies:

The three pivotal trials were multicenter, randomized, double blind, parallel, placebo controlled studies.

Patients over the age of 18 with stable spasticity associated with significant discomfort or functional impairment were enrolled. Two scales were used to select patients. The Ashworth Scale rates the muscle tone in a limb or muscle

group and is summarized as follows:

Ashworth Scale	
Rating	Description
0	No increase in tone
1	Slight increase in tone, giving "catch" when the limb is moved in flexion or extension
2	More marked increase in tone but the limb is easily flexed
3	Considerable increase in tone, passive movement difficult
4	Limb rigid in flexion or extension

Muscle spasm, measured by the Muscle Spasm Type and Frequency Scale, is summarized as follows:

Muscle Spasm Type and Frequency Scale	
Rating	Description
0	Absent
1	provoked by painful stimuli only
2	provoked by light touch, light pressure and/or occasional spontaneously (<5/day and/or <2/night)
3	Provoked by passive movement and/or frequently spontaneous (>5/day and/or >2/night)

Patients had to have a score of 2 or more in the most severely affected limb in both scales to be eligible.

Following a screening and washout phase (all patients were required to be off anti spasticity medication for two weeks prior to the baseline assessment), patients were stratified by the Ashworth Scale score of the most severely affected limb, into mild (score 2), moderate (score 3), and severe (score 4) groups and then randomized to either drug or placebo.

Over the next three weeks, the patients were titrated from 2 mg/day to a maximum of 36 mg/day (12 mg tid). The dosage was determined by weekly

assessments of efficacy and tolerability by the physician prescriber.

The dose used at the end of the Titration Phase was continued in the Plateau Phase which lasted 9 weeks in studies 502 and 001 and 4 weeks in study 003.

After the Plateau Phase, the study treatment was tapered off over one week with a final assessment taking place one week later. All patients in study 001 and 003 were then eligible for an open label extension phase (study 002 and study 004).

4.3. Outcome measures:

The outcome measures evaluated the signs and symptoms associated with spasticity and functional capacity.

The primary outcome measure in all studies was the assessment of muscle tone with the Ashworth Scale. An assessor evaluated 10 muscle groups on both sides (20 muscle groups total) in studies 502 and 001 and 3 muscle groups in the lower extremities (6 muscle groups total) in patients with spinal injury in study 003. The frequency of spasms from counts kept in the patient's diary was designated as a secondary outcome measure in study 001 and 003. In study 502, the frequency of spasms was assessed by the patient at each visit. Study 003 had a third primary outcome measure, the pendulum test, to assess muscle tone. In this test, the angular displacement of the first swing of the right leg was recorded.

Functional measures were considered secondary outcome measures. They included pain and disability from spasms, time to walk 8 meters, activities of daily living and the patient's comfort included a self assessment of overall disability and discomfort, sleep quality, ease of active or passive physical therapy and nursing care. An overall assessment of the efficacy or benefit of the drug were assessed with global evaluations by physician prescribers, assessors and patients.

4.4. Blinding of assessors of muscle tone

In study 001 and 003, in order to protect the blinding of the study, the rater of the signs of spasticity was performed by an assessor who was not involved in the care of the patient (physician prescriber). The prescribing physician who was responsible for titrating the patient's dose and therefore would be aware of all AEs did not assess the muscle tone in these studies. This precaution to protect the blind was not used in study 502 where all centers used a single individual to serve as both the assessor and prescriber.

4.5. Results of study 502

4.5.1. Patient disposition and demographics:

187 patients were enrolled at 16 centers in the UK (range 1 to 22 patients per center). There were no significant differences in demographics reported between the two groups. There were 2 females to every male. The average age was 46 with 90% having an Ashworth score of 2 or 3 at baseline in the most severely affected muscle. The disposition of the patients is summarized as follows:

Disposition for study 502			
Treatment group	Randomized	Completed study	Discontinued for AEs
Placebo	93	71	4
Tizanidine	94	65	16

14 placebo and 12 tizanidine patients discontinued for lack of efficacy.

4.5.2. Ashworth Scale:

The decrease in the muscle tone as measured by the change in the Ashworth scale from baseline was greater in the patients receiving tizanidine as compared to patients on placebo. The tizanidine group had higher scores (increase tone) at baseline though the differences did not reach statistical significance. Both groups improved during the treatment phase. After 12 weeks of treatment, the patients on placebo improved by 1.2 points while those on tizanidine improved by 5 points. The difference was statistically significant. Using the LOCF data subset, the tizanidine group improvement of 3.88 was statistically better than the placebo group improvement of 1.53 points. An analysis of the data adjusting for the difference at baseline and for strata were also statistically significant in favor of the drug.

Ashworth Scale scores	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	16.8 (93)	18.5 (94)		0.3
End of plateau phase	15.6 (71)	13.5 (65)	3.8	0.0000
LOCF	15.3 (93)	14.6 (94)	2.3	0.0072

4.5.3. Frequency of spasms:

The frequency of spasms was not a primary outcome measure in this study. There was a decrease in the frequency of spasms in both groups. The change from baseline and percent reduction were similar between groups. The difference was not statistically significant. The results are summarized as follows:

Frequency of Spasms	Placebo (N = 93)	Tizanidine (N=94)	Treatment effect
Baseline	5.1	6.3	
LOCF (% reduction)	4.4 (14%)	5.5 (13%)	0.1

4.5.4. Global assessments:

In the physician assessor/prescriber's global assessment of efficacy, the placebo group had a mean scored of 4.30 and the tizanidine group scored 3.8. Only a minority of patients had a good or very good rating. The comparison of the groups resulted in a p value of 0.002. The results are summarized as follows:

Clinician's global	Very Good	Good	Moderate	Slight	None
Placebo (n=74)	4%	3%	8%	30%	55%
Tizanidine (N= 64)	1.6%	14%	19%	34%	31%

In the patient's global assessment, the placebo group had a mean score of 4.08 compared to a tizanidine score of 3.81. This difference was not statistically significant.

4.5.5. Other outcome variables:

The pain and disability due to muscle spasms, walking time, ADL, muscle strength and reflexes all showed slightly greater decreases from baseline measurements in the tizanidine group when compared to placebo though the differences did not reach statistical significance.

4.6. Results of study 001:

This study was similar to study 502. The primary outcome was the muscle tone as measured by the Ashworth Scale and the frequency of spasms by the patients

diary. In this study, each center provided an independent assessor and prescriber. The only contact the assessor had with the patient was to evaluate the signs of spasticity which they did in the presence of the physician prescriber.

4.6.1. Demographics and disposition:

15 centers enrolled 257 patients and all but one patient received drug. After the sponsor reviewed the adverse events, it was found that some of the placebo patients in center 4 exhibited AEs that were usually associated with the drug. Assay of vials returned by the patients revealed that at least 3 placebo patients enrolled at center 4 received some tizanidine tablets. The sponsor chose to exclude this center from their main analysis. It was reported that the sponsor sampled other centers for similar mix ups and did not find any problems. Center 4 had the largest enrollment with 36 patients.

The demographics were similar between groups with a mean age of about 45. 60% of the patients were female. 80% of the patients had an Ashworth score of 2 or 3 at baseline in the most severely affected muscle. 14 placebo and 8 tizanidine patients discontinued for lack of efficacy. The disposition of patients excluding center 4 is as follows:

Disposition excluding center 4			
Treatment group	Randomized	Completed study	Discontinued for AEs
Placebo	109	77	9
Tizanidine	112	84	16

4.6.2. Ashworth scale:

The sponsor's analysis excluded patients from center 4. The patients in center 4 had higher mean baseline scores than the mean of the other centers combined. Inclusion or exclusion of center 4 did not change the statistical significance of the difference. The changes in the Ashworth scores were in favor of placebo but the differences were not statistically significant. The results are as follows:

Ashworth Scale scores (excluding center 4)	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	15.0 (108)	13.0 (111)		0.15
End of plateau phase	12.4 (76)	10.8 (83)	0.4#	0.99
LOCF	12.2 (104)	11.3 (105)	1.1#	0.46

#changes in favor of placebo

Evaluating the Ashworth scale for the lower extremities showed the same trends as with the total score. The placebo group had statistically significant higher scores at baseline. The results are as follows:

Ashworth Scale scores for the lower extremities (excluding center 4)	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	12.8 (108)	10.4 (111)		0.004
End of plateau phase	10.9 (76)	9.5 (83)	1.0#	0.47
LOCF	10.8 (104)	10.0 (105)	1.6#	0.19

#changes in favor of placebo

When adjusting for strata of mild, moderate or severe, the mean changes from baseline were in favor of placebo for the mild to moderate group and in favor of tizanidine for the severe group. No differences were statistically significant.

Subgroup analyses based on age, sex or race revealed no improvements for tizanidine over placebo.

4.6.3. Frequency of spasms:

The counts of spasms and clonus were not normally distributed and to normalize the data the sponsor transformed the data to a response ratio (visit count-baseline count/ visit count + baseline count). The frequency of spasms was lower in the tizanidine group at baseline. The response ratio was in favor of tizanidine for both the Observed cases and LOCF data subset. The results are as follows:

Spasms (excluding center 4)	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	8.9 (108)	7.9 (111)		0.31
Response ratio				
End of plateau phase	-0.33 (76)	-0.50 (83)	0.17	0.13
LOCF	-0.26 (104)	-0.44 (105)	0.18	0.03

For the LOCF data subset, the nominal p value was 0.03. Alternative analyses were performed by the division's statistical consultant, J. Mele. An analysis adjusting for baseline found a p value of 0.06 for the LOCF and 0.13 for the observed cases (without center 4). An analysis evaluating the frequency of spasms over the entire plateau phase adjusting for baseline did not demonstrate statistical significance but after adjusting for strata the p value was 0.04. The frequency of spasms in the different strata were in favor of placebo for the mild group and in favor of tizanidine for the moderate and severe group though no differences were statistically significant.

4.6.4. Global assessments:

The prescriber and the assessor were asked to rate the overall effects of treatment by rating the improvement in the symptoms of spasticity along with the AEs on a 10 point scale anchored by "Not at all satisfied" to "Very satisfied". The maximum score was 11.5 though the in the CRF, the line was only 10 mm long.

Excluding center 4, the global assessments favored the patients on tizanidine over placebo. The differences were nominally significant for the physician prescriber (p=0.043) and the patient (p=0.011) but not for the physician assessor (p=0.28). The results are as follows:

Endpoint Global (excluding center 4)	Placebo	Tizanidine	Treatment effect	p value
Assessor	4.3	4.9	0.6	0.28
Prescriber	4.0	5.1	1.1	0.04

The greatest changes for the Ashworth scale was seen in those patients with a global rating ≥ 6 .

4.6.5. Other efficacy variables:

No statistically significant differences were noted on for the evaluation of muscle strength, DTRs, the type and frequency of spasms, pain and disability due to spasm, walking times or ADL scores.

4.7. Results of study 003

This study was similar to the previous studies except the spasticity in these patients were related to a spinal cord injury not MS and the maintenance phase was only 4 weeks long for a total exposure of 7 weeks instead of 12 weeks in the MS studies. Randomization was not stratified by the baseline Ashworth scale. The pendulum test was a primary outcome measure in this study in addition to the Ashworth scale and the frequency of spasms. The efficacy rater was a physical therapist who also was responsible for completing the ADL by interviewing the patient .

4.7.1. Disposition and demographics:

124 patients were enrolled at 14 centers. 6 patients did not receive study treatment. 59 patients received tizanidine and 59 received placebo. Patients were aged 15 to 69 with a mean age of 36, 88% were males. The demographics were similar between groups. 8 patients in the placebo group and 3 in the tizanidine group discontinued for lack of efficacy. The disposition is summarized as follows:

Disposition for study 003			
Treatment group	Randomized/treated	Completed study	Discontinued for AEs
Placebo	63/59	46	5
Tizanidine	61/59	42	11

4.7.2. Ashworth Scale:

14 patients had baseline data but no Ashworth score on treatment (10 on tizanidine and 4 on placebo) though 13 of the 14 patients had spasm counts during the plateau phase. There was a statistically significant decrease in muscle tone in the tizanidine group when compared to the placebo group for both the Observed cases and LOCF data sets. The percentage of patients who improved (showed a

decrease in the Ashworth score) was 46% for the placebo group and 68% for the tizanidine group ($p = 0.03$). An analysis adjusted for baseline differences also demonstrated a statistically significant difference. A comparison of groups in the 3 strata were in favor of the tizanidine group. Subset analyses suggested that more severely affected and younger patients may be more responsive while sex of the patient, race and duration of the injury did not affect treatment.

Ashworth Scale scores	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	10.7 (59)	11.8 (59)		0.18
Week 7 (end of plateau)	10.1 (38)	7.4 (37)	3.8	<0.0001
LOCF	10.3 (55)	7.4 (49)	4.0	<0.0001

4.7.3. Frequency of spasms:

A primary outcome was the total number of daytime spasms and nighttime awakenings. Since there were few nighttime awakenings, the daytime spasms was analyzed separately. Because the number of spasms was not normally distributed they were converted to response ratios as in study 001. The spasm response ratio was decreased in the tizanidine group compared to placebo but, for completers, the differences were not statistically significant. The sponsor did not provide an analysis of the LOCF data subset. The results are summarized below.

Spasms	Placebo (N)	Tizanidine (N)	Treatment effect
Baseline	15.0 (59)	19.1 (56)	
Completers response ratios	-0.12	-0.33	0.34

The division's statistical consultant analyzed the LOCF data subset and found a nominal p value of 0.04 in favor of the drug which appeared to from a higher spasm rate in placebo drop outs compared to placebo completers. As in study 001, an analysis was performed to evaluate the reduction of spasms over the entire plateau phase. This evaluation did not find a significant difference between groups with a p value of 0.14.

4.7.4. Pendulum test:

This test was an additional primary outcome measure in this study. The median

degrees of angular displacement of the first swing of the right leg was used in this test. The results are summarized as follows:

Pendulum test	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	48.2 (57)	40.1 (55)		
Completers	56.1 (36)	60.2 (35)	12.2	0.01
LOCF	46.0 (53)	63.2 (45)	15.3	0.004

4.7.5. Global assessment:

The global scores were rated by the physical therapist by drawing a line on a scale to represent the patient's functional capacity from "minimal function and interactive capacity" to "normal function and interactive capacity". There was also a patient global which used the anchor points of "spasticity interferes with all functions" and "spasticity does not interfere with any functions". This score was measured at baseline and the end of the plateau phase. There was no significant differences between groups. The results for the therapist's global are as follows:

Clinician's Global	Placebo (N)	Tizanidine (N)	Treatment effect
Baseline	6.4 (58)	6.0 (58)	
Completers	6.8 (36)	6.4 (37)	0
LOCF	6.8 (50)	6.7 (45)	0.3

4.7.6. Other outcome variables:

There were no statistically significant differences between groups for change in muscle strength, change in deep tendon reflexes, pain and disability due to muscle spasm and ADL as measured by the modified Klein-Bell.

4.8. Results of the supportive study S-1:

This study was completed in 1987 and was part of the approval package for the Canadian authorities. The study was turned down for the lack of the ability "to provide evidence in support of the efficacy of tizanidine".

This was a double blind, parallel, placebo controlled study in patients with MS. The patients were titrated over 3 weeks followed by a maintenance phase of 5 weeks for a total treatment duration of 8 weeks. No primary outcome measures were defined. Muscle tone, strength, DTRs and functional measures were assessed. Muscle tone was assessed by measuring 11 muscle groups. The muscle groups were different from those tested in the other studies. There was no mention of a separate assessor and prescriber.

4.8.1. Disposition and demographics:

66 patients were enrolled with 59 completing the study. For the endpoint, 32 patients were in the placebo group and 33 in the tizanidine group. 50% were female with an average age about 45. Most patients had complaints of spastic paraparesis. More placebo patients had previously been treated with antispasmodic drugs. Compared to the other MS studies, the mean dose was lower and the duration of treatment was shorter.

4.8.2. Muscle tone

Muscle tone was not assessed with the Ashworth scale. The scale was 0 to 6. A score of 0 = no movement, 1 = a severe increase in spasticity, 2 = a moderate increase in spasticity, 3 = a slight increase in spasticity, 4 = normal tone. A score of 5 and 6 was for hypotonia. The sponsor reported an improvement in both groups with greater improvement in the tizanidine group. The sponsor reported that the differences were statistically significant but the p value reported in the NDA was 0.21.

Neither the sponsor or the division's statistical consultant were able to replicate the results presented in the NDA. The division's statistical consultant recoded the scores to the Ashworth scores. While the changes were in favor of tizanidine, the statistical significance of the difference depended on the data subset used in the analysis and the method of scoring the muscle tone. It is somewhat difficult to compare these scores with the other studies because the original scale was different and the muscle groups tested were different. With these problems in mind, the magnitude of the treatment difference was similar to study 502 and 001. The results following recoding of the original scores are as follows:

Recoded Ashworth scale for study S-1	Placebo (N)	Tizanidine (N)	Treatment effect	p value
Baseline	18.5	15.5		0.23
Completers	17.1	11.9	2.2	0.02
LOCF	16.9	12.4	1.5	.08

4.8.3. Other outcome variables

The number of spasms was not counted in this study. The functional measures (disability status, ambulation index, upper extremity index) and the global assessments by the patient and the investigator for anti spasticity efficacy were not statistically significant.

4.9. Results of supportive study S-2

This was a two 4 week cross over study evaluating patients with MS and chronic myelopathy. Since there were no washout periods, only the first period was analyzed. There were 32 patients enrolled. The Ashworth score changed by 0.1 in the placebo group and 0.3 in the tizanidine group. There were no statistically significant difference between groups.

4.10. Results of other studies:

There were 15 trials comparing tizanidine with baclofen and 6 comparing tizanidine with diazepam. There were no differences between the groups reported.

5. Assessment of the regulatory requirement for substantial evidence of efficacy

5.1. Indication:

The sponsor is proposing tizanidine as a treatment of spasticity of spinal origin and has offered three studies as pivotal in providing evidence for efficacy. In study 003, they have evaluated patients with spasticity as a result of spinal cord injury (92% from trauma) and in studies 502 and 001, the spasticity was from multiple sclerosis. Spasticity in patients with MS can be a result of spinal or supraspinal lesions. In the protocol, the origin of the spasticity was not a

consideration. I must assume that in the population of patients with MS, the spasticity could have been related to spinal and/or supraspinal lesions. Without information on the origin of the spasticity in the MS patients, it cannot be confirmed that the results are specific for spasticity of spinal cord origin. The studies are evaluating spasticity as a result of MS or spinal injury.

5.2. Evidence necessary to demonstrate efficacy for treatments for spasticity

Spasticity is characterized by an increase in muscle tone. The presence of increase tone by itself does not warrant treatment and can be, at times, necessary for a patient to perform daily activities. Treatment is usually reserved for when symptoms of spasticity contribute to some level of discomfort or disability. An effective treatment for spasticity, while reducing muscle tone, should be able to relieve or help these disturbing symptoms without eliminating beneficial effects of an increase in muscle tone.

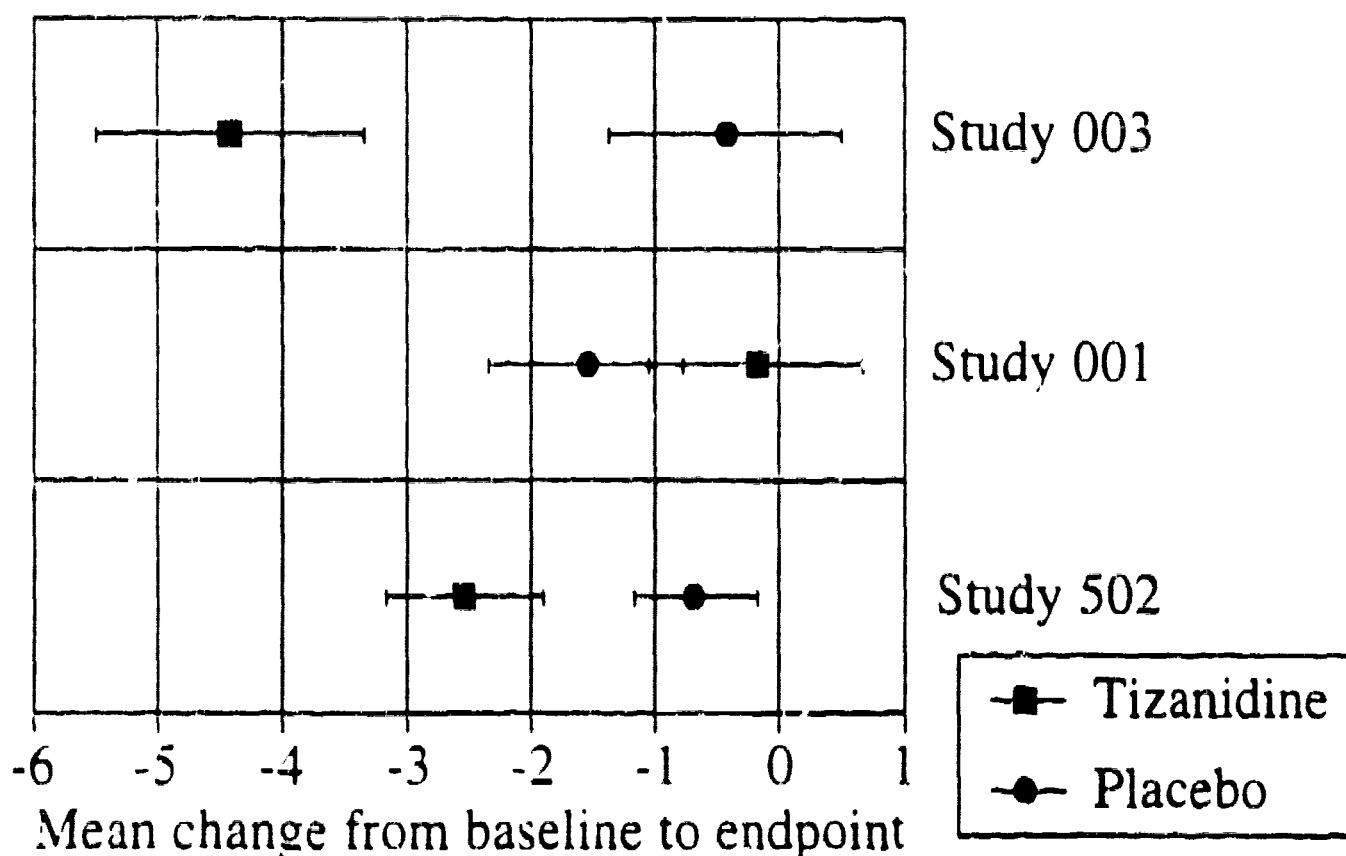
In the evaluation of the effectiveness of tizanidine and other antispastic drugs (for example, intrathecal baclofen for spasticity of spinal cord origin), the division request a dual outcome measure of the antispastic effect. Changes in muscle tone were required to be accompanied by a measurement that would validate the clinical usefulness of the changes seen in the Ashworth scale. The frequency of spasms was the clinical measurement used by the sponsor in the design of study 001 and 003. Study 502, already completed by Sandoz, measured the frequency of spasms, but it was a secondary outcome measure. In the pre-NDA meeting between the sponsor and the division, it was stated by the division that both primary outcome measures, the Ashworth scale (muscle tone) and frequency of spasms, must be positive for the efficacy studies to be considered positive.

5.3. Results of the primary outcome measures of the pivotal trials -Muscle tone:

Muscle tone was measured with the Ashworth scale. Two of the three trials, 003 and 502, demonstrated a statistically significant decrease in muscle tone in patients treated with tizanidine when compared to patients treated with placebo. The degree of improvement in muscle tone was modest. In a comparison of the change scores for just the lower extremities muscle groups, there was an approximately 32% greater reduction in Ashworth score in the tizanidine group compared to placebo. In study 502, the treatment effect was smaller, with an approximately 17% greater reduction in tone from baseline for the tizanidine patients compared to placebo. Study 001 demonstrated an opposite effect

compared to study 502 with an approximately 14% greater reduction for the placebo group compared to tizanidine. The results of this comparison was taken from Table XIII and Figure 5 in the Clinical Data Summary and Results of Statistical Analysis section in the NDA submission and is summarized as follows.

Comparison of the Ashworth scale change scores for the lower extremities with 95% confidence intervals



Study 001 was undertaken as an attempt to replicate the findings of decrease in muscle tone found in study 502. The design, patient population, dosage and duration of treatment were similar. Not only was there **not** a reduction in muscle tone found in the tizanidine treated patients, the direction of change, while not statistically significant, was in favor of placebo.

5.4. Results of the primary outcome measures of the pivotal trials -frequency of spasms:

In study 502, spasm frequency was rated by the patient at the time of their follow up visit and recorded on a scale. There was a decrease in the spasms in both groups. The change from baseline was similar in both groups and the differences

did not reach statistical significance.

The frequency of spasms was taken from the counts recorded by the patients in their diaries in studies 001 and 003. In these studies, the spasm counts decreased in both groups with a greater reduction in the patients receiving tizanidine. For the completers, the difference was not statistically significant. In the analysis of the LOCF data subset, the difference between groups resulted in nominal p values of 0.03 for study 001 and 0.04 for study 003. The division's statistician, J. Mele, performed an analysis on the reduction of spasms over the entire plateau phase, adjusting for baseline and strata. The results suggested that the patients on tizanidine in study 001 had an overall decrease in spasms. This was not so for study 003 where a similar analysis suggested that overall there was no statistically significant difference between groups.

5.5. Results of the secondary outcome measures of the pivotal trials -patient's comfort, functional outcome measures and global assessments:

The outcome measures assessing pain and functional variables (walking, ADLs) were not statistically significant for any of the studies. For the global assessments, only for the physicians who prescribed the drug in study 001 and 502 was the comparison of the efficacy and tolerability of the drug and placebo groups statistically significant in favor of the drug. Patient's global assessments were statistically in favor of the drug in study 001 but not in study 502 and 003 where there was a change in muscle tone noted.

5.6 Results of supportive efficacy trials:

In the sponsor's report of study S-1, the change in muscle tone was directionally in favor of tizanidine. The changes in scores were similar in magnitude to the changes seen in study 502 and 003 but the differences did not reach statistical significance. The functional measurements and global evaluation of the antispasmodic effect were not statistically significant. The frequency of spasms was not measured.

The division's statistical consultant along with the help of the sponsor attempted to convert the muscle tone scores to the Ashworth scale. A rating of slight increase in spasticity was converted to a rating of a slight increase in tone giving a catch when the limb is moved in flexion or extension. A rating of moderate increase in spasticity was replaced with a rating of more marked increase in tone but the limb was easily moved in flexion or extension. A rating of severely

spastic was converted to a score of considerable increase in tone, passive movement difficult. A score of no movement was converted to a score of limb rigid in flexion and extension. With these converted scores, the completers on tizanidine had a statistically significant decrease in muscle tone when compared to placebo. Using the LOCF data subset, the differences were not statistically significant.

While the statistical consultant felt that this data was supportive but not definitive of the efficacy of the drug, I would conclude that the usefulness is somewhat limited and the validity of the post hoc conversion of the scores is questionable. The measurement of muscle tone is difficult to compare with the pivotal studies for the following reasons: some of the muscle groups assessed were different in study S-1 and in the pivotal studies, in study S-1, only the "affected limbs" were assessed, the rater of muscle tone did not originally use the Ashworth scale and the two scales may not be directly convertible (especially ratings of 1, 2 and 3), the rater was not instructed on measuring tone as in the pivotal studies, there were 4 different raters at one center and the same patients may have been rated by different assessors during the study, the rater may have also been the prescriber, some patients in study S-1 were rated as having hypotonia.

Study S-2 did not demonstrate a difference from placebo and tizanidine was not found superior or inferior to baclofen or diazepam in the active controlled trials.

5.7. Clinical significance of the findings

Based on the criteria set in the pre NDA meeting, only one study, 003, was close to being considered positive. Study 001 failed to show an improvement in muscle tone. Study 502 while showing a statistically significant effect on muscle tone, failed to show a decrease in spasms. Study 003 showed a statistically significant decrease in muscle tone and an analysis dependent statistically significant reduction in spasms though when the frequency of spasms over the entire plateau phase was considered, there was no difference.

It could be argued that with any consistent finding of an effect in the treatment of spasticity in two independent studies would satisfy the regulatory requirements for efficacy even though, because of the lack of a clear reduction in the frequency of spasms, the division's requirements for positive efficacy studies were not fulfilled. The finding of a small to moderate reduction in muscle tone in studies 502 and 003, respectively, without a sustained or consistent change in any functional or clinical measures suggests an effect with questionable benefit.

5.8 Potential bias introduced by unblinding

Because the findings of decreased muscle tone found in study 003 and 502 were not replicated in study 001, the validity of the positive findings comes into question. The sponsor offers explanations as to why study 001 was not positive.

- (1) The sponsor notes that the assessment of the Ashworth scale were delayed in respect to the time of dosing which may lead to a reduction in the effect seen in these patients. The division's statistical consultant performed an analysis of a subgroup of patients with a known time of assessment in relationship to dosing. The analysis shows that placebo continues to beat tizanidine at time points < 3 hours and > 3 hours post dosing suggesting that this is not the explanation for the lack of a drug effect.
- (2) The sponsor also states that the unusually large placebo effect may be the reason for the lack of efficacy in this study. A review of the percent change for the Ashworth scale shows not only a larger placebo response but also a smaller tizanidine response in study 001 when compared to study 003 and 502. The reduced drug effect was not caused by the higher placebo effect.
- (3) The baseline Ashworth scores were also suggested to be an explanation for the differences in the studies. Only in study 001 were the baseline scores for the Ashworth scale better in the tizanidine group compared to the placebo group. In both study 003 and 502, the baseline scores indicated that the tizanidine group had greater muscle tone than the placebo group. To evaluate this difference, the scores were adjusted for baseline differences. This did not change the statistical significance any of the studies.

Another possible explanation for the difference between study 001 and studies 003 and 502 was the effectiveness of the blinding for the Ashworth Scale assessor. In a symposium held to discuss the role of tizanidine in the treatment of spasticity (*Neurology* 44 (suppl 9) November 1994), an investigator noted that "In view of the high frequency of side effects, it is difficult to accept that this was a true double blind study. Fatigue and somnolence was significant at our institution. It was easy for all persons involved to know which was the active agent and which the placebo". Both Dr. Charles Smith, the lead author in the paper on study 001, and Dr. Lataste, from the CNS research department of Sandoz agreed. It was also noted by an investigator that because the Ashworth scale is an ordinal scale, the "assessor has to make judgements based on highly subjective perception". During the study, "criteria for scoring may have changed unconsciously, and a 2 could become a 3 or a 3 a 4". With these factors operating, unblinding of an assessor could have led to changes in the Ashworth scale enough to account for small changes in the score seen in study 502 and 003.

The issue of unblinding was raised because certain adverse events are much more

frequent in the tizanidine patients compared to placebo. These AEs included dry mouth (49% tizanidine vs 10% placebo), somnolence (48% vs 9%) and asthenia (39% vs 14%). In study 502, the same clinician assessed the Ashworth scale and prescribe treatment. This would allow the assessor to know the AEs suffered by the patient and therefore jeopardize the blind. In study 003, the assessor was a physical therapist who was not involved with treatment. This would reduce the chances for unblinding but because the physical therapist also interviewed the patient for the scoring of the ADL, they could have been informed of AEs suffered by the patient. Only in study 001, was the blind carefully maintained with the assessors evaluating the patients with no information regarding the patients symptoms passed on to them.

These points raise the possibility that the changes in the Ashworth scale in study 502 and 003 were a result of a bias introduced by unblinding. Possibly, the only reason that study 001 was not positive, when a similar study in similar patients (study 502) was positive, was that the assessor of the Ashworth in study 001 was the only one that was truly blind to the treatment. In study 001, both the prescriber and patient, both unblinded to AEs, had statistically significant ratings in favor of the drug in global assessments while the blinded assessors' ratings were not statistically in favor of the drug.

In order to investigate this possibility of bias introduced by unblinding, the division's consulting statistician performed additional analyses. She compared the Ashworth scores in patients with and without the most common AEs (dry mouth, asthenia and somnolence). The hypothesis was that if there was bias introduced by unblinding due to side effects, patients, either on placebo or drug, with the side effects would have better scores than their counterparts without these side effects.

In study 003, placebo or tizanidine patients with side effects had very similar scores compared to placebo or tizanidine patients without side effects. The direction of change, though small, was in favor of patients without side effects. Even though the numbers of patients in the groups were small, the findings did not suggest a problem with bias introduced by unblinding of the assessor due to the side effect profile. The results are summarized as follows:

Ashworth scores for patients in study 003 with and without common side effects				
	N	Base-line	Endpoint change	Patients with an improvement in Ashworth
Placebo with side effects	12	10.2	+0.7	33%
Placebo without side effects	43	10.9	-0.7	53%
Tizanidine with side effects	36	12.0	-4.4	81%
Tizanidine without side effects	13	11.5	-4.5	85%

In study 502, placebo or tizanidine patients with side effects had better scores than placebo or tizanidine patients, respectively, without side effects. The number of patients in each group are larger than in study 003. The differences between groups was much larger than that seen in study 003 and support the hypothesis that bias produced by knowledge of the side effects of the drug may explain the differences in the Ashworth scale scores in the tizanidine and placebo patients. The results are summarized as follows:

Ashworth scores for patients in study 502 with and without common side effects				
	N	Baseline	Endpoint change	Patients with an improvement in Ashworth
Placebo with side effects	26	15.6	-2.4	62%
Placebo without side effects	67	17.3	-1.2	45%
Tizanidine with side effects	74	18.3	-4.2	76%
Tizanidine without side effects	20	19.0	-2.7	55%

5.9. Comments

Study 001 failed to demonstrate substantial evidence of efficacy. The change in muscle tone was in not statistically significant and directionally was in favor of placebo. Study 502, while demonstrating a difference between groups in muscle tone statistically in favor of the drug, failed to demonstrate an effect on any functional measure except for the physician's global rating. The validity of this study is questioned by the possibility of a bias introduced by unblinding introduced by using the same clinician as the assessor and prescriber. Study 003

demonstrated a statistically significant treatment difference in muscle tone in the tizanidine group. The study also demonstrated a difference in the frequency of spasms though the effect over the entire plateau phase was not statistically significant. The reason for the differences in the studies is not clear and many possibilities can be considered. The drug may have an effect only in patients with spasticity from spinal cord injury.

6. Safety Summary

6.1 Safety Database:

To support the claim that tizanidine is safe for the treatment of spasticity, the sponsor has submitted information from clinical trials in patients with spasticity and healthy volunteers. They have also provided information from post marketing surveillance.

The sponsor states that 3903 patients have been exposed to tizanidine in clinical trials and an additional 13 million patients exposed to the drug from marketing. From the population of 3903, 536 subjects have been involved in clinical pharmacology studies which are short term studies with a duration of no more than 14 days. An additional 736 patients with acute muscle spasms have been treated. These patients have been treated for a shorter duration (usually 7 days) with low doses (6 to 12 mg/day). An additional 1576 patients have been treated in Asia. In these studies, the dose was very low (usually 3 to 9 mg/day). The information of these studies is only contained in summaries from Sandoz.

From the population of 3903, 955 have been in studies evaluating spasticity (placebo controlled, active controlled and open studies). From this population, approximately 300 patients in clinical trials have been exposed for > 3 months with about 200 on treatment for > 7 months. 142 had exposure of > 1 year with the maximum exposure of 3 years. The numbers are from a table supplied from the sponsor in a submission dated 7/7/94.

In all of the primary efficacy trials, the dose was titrated over 3 weeks from 2 mg/day to a maximum of 36 mg/day, given as 12 mg tid. The dose was then maintained for up to 9 weeks. Of the 124 patients receiving a maintenance dose of > 9 weeks, 75% received an average dose of ≥ 20 mg/day. Approximately one third received an average daily dose of > 35 mg/day.

In the supportive trials, the mean maintenance dose was 18 mg/day given bid or tid.

In the long term trials, a summary of the exposure of the drug (dose and duration) has not been clearly presented in the sponsor's summary. In the 8 long term trials sponsored by Sandoz, 127 patients were treated for up to 1 year with an average daily dose of 14 mg. Three of the studies had an average dose of 7.6 mg/day with a range of 5 to 9 mg/day. In 5 trials, the average dose was 16.7 mg/day with a range of 15 to 20 mg/day. The exact numbers of patients receiving each dose and the duration of exposure was not provided.

The sponsor notes that the drug has been marketed in over 30 countries and estimates that 13 million patients have received the drug. 50% of the exposure is in Japan where the recommended dose is 3 mg/day. In the rest of the world, the sponsor notes that a dose of "9 mg dose is accepted". The sponsor assumes an average duration of treatment is 8.5 days. The safety information from this group is not of the same quality as information obtained from clinical trials.

6.2. Adequacy of the safety data base:

In the efficacy studies, the doses were titrated up to a total dose of 36 mg/day. The sponsor's claims for efficacy is based on study 502 and 003 where the average daily dose was approximately 30 mg. The sponsor notes in their labeling that the maintenance dose is 12 to 24 mg/day though efficacy was not demonstrated at these doses by the pivotal efficacy trials. The maintenance dose should be closer to 30 mg/day as supported by the efficacy studies. It is possible that a lower dose would also be effective but evidence supporting this claim from the placebo controlled trials has not been presented by the sponsor in the NDA.

If a dose of 30 mg/day is to be described in labeling as the dose where efficacy was demonstrated, the safety data should also be based on this dosing range. From the information provided in Dr. Rouzer-Kammeyer's review, the sponsor has not demonstrated that any patient has been exposed to this dose for more than 3 months. Some of the long term exposure, for example, > 3 months, which was already small (only 330 patients treated over 3 months), involved average doses of 14 mg/day. The highest average dose was 20 mg/day. The exact numbers of patients exposed to these doses were not present in the clinical review or in the sponsor's summary of safety.

The argument of safety being supported by the large post marketing experience is problematic for two reasons. One, the safety data obtained from post marketing surveillance is insensitive to many of the adverse effect of a drug and two, most of the duration and exposure to tizanidine, as estimated by the sponsor, is well

below the dose and duration need to assess the safety of the drug in the treatment of spasticity.

These numbers suggest that the long term safety data base for the use of tizanidine in doses found to be effective is insufficient to adequately assess the safety in the treatment of a chronic condition such as spasticity.

The sponsor needs to provide more evidence that the drug is safe when used at demonstrated effective dose for the durations of >3 to 6 months. The dose exposure for patients in the studies should also be provided. A chart displaying the days of exposure by maintenance dose for all clinical trials should be constructed. The number of patients on each of the maintenance doses should be listed by the duration that the patients were on the drug.

6.3. Adverse events:

Adverse events occurring in patients on tizanidine were frequent, usually mild to moderate in severity and, in general, reversible with discontinuation of the drug. The most frequent AEs were dry mouth, somnolence, asthenia and dizziness. These events were not considered to be serious and occurred early in the clinical course and remained unchanged or slightly decreased through 6 weeks.

To facilitate labeling, the sponsor should provide two cumulative listing of treatment emergent AEs. One including all treatment emergent AEs occurring in placebo controlled trials for spasticity and another with information from all clinical trials for the indication of spasticity comparing the incidence of AEs in patients receiving tizanidine and those receiving placebo. All treatment emergent AEs, whether or not considered drug related, with an incidence higher in the tizanidine group compared to placebo should be included. A cumulative listing of AEs obtained from post marketing surveillance should also be provided.

6.4. Deaths:

10 deaths have been reported in patients on tizanidine. 4 occurred in the clinical trials (N=955) and 6 were reported in post marketing surveillance.

(1) Patient 15 in Study S-17, a 52 week comparative study, died after 46 weeks of treatment. No additional information was provided.

(2) Patient 123 in study 004, the long term extension study of 003, was a 55 year old black male with a history of a C6 spinal cord injury, COPD, hypertension, CAD, angina, cardiac failure (LVEF 17%) and IDDM. The patient, who was on

placebo in study 003, was on day 69 of treatment on a dose of 24 mg/day, when he was admitted to the hospital with CHF. On day 72, the patient's BP dropped and the dose of tizanidine was decreased to 16 mg/day. The tizanidine was discontinued and two days later the patient died of cardiac failure.

(3) Patient ? in study 0013, a compassionate use study, was a 44 year old female with MS who had been on tizanidine for 6 years and was known to be on 24 mg/day. She died with complication of MS.

(4) Patient ? in study 004, the long term extension study of 003, was a 36 year old male, was on drug for 4 months and had a maximum dose of 36 mg/day. He was found dead in his apartment of unknown cause. An autopsy was pending.

(5) A 68 year old male on 4 mg/day developed cholestatic jaundice after being on treatment for 2 months. The patient was also on carbamazepine. He died 20 days later with pneumonia.

(6) A 50 year old male with cervicobrachial syndrome? on 3 mg/day died 4 days after the drug was withdrawn with cardiac failure.

(7) A 64 year old female on 9 mg/day developed an increase in sugar and subsequently died.

(8) A 70 year old male with a history of cardiac insufficiency and hypotension died of cardiac failure after treatment with 2 mg/day.

(9) A patient treated for spasticity died on respiratory failure.

(10) No information was provided for the 6th patient.

The details are insufficient to decide on the causality of the deaths. In the face of known hepatotoxicity, the death following the development of cholestatic jaundice raises questions about drug induced liver failure as the underlying cause of death. The possibility of an effect on the BP raises questions as to drug induced worsening of the cardiac disease. The sponsor should be able to provide additional information on the patient death in study S-17. The autopsy report for the 36 year old male in study 004 must be submitted.

6.5. Discontinuations:

119 out of 955 (12.5%) patients on tizanidine compared to 16 of 325 placebo patients (5%) in the clinical trials discontinued from the study for AEs. The most common reason for premature discontinuation was the occurrence of AEs in the tizanidine group and lack of efficacy for the placebo group.

The most common AEs causing discontinuations in the tizanidine group were asthenia, somnolence, dry mouth, speech disorder and dizziness. At least two patients were discontinued for orthostatic hypotension, one of whom also had bradycardia with a prolonged PR interval. Two patients had seizures.

Two placebo patient were discontinued from study 001 with serious adverse events which were suggestive of being related to a drug effect. One was patient A085 in center 8. This patient, a 28 year old male with MS, developed a macular rash with joint effusion and elevations of LFTs (ALT to 1392) beginning on day 61 at a dose of 24 mg/day. A rheumatology consultant diagnosed severe serum sickness related to the study drug. All problems resolved with discontinuation of the drug. The patient also had symptoms common to patients on drug including severe dry mouth and asthenia. The side effects, found in about 15% of placebo patient were usually not rated as severe.

Another patient in study 001 on placebo, A014 at center 2, developed thrombocytopenia.

6.6. Serious AEs:

A number of more serious AEs were discovered in the clinical trials. A more detailed analysis of the relationship to the drug needs to be undertaken prior to describing the events in labeling. In general, listing of all patients with the adverse event or lab abnormality should be provided. The listings should include the patient's ID, associated AEs and lab values, the timing of the AE or abnormal lab value, the resolution, the dose at the time of the abnormality and the action taken (if any).

The sponsor should provide a line listing for each lab parameter containing all values which were above or below the critical ranges (for example $\geq 3 \times \text{ULN}$ for the SGPT) from all patients in the clinical trials (N=955).

6.6.1. Hypersensitivity reactions:

Hypersensitivity reactions have been reported including cases of rash with fever. One patient (B211 in study 001) developed rash, fever and exfoliative dermatitis (rated as mild) on day 36. The sponsor should provide a listing of all hypersensitivity reactions with duration of treatment and dose.

6.6.2. Hepatotoxicity:

Hepatotoxicity was seen in the animal studies and patients were monitored for changes during the clinical trials. An elevation of $3 \times \text{ULN}$ ($2 \times \text{ULN}$ if the baseline value was abnormal), was considered clinically significant. In the primary clinical trials, an elevation of the transaminase occurred at least once in

57 of 285 (20%) tizanidine patients and 3 of 277 (11.2%) placebo patients ($p = 0.005$). Eleven of 227 (4.8%) tizanidine treated patients compared to 1 of 231 (0.4%) placebo treated patients had a clinically significant elevation of the ALT. The sponsor reports that in 44 studies involving 765 patients treated with tizanidine, 14 (2%) had significant elevations of the ALT.

Some of the elevations were associated with jaundice and other signs and symptoms. One patient died.

The death was from a post marketing report. The patient was a 68 year old male who was on 4 mg/day for 2 months. the patient was also reported to be on carbamazepine. He developed cholestatic jaundice followed by death after 20 days reported to be due to bronchopneumonia.

Patient 163 had a picture of hepatocellular cholestasis. She was a 46 year old BF with MS who was titrated to 12 mg/day. On day 63, the patient developed an elevation of the ALT (1392) with liver enlargement, jaundice (? bilirubin), elevated ALK PHOS (237) and abdominal pain which resolved with discontinuation of the drug with normal ALT by day 106.

Patient 006 received an accidental overdose of tizanidine. The patient developed stupor with an increase in bilirubin (2.3 mg/l) without an elevation of the ALT/AST. The bilirubin returned to normal after 1 week off the drug.

A patient from study published by Lang and Riley in patients with cranial dystonia describe a patient who developed a rash and elevation of the LFTs while on 34 mg of tizanidine.

Post marketing reports demonstrated 5 cases of hepatic dysfunction, 3 reports of hepatitis, 3 reports of jaundice and 12 reports of elevated liver enzymes.

A consultation from Dr. Gallo-Torres, M.D., Ph.D. of HFD-180 suggests that tizanidine is associated with hepatotoxicity which may be heterogeneous with both hepatocellular and cholestatic features. He suggested that the effects of the drug on liver toxicity could be better characterized by long term studies with routine evaluations of the labs including liver functioning. He also suggested studies evaluating the effects of the drug in patients with varying degrees of liver dysfunction. He suggested that labeling should contain information with an explanation of the progression to serious liver disease with the disclaimer that the relationship to tizanidine was not clear in many instances.

This drug appears to be hepatotoxic with both hepatocellular and cholestatic features. The sponsor should provide additional information in order to characterize the hepatotoxicity. The sponsor should submit a line listing of every patient in the clinical trials (N=955) with an ALT (SGPT) and/or AST (SGOT) level ≥ 2 times the ULN and/or bilirubin ≥ 1.5 x the ULN. This listing should include the patient ID, dose at the time of the elevation, dosage change with elevation (if any), ALT/AST values, time to first elevation, time to peak elevation, time to resolution, associated signs or symptoms and lab abnormalities. The studies recommended by the division's consultant should be forwarded to the sponsor as recommended studies to better characterize the effects of the drug on liver function.

6.6.3. Hallucinations:

From North American studies (001, 002, 003, and S-1) there were 13 patients with hallucinations out of 289 (4.5%) patients receiving the drug. There were no reports in 203 patients on placebo (p value 0.005 Fisher's exact test). The hallucinations are visual. In one case they were associated with depersonalization, delusions and somatic pain. The patient required psychiatric treatment with hospitalization. The hallucinations resolved but the patient continued to have slight paranoia and required psychiatric care. Another patient had the hallucinations continue for two weeks after discontinuation. 8 patients remained on treatment, 5 without a dose reduction. The hallucinations occurred as early as after 12 days of treatment. Onset in others were after > 5 months of treatment. Doses ranged from 10 to 36 mg/day.

The sponsor should provide a line listing of all patients in the tizanidine clinical trials for spasticity who have experienced hallucinations. The listing should contain the patient ID and study, time of onset, dose at onset, time to resolution, associated symptoms, action taken (if any), other drugs.

6.6.4. Corneal opacities:

Corneal opacities were observed in the animal studies. The sponsor reported that ophthalmologic examinations conducted in the primary double blind studies, long term extensions and selected supportive clinical trials failed to find evidence of corneal opacities. Dr. Carreras, a consultant from HFD-540 reviewed the data and noted that while no events of corneal clouding/opacity were found, it could not be determined if the cornea was properly evaluated in most of the study centers.

6.6.5. Hypotension and bradycardia:

In clinical pharmacology studies, the systolic BP was significantly lower in the subjects given a single 2, 4 or 8 mg dose of the drug. Mean BP was significantly lower in the 8 mg group. In study S-54, 20 healthy volunteers were withdrawn for hypotension after a single dose ranging from 6 to 14 mg. In a trial involving healthy volunteers, 1 out of 18 collapsed one hour after receiving a single dose of 4 mg. The systolic dropped by 45 and the diastolic dropped by 20 with a drop in heart rate of 24 bpm. The incidence of clinically relevant changes in supine systolic BP was 30% (77/256) in the tizanidine group compared to 13% (34/254) in the placebo group (Fisher's exact p value < 0.001).

For the evaluation of orthostatic BP (patients with spinal cord lesions were not evaluated for orthostatic hypotension because standing BPs could not be obtained), there were no differences in the placebo and tizanidine groups. Three patients on tizanidine in the supportive trials discontinued for orthostatic hypotension or hypotension. One patient also had a prolongation of the PR interval, bradycardia and syncope. In these patients, the orthostatic hypotension occurred within the first two weeks of treatment. One patient in the muscular spasm trial discontinued after 4 days on 18 mg/day because of hypotension. A 63 year old female with MS and hypertension developed hypotension one hour after a dose of 16 mg.

There did not appear to be a difference between groups in patients with an increase or decrease in BP following discontinuation of the drug.

The drug leads to a reduction of BP (systolic BP) which at times is associated with bradycardia. Some episodes may be associated with the first dose of the drug. The sponsor should attempt to characterize the effects of tizanidine on the reduction in BP. A line listing of all patients in the clinical trials (N=955) and patients in the clinical pharmacology trials with a clinically relevant reduction of systolic BP (a decrease of $\geq 20\%$ of the baseline (10% if the systolic BP was 80) or hypotension with symptoms. The listing should include the patient ID, BP measurements during the trial, the dose at the time of the reduction, the timing of the reduction in BP, contributing causes (such as a history of HBP or use of other medications).

6.6.6. Seizures:

Three patients with a history of epilepsy had an increase in seizures. One patient required an increase in the dose of phenytoin. In another patient, tizanidine was

discontinued. The third patient was not on anticonvulsants when they experienced a seizure after one week of treatment. Another seizure occurred during week 4. The sponsor conducted an open label study in patients with epilepsy and reported that tizanidine had no clinically significant effect on epilepsy.

A single patient in study 003 had a seizure. This patient was a 36 year old female who had suffered a CHI and was quadriplegic. The patient had a pronounced "dysreflexic headache" with nausea and vomiting followed by a generalized motor seizure. The patient had increased her dose to 48 mg/day for the month prior to the episode.

6.6.7. Hematology:

For the double blind studies a change from normal to low values are presented but the actual values were not provided. No patients with a normal baseline had a decrease below 3,300. No neutropenia was described. Sporadic cases of decrease in platelet counts, decrease RBC, decrease in WBC were seen.

5 cases of hematology AEs were reported in patients from post marketing reports. Thrombocytopenia were reported in 2 patients. One patient recovered with continued treatment. No details are provided for the second case. 3 cases of leukopenia including one with granulocytopenia. Information is provided on only one patient who had count of 2,900 which resolved after discontinuation of therapy.

The sponsor should provide a line listing of all patients in the tizanidine clinical trials for spasticity who have experienced abnormal hematology results above or below the critical level of WBC, neutrophil or platelet count. The listing should contain the patient ID and study, time of onset, dose at onset, time to resolution, associated symptoms, action taken (if any), other drugs.

6.7. Withdrawal:

A clinically relevant change in BP after withdrawal was defined as a change of > 20% in supine diastolic or systolic BP. The changes in the double blind studies were the same in both groups.

6.8. Comments:

In order for a drug to be approved, sufficient information about the drug is required to determine whether the drug is safe for use as described in the

labeling. In the proposed labeling, the sponsor states that the optimal therapeutic response is generally achieved at daily doses between 12 and 24 mg/day. From the pivotal efficacy trials, there is no evidence that these dose will be therapeutic (this dose range may be from the active controlled trial data). In a summary of the three efficacy trials, the sponsor states that the efficacy of tizanidine was demonstrated in these studies at daily doses of ≥ 19 mg. From the dosing in study 003, the only adequate and well controlled study which provided evidence suggesting efficacy, only 10% received doses of ≤ 24 mg/day. The average dose during the plateau phase was 32 mg/day with 69% receiving doses of 36 mg/day. Since efficacy was shown at these doses, this will likely be the doses recommended in the labeling, therefore, safety information about the drug will have to be provided from patients receiving these doses.

Information on the exact dose and duration of exposure has not been presented clearly. This is particularly true for the long term studies. The long term exposure (> 7 months) to this drug as presented in the sponsor's summary is limited to about 200 patients. From dosing information on the long term trials sponsored by Sandoz, approximately 130 of these patients have received an average dose of 14 mg/day. No patient in this group of 130 had an average dose of > 20 mg/day. The dosing in the other long term trials is not clear. It is possible that there is no or very limited long term exposure (> 6 months) to this drug at doses suggested to be therapeutic in the pivotal efficacy studies. The large safety data base, including the post marketing experience, presented by the sponsor is confined to doses lower than those used to demonstrate efficacy. The duration of most of the exposure is for < 3 months. If the PK of tizanidine is linear, then the levels at the average therapeutic dose in study 003 would be 2 times the levels at the average maintenance dose. Since there is evidence to suggest accumulation for metabolites, the levels of the metabolites may be many times higher at the therapeutic doses than the doses given in the safety data base.

The safety data base, even with lower doses, provides signals for potential safety problems with this drug. These problems include hepatotoxicity, hallucinations and alterations in BP. 4 to 5 % of patients in the trials have had elevations of the ALT > 3 x the ULN. The elevations have been associated with jaundice and in one case death. The hallucinations, occurring in 4 to 5% of patients have been associated in one case with psychosis and prolonged paranoia. Significant decreases in systolic BP occurred in 30% of tizanidine patients compared to 13% of placebo subjects and have been associated with syncope and possibly cardiac decompensation. These and other AEs including the occurrence of corneal opacities, hematology abnormalities and hypersensitivity reactions have not been well characterized by the sponsor.

7. Conclusions on the safety and efficacy of tizanidine

In regards to efficacy, the sponsor has offered three studies, 502, 001 and 003, as pivotal in providing substantial evidence for efficacy of tizanidine in the treatment of spasticity. I conclude that only one of these studies was both adequate and well controlled and provided evidence suggestive of efficacy.

Study 001 failed to demonstrate a positive effect of the tizanidine on muscle tone.

In study 502, the small difference in muscle tone between groups could be related to bias introduced by unblinding of the physician assessor/prescriber to treatment assignment.

Study 003 a modest overall reduction of muscle tone was seen in patients on tizanidine. The question of bias from unblinding were not supported by additional analyses. The effect of tizanidine on the frequency of muscle spasms was in favor of the drug but the statistical significance was analysis dependent.

In regards to safety, tizanidine produces frequent AEs which are for the most part of mild to moderate severity and, in general, reversible. Some signals for potential serious safety problems with the use of tizanidine were noted. These problems include hepatotoxicity, hallucinations, drug induced hypotension, corneal opacities and hypersensitivity reactions.

I conclude that while the safety profile found in the efficacy trials is acceptable, the long term safety information is insufficient to assess the safety of tizanidine at the doses reported to be efficacious.

In regards to the carcinogenicity studies, there are questions to the adequacy of the studies. Because of the significant difference in the metabolic profile found in humans and rodents, it is not known if the animals have had sufficient exposure to the metabolites found in humans to be an adequate test for the risk of carcinogenicity. The sponsor has not provided information on the steady state levels of any of the metabolites in either humans or animals. In order to accurately assesses the adequacy of the extent of the exposure for the carcinogenicity studies, steady state information from both the animals and humans is required. If the levels in the rodent are low compared to humans, then gene mutation assays for the major metabolites will be needed in order to provide sufficient information in labeling regarding the risk of carcinogenicity.

8. Recommendation for NDA 20-397

8.1. Regulatory action:

I recommend that the application not be approved on the grounds that:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (21 CFR §314.125 (b)(5)).

The sponsor has presented only one adequate and well controlled study, 003, providing evidence suggestive of efficacy. Study 001, while adequate and well controlled in design, failed to demonstrate substantial evidence of efficacy. In study 502, there was evidence to suggest that the measures taken for blinding were not adequate to minimize bias for the observers as required for an adequate and well controlled study (21 CFR §314.126 (b)(5)).

2. There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling (21 CFR §314.125(b)(4)).

The sponsor has not provided sufficient information on the safety of long term exposure to patients receiving the presumed therapeutic doses averaging 32 mg/day.

3. The investigations do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe under the conditions of use prescribed, recommended or suggested in its proposed labeling (21 CFR §314.125(b)(2)).

The sponsor has not determined the steady state of the major metabolites in the rodent and human which are necessary to determine the adequacy of the carcinogenicity tests.

8.2. Recommendations for the sponsor

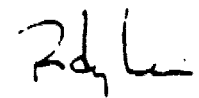
To address the issues related to non approval, the sponsor can:

1. provide evidence to indicate that bias did not play a significant role in regards to the differences seen on muscle tone found in study 502. If this is not possible, then the sponsor will need to provide substantial evidence of efficacy from an adequate and well-controlled investigation other than study 003.
2. provide sufficient long term safety data on patients receiving the therapeutic doses for durations of > 6 months.
3. characterize the major metabolites at steady state in humans as well as the mouse and rat. If the exposure to a major metabolites in the mouse and/or mouse is low in comparison to humans, then gene mutation assays will need to be performed on those metabolites.

Other issues that need to be addressed include the following:

1. Additional information is needed in regards to the extent of the exposure to the drug. Detailed dose and duration tables need to be provided.
2. Additional information is needed in regards to the serious AEs. The sponsor should provide summary information to characterize, in detail, the serious AEs including deaths, hepatotoxicity, cardiovascular effects, psychiatric effects, hypersensitivity reactions and hematological reactions.
3. Two cumulative listing of treatment emergent AEs. One including all treatment emergent AEs occurring in placebo controlled trials for spasticity and another with information from all clinical trials for the indication of spasticity comparing the incidence of AEs in patients receiving tizanidine and those receiving placebo. All treatment emergent AEs, whether or not considered drug related, with an incidence higher in the tizanidine group compared to placebo should be included. A cumulative listing of AEs obtained from post marketing surveillance should also be provided.
3. The metabolites should be isolated and the PK of the major metabolites should be characterized.

4. The isozymes involved in the metabolic process should be characterized.
5. The effect of metabolism in patients with liver impairment should be evaluated.
6. Interaction studies involving drugs of common use in the population for which the drug is intended should be evaluated. This would include antibiotics used for UTIs, analgesics, drugs for bladder control, antihypertensive agents and antidepressants.



Randy Levin, M.D.
Medical Reviewer

cc:
Original NDA
HFD-120
HFD-120/Leber/Rouzer/Higgins/Levin
r/February 2, 1995

**MEDICAL OFFICER REVIEW AND EVALUATION OF CLINICAL DATA
SAFETY REVIEW**

NDA: 20-397

Sponsor: Athena Neurosciences, Inc.

Drug: Zanaflex (tizanidine HCL) 4mg Tablets

Indication: Spasticity of Spinal Cord Origin

Date of Submission: December 3, 1983

Date Review Completed: August 26, 1994

NDA Data Cut-Off Date: August 16, 1993

Material Reviewed: Original NDA 20-397 Vol. 1-214 12-3-93
Four Month Safety Update 4-4-94

1.0 Sponsor's Proposed Labeling Indication, Dosage Form, Route of Administration, and Directions for Use

Zanaflex, a centrally acting α_2 -adrenergic agonist, is a muscle relaxant and antispastic agent which does not produce muscle weakness.

Zanaflex is indicated for treatment of spasticity of spinal cord origin. Zanaflex is effective in reducing spasticity in patients with multiple sclerosis and spinal cord trauma. Zanaflex is particularly useful for reduction of pathologic muscle tone, and painful spasms and clonus associated with spinal cord lesions and does not reduce overall muscle strength.

2.0 Background

Tizanidine was discovered and developed by Sandoz Pharma, Ltd; U.S. development of the drug for the treatment of chronic spasticity is being conducted under IND held by Athena Neurosciences, Inc.

Tizanidine has been approved in 44 countries and launched in 38 countries as shown in Sponsor's Table 1a and 1b (attached). Tizanidine is registered in Japan under the trade name Temelin and in Uruguay under the trade name Sirdalum. In France it is licensed out to Sanofi. No registration application has been withdrawn or rejected for safety reasons during the period covered by this report. No actions have been taken for reasons of safety by any regulatory authority or by the manufacturer.

3.0 Source of Studies

Information documenting the safety and tolerability of tizanidine in man is available from several sources:

- Trials sponsored by Athena Neurosciences and conducted in the U.S. in patients with chronic spasticity of spinal cord origin;
- Trials sponsored by Sandoz and conducted in Canada, Europe and South America in patients with chronic spasticity of spinal and cerebral origin;
- Trials sponsored by Sandoz and conducted in the U.S. and Europe in patients with acute painful muscle spasms;
- Clinical pharmacology and pharmacokinetic studies sponsored by Sandoz and conducted in the U.S., Europe and Australia in patients with clinical spasticity as well as in healthy volunteers;
- Trials sponsored by Sandoz and conducted in Japan in patients with spastic paralysis and painful muscle spasms; and
- Postmarketing surveillance of adverse events monitored by Sandoz since the drug's initial availability as a prescription pharmaceutical in July, 1984.

Data from the supportive Sandoz-sponsored studies summarized here were obtained from study reports that did not contain individual patient data similar in quantity and detail to the data obtained directly from case report forms in the primary clinical trials.

Consequently, the safety data were divided into three major groupings for summarization and presentation:

Primary Clinical Trials in patients with spasticity of spinal cord origin or due to multiple sclerosis (MS), which are the most recently and rigorously conducted and, with the exception of Study DS05-02, are sponsored by Athena Neurosciences, Inc. These include the two double-blind, placebo-controlled trials (AN021-001 and AN021-003) and two open-label extension studies (AN021-002 and AN021-004) in North America. Of the ongoing open-label studies, only AN021-002 had sufficient data as of the NDA cut-off date (August 16, 1993) to warrant inclusion in the NDA safety summary. Data from Study 021-004 is included in the Four-month Safety Update.

Supportive Clinical Trials in patients with an admixture of neurological diagnoses related to spasticity, which are a mixture of placebo-controlled, active-controlled and uncontrolled, short- and long-term studies, all sponsored by Sandoz Pharma, Inc.

Supportive Trials in Related Medical Conditions or Healthy Subjects, which include Trials in patients with painful muscle spasms consisting of twenty-three, short-term active-controlled studies sponsored by Sandoz.

Also included are clinical pharmacology/pharmacokinetic trials in healthy volunteer subjects:

Thirty-two single-dose or short-term; placebo-controlled, active-controlled, or open-label; Sandoz-sponsored studies.

Also, there is the Sandoz-sponsored clinical development program of tizanidine in Japan for the treatment of spastic paralysis and painful muscle spasms. Doses were lower than those found effective in U.S. and European trials in Caucasian patients. Patient specific information is not available.

Postmarketing Surveillance and Safety Profile in Published Literature

This consists of a summary of spontaneous reports of adverse events during marketed use of tizanidine, as monitored by Sandoz. The safety profile of tizanidine available from published literature was reviewed.

All patients and subjects who received tizanidine are included in the overall clinical trials safety database. Patients or subjects who were enrolled in a study but did not receive tizanidine are not included. An overview of the clinical trials with tizanidine from which safety data were collected and reviewed is presented in Table 1(attached). Figure 1 (attached) graphically depicts the disposition of all patients or subjects who received tizanidine in clinical trials.

4.0 Extent of Exposure to Tizanidine

A tabulation summarizing the duration of tizanidine treatment for subjects enrolled in all clinical studies conducted in Europe, Canada or the U.S. is provided in Table 1 (attached). These data are presented graphically in Figures 1 through 5.

The cumulative total exposed to tizanidine treatment in clinical trials is 2327. Roughly half that number, or 1054, represent short term treatment out to one month. 667 subjects were studied out to two months, 400 out to six months, with waning numbers out to 142 at 12 months and 23 subjects out to three years..

The firm estimates 15 million exposures in postmarketing experience.

5.0 Overview of Clinical Population and Studies Which are the Source of Safety Data

Tables 1 through 6 tabulate the clinical populations and studies which are the source of safety data. They are summarized as follows:

Primary efficacy placebo-controlled trials in MS (2) and Spinal Cord Injury (1)
 Supportive Placebo-Controlled Trials in MS (2)
 Active Controlled Trials- 21 Sandoz-sponsored trials with baclofen (15) or diazepam (6)
 spasticity due to various neurological states
 Uncontrolled Supportive Trials in MS, cerebral lesions, including long term use (8)
 Sandoz-sponsored Efficacy Trials in acute Musculoskeletal Spasms (25; PBO or active control)

Trials with Modified Release in volunteers or spasticity due to MS or CNS lesions

6.0 Dosage and Administration

Primary Clinical Trials

For the three primary efficacy trials (DS0502, 021-001 and 021-003) pooled which includes 264 patients in the tizanidine group and 261 in the placebo group, there was no significant difference between treatment groups in duration of exposure to treatment. The mean duration of treatment including titration and taper, was 70 days in the tizanidine group and 71 days in the placebo group. The most common duration of stable dose of study medication (plateau phase) was >9 weeks (n=124) for patients in the tizanidine group. During this period, 32 tizanidine patients received an average daily dose up to 19 mg, 32 patients received an average daily dose between 19 and 28 mg, 20 patients received between 28 and 35 mg and 40 received an average daily dose >35 mg. Of the patients who had a plateau phase > 9 weeks, a higher proportion of placebo-treated patients (88, 64%) were titrated to a daily dose > 35 mg compared to tizanidine-treated patients (40, 32%).

Supportive Clinical Trials

The mean maintenance dose of tizanidine across all supportive placebo- and active-controlled trials (excluding studies involving modified release formulation) was approximately 18mg/day, typically administered in two or three daily doses. The maximum permissible daily dose of tizanidine in these supportive studies ranged from 16 to 36 mg/day, with four trials allowing the dose to be adjusted to 36 mg/day given tid. In the short-term active-controlled studies, the mean average maintenance doses of the comparative agents, baclofen and diazepam, were 45 mg/day and 18 mg/day, respectively. In three of the long-term trials, the average daily dose of tizanidine was 7.6 mg/day (range: 5 to 9 mg/day) while in the remaining five trials it was 16.7mg/day (range: 15 to 20 mg/day). In all but one of the clinical pharmacology studies, doses of tizanidine ranged from 3 to 8 mg/day; in the remaining study (S-63), the average maintenance dose of tizanidine was 24.8 mg/day.

7.0 Adverse Events

Primary Clinical Trials

Side effects associated with tizanidine administration were frequent but generally mild. With low doses as recommended for the relief of painful muscle spasms, side effects include drowsiness, asthenia (fatigue), dizziness, dry mouth, nausea, gastrointestinal disturbances and slight reduction in blood pressure. With higher doses as recommended for spasticity (up to 36mg), the above mentioned side effects are more frequent and pronounced, and occasionally require the discontinuation of treatment. In addition, muscle weakness and insomnia may occur, and instances of hypotension and bradycardia have been observed. In some patients transient increases in hepatic transaminases and hallucinations occur.

A summary of treatment-related adverse events reported by >2% of the patients in either treatment group is presented by body system and treatment group in Table 17 (attached).

In the short-term primary studies, the overall incidence of adverse events was significantly ($p < 0.001$) greater in the tizanidine group (90% of patients) than in the placebo group (71% of patients). This difference was largely due to significantly higher incidences ($p < 0.001$) in the tizanidine group than in the placebo group of dry mouth (49% v. 10%), somnolence (48% v. 10%), asthenia (41% v. 16%) and dizziness (16% v. 4%), the four most frequently reported adverse events in the tizanidine group. The most frequently reported adverse events in the placebo group were asthenia (16%), headache (13%), dry mouth (10%) and somnolence (10%).

No instances of these four most frequently reported adverse events in the tizanidine group were considered serious by the investigator. The temporal pattern of these four ADRs was to occur early in the course of the study with substantial increase after the first week but either unchanged or slightly decreased after 6 weeks of treatment.

A significant ($p = 0.005$) difference was detected between the two treatment groups for the proportion of patients reporting cardiovascular events. This difference was due to the significantly higher ($p = 0.030$) proportion of patients who experienced hypotension in the tizanidine group (2%) compared to the placebo group (0) as well for palpitations (2% v 0). A significantly ($p = 0.03$) higher proportion of tizanidine-treated patients had elevated SGOT/AST levels reported compared with the placebo group (2% and 0, respectively). A higher proportion of patients in the tizanidine group compared with the placebo group had elevated SGPT/ALT levels reported as adverse events (3% and <1%, $p = 0.068$). In addition, hallucinations were reported by a higher, significant proportion of patients in the tizanidine group than in the placebo group (2%- 5% v 0). These serious adverse events will be discussed later in greater detail.

When the reporting rates of individual treatment-related adverse events were compared between the subsets, duration of MS appeared to influence the reporting rate of dizziness and duration of spinal cord injury seemed to influence the reporting rates of generalized spasm, hallucinations and insomnia among patients in the tizanidine group. In the tizanidine group, dizziness was reported by a higher proportion of patients with a duration of MS > 120 months (21%) compared to patients with a duration of MS < 120 months (9%). Generalized spasm, hallucinations and insomnia were all reported by a higher proportion of tizanidine-treated patients with a duration of spinal cord injury > 71 months (10% for each event) compared to patients with a duration of spinal cord injury < 71 months (0%).

Supportive Clinical Trials

The most frequently reported adverse events among tizanidine-treated patients in the supportive placebo-controlled trials (S1 and S2) were dry mouth (45%), drowsiness (35%), fatigue/tiredness (32%) and dizziness (14%).

Adverse events occurring in 3% or more of patients in the supportive active-controlled trials are listed in Table 44 (attached). As seen previously in the Sandoz-sponsored placebo-controlled studies, fatigue/tiredness (30%), dry mouth (21%) and drowsiness (15%) were the

most common adverse events reported by the tizanidine patients.

8.0 Overview of Discontinuations

Primary Clinical Trials

In the tizanidine group, the most common reason for premature discontinuation was the occurrence of adverse events. In the placebo group, the most common reason for discontinuation was insufficient effect/study medication ineffective. Fewer patients in the tizanidine group compared with the placebo group discontinued prematurely due to lack of response. Overall, 38 (14%) patients treated with tizanidine and 12 (5%) patients treated with placebo had at least one adverse event which led to discontinuation according to both the adverse event page and the discontinuation page of the case report form.

8.1 Deaths

There were four deaths associated with tizanidine administration in the NDA database. These are summarized by study in Table 2 (attached). No deaths occurred among the primary efficacy trials in tizanidine-treated patients. [One patient (#163) in the placebo group in Study 021-003 died 36 days after discontinuation from the study.]

Two deaths were reported in the four month safety update filed in April 1994. One death occurred in a patient treated with tizanidine in a long-term supportive trial. The patient (#15) who was enrolled in a 52-week double-blind comparative trial (S-17) died after 46 weeks of treatment with tizanidine. Additional treatment information and the cause of death were not provided in the study report

Patient 123 (Protocol 021-004, Center #12) a 55 year-old black male, was previously enrolled in the placebo group of Study 021-003. He had a 7-year history of C6 spinal cord injury and entered the study with a Frankel rating of B. The patient had pre-existing medical conditions consisting of tracheostomy, COPD, hypertension, coronary artery disease, angina, cardiac failure (LVEF 17%), bowel and bladder paralysis, and insulin dependent diabetes mellitus. Concomitant medications taken throughout the course of the study included captopril and digoxin for cardiac failure, glycerol trinitrate for angina, and theophylline for COPD. On Day 69, at 24 mg/day, the patient was hospitalized with increasing shortness of breath and a diagnosis of CHF. On Day 72 the dose of tizanidine was decreased to 16 mg/day and the patient was transferred to the ICU following a sudden decrease in blood pressure. He was diagnosed with a massive pleural effusion and diuresed aggressively. On Day 73 the patient was transferred back to the spinal cord unit. Tizanidine was lowered to 8 mg/day by Day 77. On Day 77 tizanidine was discontinued at the request of the patient and family who felt it was causing "too much sedation". On Day 79 the patient died in the spinal cord unit as a result of cardiac failure.

One death occurred in Canada during the tizanidine compassionate use program. A 44 year old female who had been bed bound in a chronic care facility since 1992 had been receiving tizanidine under the Sandoz Compassionate Use Study (#0013) for approximately 6 years for the treatment of multiple sclerosis. The patient died prior to beginning the Athena study. The patient had been receiving tizanidine 24 mg per day but it is unknown whether she was still taking it at the time of her death. The cause of death was complications of multiple sclerosis. It was the opinion of the investigator that the death was unrelated to tizanidine.

A fourth death in the NDA database (Canadian) was just reported 10-24-94. On 10-19-94 a 36 yo Caucasian male with SCI was found dead in his apartment. Date of death was determined to be 10-16-94. Cause is still unknown; autopsy report is pending. The patient was a participant in study AN021-003 from 6-24-93 through 8-18-93. He entered the long-term open label follow-on study AN021-004 on 8-19-93. His maximum tizanidine dose was 36 mg qd.

The sponsor states that six deaths were reported in the post-marketing surveillance data :

- 1) A 64 yo female treated with 9 mg/day tizanidine for spasticity developed an increase in blood sugar and subsequently died of "unstated other causes". No additional information is available
- 2) A second report of death was received in 1991 but no patient information was provided.
- 3) A 50 yo M was treated with 3 mg/day tizanidine for cervicobrachial syndrome; 4 days after tizanidine was withdrawn he developed cardiac failure and subsequently died.
- 4) A 68 yo M treated with 4 mg/day tizanidine developed cholestatic jaundice after two months of treatment. Tizanidine and concomitant carbamazepine were withdrawn, but the patient died 20 days later as a result of bronchopneumonia.
- 5) A 70 yo F with a history of cardiac insufficiency and hypotension was treated with 2 mg/day tizanidine for spasticity. Her cardiac insufficiency worsened and she eventually died of cardiac failure.
- 6) A patient who was treated with tizanidine (dose unspecified) for spasticity died as a result of respiratory failure. No further data was presented on this death.

Comment

The death of the 55 yo male is well-documented and appears to be related to the patient's long-standing cardiac disease; contribution by tizanidine seems remote. The information provided for the Canadian case is minimal, particularly regarding which complications of MS attributed to death. However, the long treatment exposure (six years) to tizanidine does seem to mitigate tizanidine contribution to the etiology of death. The patient who died during study S-17 is so poorly documented that it is difficult to evaluate a contribution by tizanidine. These three deaths yield a crude mortality rate of 0.2% or less, depending on how inclusive one is regarding the denominator. Lack of details precludes assessment of the six post-marketing deaths; the patient's underlying condition may be considered a likely explanation for case 1 and 5. The most worrisome case is #3, where a 50 yo male developed cardiac failure and died 4 days after tizanidine was withdrawn. Also of note for the assessment of

hepatic toxicity (see section 9.3) is the case of the 68 yo male who developed cholestatic jaundice, was withdrawn from tizanidine and carbamazepine, but died 20 days later of bronchopneumonia. The six post-marketing deaths yield a crude mortality rate of $4 \times 10^{-3}\%$

8.2 Discontinuation Due to ADR

Table 3 (attached) summarizes all discontinuations secondary to adverse events. Dropouts ranged from 5% to 20%.

Primary Clinical Trials

For the pooled efficacy trials the rate of discontinuation due to adverse events was 17% (44 patients) in the tizanidine group and 6% (15 patients) in the placebo group. The most common adverse events that led to discontinuations in the tizanidine group were asthenia (3% of patients), somnolence (3%), dry mouth (2%) and dizziness (2%). Patients in the placebo group discontinued prematurely due to dry mouth and/or asthenia (<1% of patients). No patients in the placebo group discontinued due to dizziness or somnolence.

Supportive Clinical Trials

Across all of the short-term, Sandoz-sponsored supportive trials with tizanidine in spasticity (placebo-controlled, active-controlled, clinical pharmacology, uncontrolled modified release), 90 patients discontinued study treatment prematurely due to adverse event. Of these, 37/623 (6%) withdrew from tizanidine treatment, 34/330 (10%) from baclofen treatment, 18/75 (24%) from diazepam treatment and 1/93 (1%) from placebo treatment.

The median dose of active study medication at the time of discontinuation was 10 mg/day tizanidine, 30 mg/day baclofen and 10 mg/day diazepam. The two most common adverse events resulting in premature discontinuation among the tizanidine treated patients were drowsiness or tiredness (n=9), weakness (n=8) or a combination of these (n=5). Among baclofen-treated patients, weakness (n=10) and gastrointestinal complaints (n=12) were the most common adverse events leading to early discontinuation, while 14 of the 18 diazepam treated patients discontinued for fatigue/tiredness.

Seven of the 142 patients who received tizanidine (5%) and three of the 15 patients who received baclofen (20%) in Sandoz-sponsored supportive long-term studies discontinued prematurely due to an adverse event. Four of the seven tizanidine patients and all three of the baclofen patients who discontinued for adverse events did so within the initial three months of therapy. Among the tizanidine patients, muscle weakness and/or tiredness were the most common reasons for early withdrawal.

8.3 Dose-Reduction

The firm was asked to provide a summary of dose reductions and their relationship to adverse events. Tables 1-3 are a listing of patients who had dose changes during plateau and who experienced adverse events in the three primary placebo-controlled trials. Study DS-0502 is the only study in which the adverse event form allowed for the recording of a dose reduction associated with an adverse event. There were seventeen. For studies AN021-001 and AN021-003 where a temporal relationship could not be estimated with certainty, a conservative approach was taken by listing all those patients who experienced an adverse event during plateau and who also had a dose reduction.

9.0 Serious Adverse Events

9.1 Ophthalmology Findings

Due to a signal of corneal opacities observed in the animal studies, ophthalmologic examinations were performed in Studies 021-001, 021-003 and open label studies 021-002 and 021-004 (but not in Study DSO502). The findings in animal studies were predominantly signs of corneal pathology or trauma.

Primary Clinical Trials

Sponsor's Table 40 lists ophthalmological data for patients who had changes in eye examinations, intraocular pressure or slit-lamp measures in the primary double-blind studies 021-001, 021-003 and in the open-label Study 021-002. Data for Study 021-004 and additional data for Study 021-002 is found in the Four-Month Safety Update. There were great variations in the findings, which were relatively similarly distributed among the tizanidine and PBO groups. Sponsor's analysis finds no clear evidence for an increased severity of findings, including corneal lesions of any type in patients using tizanidine.

Supportive Clinical Trials

Ophthalmologic evaluations were conducted in six of the supportive long-term trials, in one of the supportive placebo-controlled trials, and in one of the supportive active-controlled trials. The evaluations conducted in each of these studies are listed below:

Evaluation	Study Reference
Examination	S-1, S-5, S-16B, S-17, S-24, S-25, S-27, S-28
Visual Acuity	S-1, S-5, S-16B, S-17, S-24, S-28
Visual Field	S-1, S-5, S-16B, S-24, S-27, S-28
Gonioscopy	S-16B, S-17
Fundoscopy	S-16B, S-17, S-24, S-27, S-28
Slit Lamp Exam	S-16B, S-17, S-27, S-28
Tonometry	S-16B, S-28

In each of the eight supportive studies, evaluations were conducted at baseline and at specified intervals during treatment. Three of the eight studies reported no clinically significant ophthalmologic abnormalities or changes in patients treated with tizanidine (S-16B, S-24, S-

27).

In the supportive double-blind placebo-controlled trial (S-1), no new ophthalmologic abnormalities were observed nor were any changes in visual acuity apparent following tizanidine treatment. One patient in the tizanidine group and two in the placebo group exhibited a greater impairment in either the left or right visual field at the end of the 8-week study compared to baseline values. These changes were interpreted to be likely a consequence of the patient's underlying disease (multiple sclerosis). In the supportive, double-blind crossover study with baclofen (S-5), 14 tizanidine patients and 16 baclofen patients had a decrease in either the left or right visual field that was considered to be related to MS. One patient in this study exhibited transient abnormal left external ocular movements (EOM) while on tizanidine that were not present at the study's end; a second patient developed a new opacity while on baclofen.

A 26-year old male receiving one year of tizanidine 3 mg/day demonstrated the start of cataracts on slit lamp exam. He had also been treated for three years with the piperazine derivative, pipemidic acid for a chronic UTI.

Comment

The ophthalmology data was reviewed by an FDA ophthalmologist (Dr. Tony Carerras). He commented that the data was not well collected, that is, there was no control group, the examiners were not blinded, and that the individual subparts of the examination were not standardized. He comments

Although the original concern of corneal clouding/opacity was not reported in any of the clinical studies, it cannot be determined if the cornea was properly evaluated. There are too many inconsistencies in the reported data to assume that the examinations were properly performed. Even though detailed information on some ophthalmic parameters appears to have been collected in some of the studies, the data as reported did not allow for quantitative evaluation or sound scientific conclusions.

Note: It is prudent to include the following statement in the labeling:

There were findings in animal studies of corneal opacities. While there was no clear evidence that tizanidine induces ocular pathology, periodic assessment of ophthalmologic functions during prolonged therapy is advisable.

9.2 Tizanidine Induced Hallucinations

Hallucinations have been reported in 12 out of 332 (4%) patients treated with tizanidine in North American clinical trials (protocols -001, -002, -003, 004 and DS-2N{S-1}). There were no reports of hallucinations from the 201 control patients who were treated with placebo in the same protocols. Information on each of these 12 patients is summarized in Sponsor's Table 1 (attached).

Eight of the 12 patients who reported hallucinations were receiving concomitant medications, whose product labels list hallucinations as an adverse event (Patient # 43, 088, 105, 192, 199, 211, 230, and 387). The concomitant medications were considered by the investigator to be the specific cause of the hallucinations in three patients (Patient 192 on Prozac, Patient 211 on

Elavil, and Patient 230 on Sinequan).

Regarding duration of tizanidine treatment prior to the onset of hallucinations, 8 of the patients were treated between 12 and 36 days, and 4 were treated for 5 months or longer (Patients 042, 192, 230, and 387). These durations of tizanidine therapy do not include possible exposure to tizanidine during double-blind placebo controlled trials (Protocols -001 and -003) prior to entering the long term protocols -002 and -004. This is applicable only to patients 042 and 192, both already in the long term group.

Investigators assessed the report of hallucinations as "definitely" related to tizanidine treatment in 4 patients (43, 082, 119, and 179), "possibly related" in 4 patients (088, 105, 211 and 387) "not related" in 3 patients (192, 199 and 230), and of "unknown" relationship in patient 042.

Hallucinations led to patient withdrawal from the study in 4 patients (Patients #082, 088, 119 and 199). The remaining 8 patients continued in the study, 5 at the same dose (Patients 042, 43, 192, 211, and 230) and 3 at a reduced dose of tizanidine (Patients #105, 179, and 387). None of the reporting patients had a prior history of hallucinations. The sponsor states that all patients recovered without sequelae, although Patient 082 continued to have hallucinations for two weeks after tizanidine was stopped. Another patient #088 had a severe reaction with hallucinations, depersonalization, delusions and somatic pain beginning on Day 23 at 36 mg/day. The patient was hospitalized. On Day 25 at 10 mg/day the patient was prematurely discontinued from the study. The blind was broken six days after the study drug was stopped and the hallucinations were continuing. On Day 48 the patient had been discharged from the hospital and was not hallucinating. However, the patient was suffering from slight paranoid ideations and was under psychiatric care.

Analysis of the Four-Month Safety Update of ongoing extension trials 002 and 004 yield three additional cases (Patient #002, 022, 084) of hallucinations not captured in the NDA data discussed above. To review the experience in the two ongoing trials, five patients (5/117 or 4%) in Study 021-002 and three patients (3/62 or 5%) in Study 021-004 experienced hallucinations while receiving tizanidine (Sponsor's Table VII and VIII, attached). The hallucinations were mild or moderate in severity. In Study 002, three of the cases (002, 387, 192) were considered by the investigators to be possibly related to study drug, one was considered related (105) and the fifth was considered to be not related (230). Each of these five patients was also receiving a concomitant drug with hallucination in the product labeling. In Study 004, the three cases were considered possibly related (022, 082) or related (084) to tizanidine. All three patients had been in the placebo treatment group of Study 021-003. One of the three patients was receiving a concomitant drug with hallucination in the product labeling. However, within the two studies, there was only one dropout due to hallucination, patient 082 in Protocol 004.

In addition to the North American clinical trials experience, 3 tizanidine patients out of 396 participating in European active-controlled studies were reported to have hallucinations. One of these patients (S-23) was dropped early in the study, and the other (S-3) developed marked

hallucinations on day 10 while receiving 18 mg/d of tizanidine. The patient remained in the study although the hallucinations persisted. In the third patient, the investigator reported that hallucinations were a pre-existing condition. In the same clinical trials there were 3 reports of hallucinations in the baclofen control group out of 310 patients treated.

Postmarketing surveillance data compiled by Sandoz covering the time period of July 1 1984 to February 1993 yielded 16 reports of hallucinations but no details related to dosing or duration of treatment were provided. Estimates of exposure to tizanidine based on marketing data yield an extrapolation as high as 15 million patients treated since 1984, primarily in Japan and Germany.

Based on an outside consultants review, the sponsor concludes that tizanidine treatment may be associated with hallucinations in up to 1-4% of patients treated in clinical studies. The majority of the events occurred in the first 5 weeks of treatment and occurred in patients receiving concomitant therapy with other drugs in which hallucinations have been reported, most often anti-depressant drugs. Lowering the dose or withdrawing tizanidine or withdrawing the concomitant drug has resulted in complete recovery, and in some patients hallucinations ceased in the face of continued tizanidine dosing at the same dose. The sponsor states that no patient developed transient or permanent psychosis in association with hallucinations.

Comment

This reviewer generally agrees with the sponsor's consultant review of the hallucinations, except for the last statement that no patient developed psychosis in association with hallucinations. They are formed visual hallucinations without associated delusions with the exception of one case #088, who did appear to have developed a transient psychosis and was still under psychiatric treatment. Hallucinations occur commonly in patients receiving high doses (near 36 mg) tizanidine often with concomitant drugs also associated with hallucinations. Hallucinations were not observed in normal volunteers treated with lower doses in Phase I and pharmacokinetic/pharmacodynamic studies. Hallucinations occurred more frequently in spinal cord injury patients than in MS patients, and many of the patients tolerated them well in the face of continued or repeated tizanidine dose. A discussion of hallucinations should occur in the product labeling.

9.3 Hepatotoxicity

Due to a signal from the animal studies that the liver might be a target for toxicity, an outside consultant was engaged to assess liver function in tizanidine treated patients. The material reviewed include evaluations from the three placebo-controlled studies DS-0502, AN021-001 and AN021-003, one long term open label study AN021-002 and Sandoz clinical trials, post-marketing spontaneous reports and literature survey.

The clinically relevant values for SGOT/AST, SGPT/ALT, and alkaline phosphatase were defined as three times the upper normal range, or twice the baseline value if the baseline

value was higher than the upper normal range.

Primary Clinical Trials

Attached are scatter plots of SGPT, SGOT, alkaline phosphatase, and total bilirubin from baseline/endpoint data from the three primary controlled trials.

For the three primary trials, significant differences were observed between the tizanidine and PBO groups in the number of patients with treatment-emergent clinically relevant SGPT/ALT ($p=0.003$) and SGOT/AST levels ($p=0.028$). Eleven (4.8%) patients in the tizanidine group and one (0.4%) patient in the PBO group had treatment-emergent clinically relevant SGPT/ALT levels. Clinically relevant treatment-emergent SGOT/AST levels were only observed in tizanidine-treated patients (5, 2.4%). There was one report of a relevant alkaline phosphatase level in a tizanidine-treated patient and none in PBO-treated patients.

Table 34

**Patients With Treatment-Emergent Clinically Relevant Liver
Parameters by Treatment Group
Double-Blind Primary Studies**

Laboratory Parameter/Units	Placebo N (%) ^d	Tizanidine N (%) ^d	p-value ^c
Clinically Relevant Values:			
SGPT/ALT ^a (U/L)	1/231 (0.4)	11/227 (4.8)	0.003
SGOT/AST ^a (U/L)	0/214 (0.0)	5/208 (2.4)	0.028
Alkaline Phosphatase ^b (U/L)	0/248 (0.0)	1/249 (0.4)	n.s.

a 3x the upper normal range or 2x baseline if value is higher than upper normal range at baseline

b 2x upper normal range or 2x baseline if value is higher than upper normal range at baseline

c Two-tailed Fisher's exact test, no correction for multiple comparisons

d Percents are based on the number of patients with any post-baseline value for given parameter

In study DS-0502 there were 12 reports of elevated transaminase levels in the 94 tizanidine patients (13%) and 11 in the 93 placebo patients (12%). Of these, five tizanidine and 6 placebo patients had abnormal baseline values (mild, within three times upper normal range) and were excluded by the firm from further analysis. Six tizanidine patients and 3 placebo patients had elevated transaminase levels at only one time interval. However, that elevation could be significant; patient 301/9 had elevations from the final titration visit to the third plateau visit in SGOT (22 to 182), gamma GT (42 to 171), bilirubin (4 to 27) suggesting a cholestatic process. The only tizanidine treated patients with elevated transaminase levels at more than one time interval was patient 303/10 who lacked a baseline value. His SGPT diminished from 116 to 43 while receiving tizanidine treatment suggesting that his baseline was probably elevated.

In study AN021-001, 30/131 (23%) tizanidine patients and 13/125 (10%) placebo patients had elevated transaminase values at least once during the study. Six of the 30 patients (tizanidine) and 5/13 placebo patients had the finding at baseline and are not considered further. Of the

24 remaining tizanidine patients, 17 had single elevations all in the mild to moderate range (SGPT values 49 to 174). In ten of these patients it was only the final value that was elevated. The remaining single elevations occurred in mid-study and were followed by normal values. In the placebo group 5 of the 8 patients had a single elevated transaminase value only at the final test and one had a mid-study elevation followed by normal values. Seven tizanidine patients had elevated transaminase levels at two or more times and in the final test. One tizanidine patient (#163/14) developed significant but transient liver disease attributed by the investigator to tizanidine. By Day 63 at 12 mg/day, the patient had hepatic enlargement, jaundice, and elevated liver enzymes (alkaline phosphatase 237, SGOT/AST 716, SGPT/ALT 1392) associated with abdominal pain and a 5 lb weight loss. She was discontinued on Day 69. She eventually recovered (liver enzyme values returned to within normal limits) on Day 106 following tizanidine withdrawal. This case of cholestasis is almost certainly caused by tizanidine.

In Study AN021-003, 18/59 (31%) tizanidine patients and 5/59 (8%) placebo patients had elevated transaminase values sometime during the trial. 8/18 (44%) with elevations had abnormalities present at baseline and are not considered further by the firm. Of the ten tizanidine patients with normal baseline and developed elevated transaminase levels during treatment, none resulted in significant liver disease and in two cases were the elevations considered by the investigator to be due to tizanidine.

Patient 036/2 had normal baseline and titration period values and then developed an SGOT/AST of 122 and an SGPT/ALT of 399 on Day 43 at 10 mg/day during the plateau. The patient was asymptomatic. Tizanidine was stopped and the final values were SGOT 49 and SGPT 184 indicating early recovery. Patient 097/5 had normal values until the tizanidine taper, Day 57, when the SGOT was 368 and the SGPT 819 and were associated with elevated alkaline phosphatase and LDH. Study drug was stopped and the abnormal values resolved by Day 71 with SGOT/AST at 15 and SGPT/ALT at 32. The patient then began open-label treatment with tizanidine without additional transaminase elevations. [The sponsor suggests that the event was due to lab error.] Six tizanidine patients had elevated transaminase values at the final time period. There were two comparable placebo patients.

In study AN021-002 an open-label extension from Study 001, 23/161 (14%) patients were reported to have elevated transaminase values, one or more times. A number of patients who entered the study with mild to moderate baseline abnormalities had these values decrease or return to normal while continuing tizanidine treatment.

In studies AN021-001 and AN021-003 there were more abnormalities in liver function test results reported in the tizanidine treated patients than in the placebo control groups. However, in study DS-0502 there was no significant difference between tizanidine and PBO patients. In the open-label study AN021-002 a number of patients demonstrated returns to normal in liver function tests while continuing to receive tizanidine treatment. In all of these studies every patient was receiving multiple concomitant medications, which may confound causality assessment. Sponsor's Table XII and XIII (attached) display follow-up data for those cases

with significant transaminase elevations in Studies 001, 002, and 003. While most of the elevations are mild to moderate, there is a patient B163 with SGOT 716 and SGPT 1392. The patient withdrew from therapy.

Supportive Clinical Trials

Table XI (attached) displays clinically significant elevations of transaminases occurring in the Four Month Safety Update. Of the three patients, one patient (102) in follow-on Study 004 had extremely high values (SGOT 744, SGPT 1152) which returned to nearly normal values with tizanidine reduction.

Data was also obtained from a review of the Sandoz clinical trials and post-marketing experience. In 44 studies involving 765 patients treated with tizanidine, 14(2%) were reported to have a clinically significant increase in SGOT/AST, SGPT/ALT or GGT, defined as a 3-fold or greater increase from baseline or a 2-fold or greater increase above the upper limit of normal range. In 7 of the above patients the abnormality resolved with either continuing tizanidine treatment or discontinuation. Three additional patients were reported to be taking concomitant medications that may have been contributory. Information on these ten cases is provided in Sponsor's Table 48 (attached); dose of tizanidine at the time of elevation is not available.

From spontaneously reported post-marketing adverse events there were 5 reports of hepatic dysfunction, 3 reports of hepatitis, 3 reports of jaundice and 12 reports of increased liver enzymes. One death of a 68 y o male treated with tizanidine 4 mg/day plus CBZ for 2 months was associated with cholestatic jaundice; meds were discontinued but death occurred 20 days later of bronchopneumonia. The exposure data is estimated to be as high as 6-15 million, primarily in Japan and Germany. A cumulative frequency of adverse events reported in 130 clinical publications, including 6895 patients provides the following: hepatic enzymes increased 18(0.26%), hepatic function abnormal 2 (0.03%).

The sponsor engaged an outside consultant to assess liver function in tizanidine patients. He made the following conclusions:

The transaminase elevations in tizanidine-treated patients from studies 021-001 and 021-003 tended to be mild and transient in nature. Only one of these patients is known to have developed a clinically significant "hepatitis-like" illness, and she recovered. The Sandoz clinical trials results indicate that about 2% of patients treated with tizanidine developed abnormal transaminase levels and that those returned to normal in most cases. Spontaneous post-marketing reports include very infrequent hepatic citations as did the reports from the medical literature. The conclusion is that tizanidine treatment appears to be associated with a mild, reversible increase in transaminase test results in about 2% of patients. Progression to more serious liver disease is highly unlikely.

This same material was also reviewed by an FDA gastrointestinal consultant. He concludes that Tizanidine is associated with heterogenous liver disease, both hepatocellular and cholestatic types. There are many examples of positive dechallenge, that is, elevated transaminases decline upon Tizanidine withdrawal. He also noted a disparate frequency of

transaminase elevations in the pivotal efficacy trials as opposed to the supportive active control studies where elevations were far less frequent. This finding may be attributed to lower doses, duration of treatment, and smaller sample sizes. He made several recommendations including tests of global liver function (serum bile acids, BSP-like evaluations), liver biopsy, evaluations of bilirubin, SGOT, SGPT, Alkaline Phos, gamma-GT, and LDH

Comment

Tizanidine is associated with liver disease, both hepatocellular and cholestatic, although most cases appear to be reversible. Despite several cases of extreme elevations in transaminases, acute liver failure and death did not occur. Tizanidine increases liver parameters (SGPT/ALT and SGOT/AST) as approximately 10% of patients had shifts from within normal range at baseline to above normal range at the end of therapy, prior to taper, in these two parameters compared with 5% of placebo patients. Similar results were seen in LFTs when analyzed by mean change or clinically relevant criteria (defined as 3 times the upper limit of normal or 2 times baseline if baseline is higher than the upper normal range). In the tizanidine group mean changes of >15% from baseline to the last available measurement before taper were seen in a subset of patients for SGPT and SGOT. In the tizanidine group, an increase of 12.7 U/L (N=202) from a baseline mean value of 21.8 U/L was observed for SGPT (normal range 6-43 U/L) and an increase of 6.1 U/L (N=187) from a baseline mean value of 20 U/L was observed for SGOT (normal range 11-36 U/L). Similar changes from baseline were not seen in the placebo group. For the majority of patients with clinically relevant increases in SGPT or SGOT at any post-baseline visit, the values returned to normal by the end of the study, either during treatment or after drug discontinuation. Two patients discontinued due to abnormal LFTs and one patient discontinued due to bilirubinemia.

This reviewer agrees generally with the above conclusions by the sponsor's consultant. However, the frequency of elevated transaminases is probably underestimated by the 2% figure (more like 4 to 5%), and the progression to serious liver disease is unlikely rather than "highly" unlikely.

Note: It is recommended that the following statement should appear in the labeling: Tizanidine treatment is associated with a mild to moderate reversible increase in transaminase values in about 4-5% of patients. Progression to more serious liver disease (hepatitis, cholestatic jaundice) occurs occasionally. Periodic assessment of hepatic functions during prolonged therapy is advisable.

9.4 Cardiovascular: Orthostatic Hypotension and Bradycardia Primary Clinical Trials

The differences between the standing and the supine (sitting or lying) systolic and diastolic blood pressure were analyzed. Orthostatic hypotension was defined as any decrease in blood pressure from supine (systolic or diastolic) to standing of 20 mmHg or more. If the baseline systolic blood pressure was 80 mmHg or less a decrease of 10 mmHg was considered

orthostatic hypotension. Patients from Study 021-003 (spinal cord injury) were excluded from this analysis because no standing blood pressure was obtained for these patients.

Consistent with its alpha-2 adrenergic agonist properties, tizanidine treatment has been typically associated with a modest reduction in blood pressure and a slight bradycardia.

In the single dose clinical pharmacology crossover trial S-87 (N=16), systolic and diastolic blood pressure and heart rate were measured immediately prior to and at 1, 2, 3, 4, 6 and 8 hours after administration of 2, 4, or 8 mg tizanidine or placebo. Mean systolic and diastolic blood pressure were significantly lower 1 and 2 hours after treatment with 4 and 8 mg tizanidine relative to mean values in the placebo group (Table 47 attached). Mean blood pressure values in the 8 mg group were also significantly lower than those in the placebo group at the 4-hour measurement. In addition, mean systolic blood pressure was significantly lower in the 2 mg tizanidine group compared to the placebo group 2 hours after dosing. The maximum mean percent reductions in systolic BP compared to mean baseline values following placebo or the 2, 4 and 8 mg tizanidine doses were 4.4%, 4.6%, 8.9% and 15.8%, respectively. The respective maximum mean percent reductions in diastolic BP in these groups were 2.7%, 2.9%, 10.2% and 15.3%. No significant changes in heart rate with tizanidine were observed.

In clinical efficacy and safety trials with tizanidine in patients with spasticity, mean changes in systolic and diastolic blood pressure and heart rate relative to baseline values were not clinically significant. When changes in blood pressure or heart rate occurred, they were generally between 5 and 10 mmHg and 5 and 10 bpm, respectively. For the three double-blind primary trials, no clinically meaningful mean differences between standing and supine systolic or diastolic blood pressures were observed at baseline, the last visit before taper or the final visit in either treatment group. Tizanidine had no apparent effect on mean orthostatic blood pressure.

Table 38
Incidence Rates of Orthostatic Hypotension by Treatment Group
Double-Blind Primary Studies

Number (%) of Pts. With Orthostatic Hypotension ^a :	Placebo N (%)	Tizanidine N (%)
Any Post-Baseline Visit Before Taper ^b	37/183 (20)	37/176 (21)
End of Plateau ^c	10/183 (5)	13/176 (7)
Final Visit (After Taper) ^d	7/142 (5)	4/139 (3)

a Decreases of ≥ 20 mmHg from supine (lying/sitting) to standing systolic blood pressure, if the baseline for supine systolic blood pressure is > 80 mmHg. Otherwise, the relevant decrease is 10 mmHg

b Percents are based on the number of patients with baseline data and any post-baseline data

c Percents are based on the number of patients with baseline data and data at the end of plateau

d Percents are based on the number of patients with baseline data and data at final visit

For the double-blind primary studies, no notable differences were found between the treatment

groups when the incidence rates of orthostatic hypotension at various time points throughout the study were analyzed.

Supportive Clinical Trials

However, a few individual patients or healthy volunteers, when treated with a single dose of tizanidine have shown clinically meaningful blood pressure decreases and symptoms of hypotension.

There were a few reports of cardiovascular adverse events in the supportive active-controlled trials. Orthostatic hypotension was reported in six tizanidine and two baclofen patients; hypotension was reported in two additional tizanidine patients and three diazepam patients. Three tizanidine and five baclofen patients reported palpitations. Bradycardia was reported in three tizanidine patients; one tizanidine patient had increased PR interval and one had syncope.

Three patients discontinued tizanidine therapy because of hypotension or orthostatic hypotension. The respective doses of tizanidine at the onset of this event in these three patients were 8, 10, and 16 mg/day. Orthostatic hypotension was noted in four patients treated with tizanidine in study S-3 but did not lead to study withdrawal. The daily dose of tizanidine ranged from 6 to 32 mg in these patients. In all of these patients, the onset of orthostatic hypotension was within the first 2 weeks of tizanidine initiation.

In the 6-day study (S-60), one patient out of twelve had a transient drop in blood pressure (90/70 mm Hg) 45 minutes after ingestion of tizanidine 6 mg. This patient was hypertensive and was receiving alpha-methyl dopa; blood pressure returned to normal within 1.5 hours.

In Study S-88 involving 18 healthy volunteers, one subject reportedly collapsed one hour after a single dose of tizanidine 4 mg. The subject's systolic and diastolic blood pressures were reduced by 45 and 20 mmHg, respectively; pulse was lowered by 24 bpm. All measures returned to baseline within 12 hours post-dose. No change in mean blood pressure or pulse rate was observed following 4-6 weeks of tizanidine treatment in the clinical pharmacology trial S-63.

A total of eight patients experienced hypotension during treatment with the modified release formulation in six trials. In all but one of these patients, the hypotension was reported as transient. One patient in study S-48 had a sustained reduction in diastolic blood pressure throughout the 6-week trial (baseline value of 108 mmHg; on trial values ranging from 75 to 80 mmHg). Systolic blood pressure remained fairly constant during the study period (140 mmHg). Four of the indicated episodes of hypotension were recorded as adverse events, but no patient discontinued treatment with the modified release formulation of tizanidine for hypotension or other cardiovascular abnormalities.

Tizanidine treatment was discontinued on the fourth study day at 18 mg in one patient

(#1129) in an acute musculoskeletal spasm trial (S-90) because of hypotension; systolic and diastolic blood pressure in this patient was 120/74 mmHg at baseline and dropped to 90/62 mmHg on Day 4. The patient also experienced drowsiness and lethargy on this day.

Healthy volunteers seem to be especially sensitive to hypotensive effects of tizanidine. In study S-54 involving 20 healthy volunteers, four were withdrawn due to hypotension after a single dose of tizanidine, as detailed in the following table:

SUBJECT	DOSE (mg)	BP DROP systolic/diastolic	HOURS post dose	SYMPTOMS
A	6	32/30	2	none noted
B	10	10/15	4	weakness, drowsiness, dizziness
C	14	30/55	1	fainting, bradycardia, depression
D	14	15/05	2	weakness, drowsiness, bradycardia

Patient 5538, a 63 year old white female with multiple sclerosis and hypertension, was enrolled into Study 005. Concomitant meds were Vasotec 10 mg qid, Oxybutynin 10 mg bid, and Naprosyn 500 mg bid. Predosing supine blood pressure was 102/70 and pulse was 72; sitting blood pressure was 92/70 and pulse 72. One hour after administration of tizanidine 16 mg, as she was helped from the examination table, she became dizzy and went limp without loss of consciousness. Blood pressure was 60/0 and pulse was weak. IV fluids, oxygen, and epinephrine 2 mg IV were administered. Blood pressure responded and rose from 68/42 to 138/112. She was hospitalized in the ICU for supportive care and discharged the next day.

Electrocardiograms (ECG) were recorded at baseline and at the end of study treatment in 21 of the 23 supportive controlled trials (not performed in studies S-7 and S-23). New ECG abnormalities were reported for 4 of the 414 patients treated with tizanidine in these studies. One patient in study S-3 had a minor prolongation of the PR interval (0.02 msec) on study day 13 (12mg/day) that was accompanied by bradycardia, orthostatic hypotension and syncope. This patient discontinued the trial prematurely for these events. Two other patients had unspecified T-wave changes (S-5, S-10) and a fourth patient with a normal baseline ECG had an unspecified, borderline ECG abnormality following tizanidine treatment (S-10).

Comment

Labeling should include a discussion of the occurrence of orthostatic hypotension and bradycardia, in addition to interactions with other antihypertension drugs. The ECG findings should be listed in the table of adverse events. The following statement should appear in labeling: Concomitant use of Zanaflex with antihypertensives, including diuretics, may occasionally cause hypotension and bradycardia.

Comment

This appears to be an idiosyncratic case of hypersensitivity reaction. This needs to appear in the labelling.

10.0 Pregnancy

The Sandoz Drug Monitoring Center has received two reports of women taking tizanidine during some stage of their pregnancy.

DW/89/00235/SUD: A 34 yo female was treated for 4 days with tizanidine at a daily dose of 4 mg for cervical syndrome around the sixth week of gestation; a healthy term infant was born.

DW/92/00592/SUD: A 16 year old female made a suicide attempt in the fifth month of gestation. She ingested approximately 40 tizanidine tablets (2 or 4 mg). The intoxication was successfully treated with forced diuresis, activated charcoal and sodium sulphate. No information on the outcome of the pregnancy was available.

Another gravid female exposed to tizanidine in Study AN021-001 chose an elective abortion.

11.0 Overdose

Only two significant overdosage have been reported.

Attempted suicide by a 46 year-old male with multiple sclerosis resulted in coma soon after the ingestion of 100 tablets of 4 mg tizanidine. There was no nystagmus or pupillary dilation. The patient had marked respiratory depression with Cheyne-Stokes respiration. Gastric lavage and forced diuresis with furosemide and mannitol were instituted. The patient recovered several hours later without sequelae. Laboratory tests were normal.

Patient C213, a 41 year old white male with multiple sclerosis and depression completed Study 001 and continued in the open-label follow-on Study 002 as of 5-5-93. On 9-9-94 the patient took an overdose of 20 tablets of tizanidine 4 mg. Upon admission to a psychiatric hospital, the patient was drowsy but not unconscious. He underwent gastric lavage and IV fluids were started. The patient was in stable condition on 9-14-94 and discharged. The patient was to be restarted on tizanidine as of 9-23-94.

Patient 006/2 (Study -003) apparently received an accidental overdose of tizanidine (patient took five tablets AM and PM dose too close together on Day 23) and developed an increase in total bilirubin to 2.3 mg/ul (baseline bilirubin 0.8 mg/dL). The patient was discontinued on Day 23 at 24 mg/day. Other liver function tests including transaminases remained in the normal range. The bilirubin returned to normal in a week after tizanidine was stopped.

There are three spontaneous reports of tizanidine overdoses from post-marketing surveillance.

9.5 Seizures

Two epileptic patients receiving open-label tizanidine in a long-term trial (S-28) experienced an increase in seizures, one at month 2 and one at month 11. Both patients were receiving concomitant therapy with phenytoin and blood samples revealed that plasma phenytoin levels were below therapeutic concentrations. The dose of phenytoin was increased in one patient and the patient's disease state stabilized without further incident. Tizanidine was discontinued in the second patient since the study was nearly completed (patient received 11 of specified 12 months of treatment).

One patient participating in an 8-week, double-blind comparative trial (S-99) experienced a seizure after receiving treatment with tizanidine for one week. The dose was decreased from 20 mg/day to 4 mg/day; the patient again experienced a seizure during week 4 of treatment and was discontinued from the study. The patient had a history of epilepsy but was not receiving any antiepileptic medication during the study.

A 36 yo female S/P MVA 12-9-88 with a history of mild head trauma, C5-6 quadriplegia and "dysreflexic headaches entered AN021-003 on 6-4-93 and continued in the open-label study AN021-004 on 7-29-93. On 3-10-94 the patient experienced a pronounced dysreflexic headache with nausea and vomiting. Patient was taken to the ER and had a generalized motor seizure. She was treated with a loading dose of Dilantin. On 3-21-94 the patient was seen for an unscheduled study visit at which time she revealed she had independently increased her dose of tizanidine from 35 to 48 mg/day for the past month in hopes of increasing its therapeutic effect. She was instructed to decrease the dose to the prescribed 36 mg/day.

In an open-label study specifically designed to explore possible effects on seizure rate in patients with epilepsy (S-65), it was concluded that tizanidine had no clinically significant effect on this disorder.

Comment

Labeling should include convulsions in the listing of adverse events.

9.6 Miscellaneous

A case of severe serum sickness occurred in patient #A085, Center 8.

This was a 28yo WM with a 3 y Hx of MS of moderate severity marked by periods of remission and exacerbation... On Day 61, at 24 mg/day, the patient experienced severe arthrosis (polyarticular joint effusions) and severe rash. On Day 63, at 24 mg/day, the symptoms worsened and the patient was consequently hospitalized. On admission, the patient presented with a severe erythematous rash over his face, chest and back and a temperature of 100.7. At this time, the patient was discontinued from the study and received anti-inflammatory medication for joint pain and the left knee was tapped for excessive fluid. In addition, laboratory tests revealed severely elevated OT(716 U/L) and PT (1392 U/L) values. The consulting rheumatologist considered the event to be severe serum sickness related to the study drug. By day 65, at 24 mg/day, the joint effusion, rash and fever had resolved and the elevated transaminase values had returned to near normal levels (SGOT:43 U/L; SGPT:92 U/L). F/U examination on Day 77 at 24 mg/day revealed no abnormalities.

Two reports were received between 1-1-91 and 4-92. The first overdose of 80 mg of tizanidine occurred in a female patient of unknown age who recovered. The second overdose of 2 mg of tizanidine occurred in a 2 year old female who recovered. The third overdose was reported between 4-1-92 and 2-28-93 but no further information is available.

Note: The following should appear in the labeling:

Should overdose occur, the following treatment is suggested:

Monitoring of the cardiovascular and respiratory systems. Elimination of unabsorbed drug by emesis or gastric lavage. Symptomatic treatment, as necessary.

12.0 Laboratory Values

12.1 Treatment-Emergent Clinically Relevant Liver Parameters

With the exception of the values for SGPT/ALT and SGOT/AST, no meaningful changes from baseline in hematology or clinical chemistry parameters were observed in the tizanidine group. See section 9.3 for discussion of elevated transaminase levels.

12.2 Hematology

The firm was asked to review the database for any hematologic disorders.

SPONTANEOUS REPORTS OF HEMIC ADVERSE EVENTS Postmarketing Experience (7/84-12/93)

Parameter	Patient	Outcome
Thrombocytopenia	86/0098/GB	Recovered
Thrombocytopenia/Petechia	86/1558/NL	Improved
Leukopenia	91/00050/YU	Recovered
Anemia/Leukopenia	87/2335/SF	Improved
Granulocytopenia	92/00136/J	Recovered

Table 1 (above) summarizes hemic events from postmarketing surveillance. Five reports of hematologic events from an estimated 15 million patients treated were received. Individual patient summaries were reviewed; most of the cases can be dismissed. Case #1: the patient recovered from the mild thrombocytopenia (236,000 to 134,000) despite continued therapy with tizanidine. In the second case, the value for thrombocytopenia was not provided; non drug related etiology (allergic vasculitis) is most likely. In the third case, hypotension and leukopenia were reported in a 75 yo male treated with tizanidine 20 mg/day. He recovered

from both. Detailed information is lacking. In case 4, a 31 yo female with polyarthritis received tizanidine 4 mg tid for a year. The anemia (72 g/L) responded to iron therapy and the leukocyte count (2,900/mm) returned to normal (4,800) after discontinuation of tizanidine. However, the granulocyte count (34%-44% remained below the normal range (50-80%) and also a slight lymphocytosis persisted after the discontinuation of tizanidine. In the fifth case, an 86 yo female received tizanidine 3 mg/day for lumbar pain plus amantadine, levodopa and ticlopidine. Granulocytopenia (value unstated) resolved with discontinuation of tizanidine. Granulocytopenia is a well-documented side effect of ticlopidine.

For the primary efficacy studies (DS0502, AN021-001, AN021-003) a table of changes from normal to low in hemic parameters (lymphocytes, monocytes, neutrophils, platelets, WBC) is presented; however, laboratory values are not given. There was no difference in percent change from normal to low between tizanidine and placebo (lymphocytes 5.5%, monocytes 2.2%, neutrophils 1.4%, platelets 0.9%, WBC 2.0%).

Tables 3A-C contain summaries of hemic events from Athena long-term studies AN021-002 and AN021-004. A total of four patients experienced an adverse event (two in each study), three of which had received placebo in their earlier double-blind study. The one patient who had received tizanidine was reported to have an adverse event of leukopenia with a WBC of 2.9×10^3 . However, the patient entered study -001 with a WBC of 2.9×10^3 and had a count of 2.5×10^3 at the end of the study.

Tables 4A-D summarize hematology reports of interest by clinical trial category (Only patients with values in the normal range at baseline are included). In the short-term studies, three tizanidine patients were found to have decreases of 12-33% in their WBC; however, none fell below 3.3×10^3 . No neutropenias were described. There were sporadic cases of decreased platelets (150,000 to 124,000), decreased RBC and hemoglobin, decreased WBC, but none were systematic.

The following table summarizes the significant findings seen in the Sandoz long-term studies:

Parameter	Study	Patient	Decrease	
			from	to
WBC	S-17	8	1.5×10^3	0.5×10^3
WBC	S-17	25	5.6×10^3	2.4×10^3
WBC	S-24	5	4.1×10^3	3.3×10^3
WBC	S-27	4	6.7×10^3	3.7×10^3
WBC	S-28	13	4.4×10^3	1.6×10^3

Tizanidine had no clinically meaningful effect on any hematology parameter (hemoglobin, hematocrit, WBC with differential) when analyzed by mean change or shift analyses.

Comment:

Based on the available information, for a sample size of roughly 2327 and postmarketing experience in 15 million, tizanidine does not appear to cause significant bone marrow suppression.

13.0 Physiological Parameters-Vital Signs

There were no clinically meaningful differences in change from baseline in pulse between the tizanidine and PBO groups. For systolic or diastolic blood pressure changes, please refer to section 9.4.

13.2 Withdrawal Phenomenon

A clinically relevant change was defined as a > 20% change in supine diastolic or systolic blood pressure between the last measurement on study drug and the final visit after taper.

Table 39
Incidence of Clinically Relevant Changes in Blood Pressure After Withdrawal
of Treatment
Double-Blind Primary Studies

	Placebo N (%)	Tizanidine N (%)
Decreases in Supine ^a Systolic or Diastolic Blood Pressure of 20% or More	14/203 (7%)	14/188 (7%)
Increases in Supine ^a Systolic or Diastolic Blood Pressure of 20% or More	28/203 (14%)	28/188 (15%)

^a Supine: may be sitting or lying

Note: Percentages are based on the number of patients with measurements both on drug and after drug withdrawal

There were 14(7%) patients in the tizanidine group and 14 (7%) patients in the PBO group who met the criteria for clinically relevant decreases in supine systolic or diastolic blood pressure between the last measurement on study medication and the final visit after taper. There were 28(15%) patients in the tizanidine group and 28 (14%) patients in the PBO group who met the criteria for clinically relevant increases in supine systolic or diastolic blood pressure between the last measurement on study medication and the final visit after taper.

There were 25(13%) patients in the tizanidine group and 19(9%) patients in the PBO group

who met the criteria for clinically relevant increases in blood pressure from baseline to the final visit after taper. The data indicates that the proportion of tizanidine patients and the proportion of PBO patients that experienced changes in blood pressure levels between the last measurement on study drug and the final visit or between baseline and the final visit were similar, suggesting that rebound hypertension is unlikely to occur following withdrawal from tizanidine treatment.

14.0 Safety in Non-MS Patients

14.1 Trials in Healthy Subjects

Sandoz sponsored a total of 32 studies of tizanidine in healthy subjects; nine of which were conducted in the U.S. 190 males were treated with tizanidine in these nine U.S. trials. Nineteen of these studies were pharmacokinetic studies. The most common adverse events were drowsiness, fatigue, dry mouth and dizziness.

Hypotension was reported as an adverse event in six tizanidine-treated subjects from the non-U.S. trials; three of these discontinued prematurely due to this event. Two other subjects were discontinued prematurely due to bradycardia; both of these subjects also experienced clinically significant reductions in blood pressure. All of these subjects recovered without treatment.

ECG abnormalities were reported for two subjects treated with tizanidine in non-U.S. trials. Sinus arrhythmia was noted in one subject after ingestion of the first 12 mg dose of the modified release formulation as well as after subsequent doses; the subject discontinued treatment after 2 days due to tiredness. An increased PQ interval was reported in a 25 year male 2 hours after ingestion of 12 mg modified release tizanidine.

14.2 Acute Musculoskeletal Spasms

Sandoz Pharma, Ltd. sponsored 23 double-blind, comparative trials of tizanidine in patients with acute musculoskeletal spasms; 19 were conducted outside the U.S. and four were conducted in the U.S. 405 out of 929 patients participating in the four U.S. trials were treated with tizanidine. Treatment in all but two of the studies was administered for 7 days (the remaining trials were of 10 and 14 days duration) compared to the average duration of 6 to 8 weeks for the studies in chronic spasticity. The daily dose of tizanidine administered in the acute spasm trials generally ranged from 6 to 12 mg, compared to the mean maintenance dose of 18 mg/day in the chronic spasticity study.

Drowsiness (37%) and dry mouth (27%) were the most commonly reported adverse events among tizanidine treated patients. The most common adverse event resulting in premature discontinuation among the tizanidine-treated patients was drowsiness, similar to that outcome observed in the trials in chronic spasticity.

14.3 Trials in Japanese Subjects

Sandoz Pharma, Ltd. conducted 55 clinical studies in Japan using a 1-mg tablet of tizanidine. Fifty of these studies assessed the efficacy and safety of the drug: 34 conducted in patients with "spastic paralysis" and 16 in patients with painful myotonic diseases. A total of 786 patients with spastic paralysis were treated with tizanidine. The dosage ranged from 1 mg once daily to 3 mg tid in 20 of the 22 studies where the information was provided. The maintenance dosage was 2 to 3 mg tid for 4 to 76 weeks. Adverse events were reported in 228 of the 786 patients (29%); dry mouth and drowsiness were the most common side effects. Abnormal laboratory values were reported for 15 patients (2%); 14/15 of these abnormal findings consisted of increases in SGOT/AST, SGPT/ALT and/or LDH. In general, patients with an abnormal increase in these laboratory values were reported to be asymptomatic and normalized in all cases, some following treatment discontinuation.

790 patients were treated with tizanidine in 16 Japanese trials in painful myotonic diseases. The dosage of tizanidine was generally 1 mg and study treatment was administered for 2 to 21 weeks. Adverse events were reported in 50 of the 628 patients (8%) for whom information was available. Dry mouth and drowsiness were the most common adverse events; abnormal laboratory values were reported for four patients and consisted of increased hepatic enzymes.

15.0 Adverse Events during Postmarketing Surveillance

Spontaneous reports of adverse events occurring with tizanidine have been collected worldwide and analyzed by Sandoz Pharma, Ltd. since the product's initial introduction to the market in July, 1984. Sponsor's Table 70 summarizes the number of spontaneous reports of adverse events received by Sandoz during the various reporting intervals (most recent 4/1/92 to 2/28/93). Sandoz estimates that approximately 15 million patients have been treated with tizanidine from July, 1984 through February, 1993.

Generally, the adverse event profile reported among patients receiving marketed tizanidine was similar to that observed during clinical testing. Those frequent events seen during clinical trials with tizanidine—somnolence, fatigue, sleep disturbance, dizziness, gastrointestinal symptoms and hypotension—were also spontaneously reported. Ophthalmologic events reported by some postmarketed users included abnormal accommodation leading to blurred vision, ptosis and glaucoma. Increases in hepatic enzymes, including occasional reports of hepatitis and icterus were reported. Edema, including facial edema, was reported in several patients during postmarketing use.

There were six spontaneous reports of death. These were presented and discussed under section 8.1 Deaths.

Two spontaneous reports of hospitalization were received: one in a patient having delusion,

cardiac arrest, esophageal ulceration and the other in a patient who abused tizanidine 80mg along with alcohol. This latter patient developed bradycardia, syncope, hypotension and rebound phenomenon.

There were two spontaneous reports of intentional overdose with tizanidine in addition to the one described above. All three patients recovered.

16.0 Four Month Safety Update (April 4, 1994)

Two clinical studies are ongoing: Study 021-002 and Study 021-004 which are open-label extensions of Studies 021-001 and 021-003, respectively. This update includes data from August 16, 1993 to December 31, 1993 for Study 021-002 and from May 13, 1993 to December 31, 1993 for Study 021-004

16.1 Study 021-002

Patients entered to date: 166; Patients included in this report: 117

Of the ongoing 117 patients, 44% (51 patients) were exposed to tizanidine for greater than 12 months; 9 were exposed for 18 months; 3 were exposed less than 1 month to date. The most frequently reported treatment-related adverse events were somnolence (20, 17%), asthenia (16, 14%) and dry mouth (14, 12%). Five patients experienced hallucinations. Seven patients were discontinued due to adverse events. Eleven patients experienced a clinically significant change (>20% decrease from baseline) in supine diastolic and/or systolic blood pressure at any visit while on tizanidine. One patient experienced a significant increase in SGPT to 63 U/L on day 28 of study.

16.2 Study 021-004

Patients entered to date: 62; Patients included in this report: 58.

The majority of patients (33) received tizanidine for 4-5 months. One was treated for eight months. The most frequently reported events were somnolence (25, 40%), dry mouth (18, 29%), and asthenia (13, 21%). Three patients (all placebo patients in Study 021-003) experienced hallucinations. Twenty-eight patients had a clinically significant (>20% decrease from baseline) change in supine diastolic and/or supine systolic blood pressure at any visit while on tizanidine. Two patients had clinically significant changes in SGPT and SGOT; one withdrew and the other continued with return to baseline value.

All adverse events were tabulated by body system. Serious adverse events reported as 10-Day Reports included 8 (3 hallucinations) for 021-002 and 9 (1 bradycardia/syncope, 1 hallucination) for 021-004.

Table XII presents Follow-Up for clinically significant transaminases occurring in 021-001, 021-002, and 021-003.

To conclude, no new significant safety issues were revealed in this experience.

17.0 Summary and Conclusions

The safety of tizanidine was evaluated using all reported adverse events occurring in primary trials sponsored by Athena Neurosciences and Sandoz, placebo- and active-controlled studies sponsored by Sandoz, long-term controlled and open-label studies conducted by both sponsors, studies of other indications sponsored by Sandoz and the Sandoz world wide postmarketing event reporting system. The primary focus were the three well-controlled studies DSO502, 021-001 and 021-003. The secondary focus was on controlled studies conducted by Sandoz in Canada and Europe.

Data from each of these sources indicate that tizanidine is generally well-tolerated at oral doses up to 36mg/day. The most frequently reported adverse events in the three primary double-blind, placebo-controlled trials were dry mouth, somnolence and asthenia. These events generally were first noted during titration or upon reaching the maximum tolerated dosage with no clear dose-response relationship. While many patients achieved tolerance to these adverse events, they persisted throughout exposure in a subset of patients treated. Fourteen percent of all treated patients in the double-blind primary trials terminated tizanidine therapy due to adverse events.

Serious adverse events (hallucinations, elevated liver transaminases) were experienced by 5% to 10% respectively of tizanidine treated patients v. 0-2% of patients treated with placebo in the primary trials. Increases in liver function tests were generally mild to moderate, asymptomatic, and reversed either spontaneously or on reduction of dosage or withdrawal of tizanidine. In the primary studies 2.4% patients developed clinically significant increases in SGPT/ALT or SGOT/AST. There was one case of full-blown hepatitis. There were no cases of liver failure resulting in death. There were no other clinically relevant changes in laboratory values.

Tizanidine was associated with a 2-4% incidence of hallucinations in the primary efficacy studies. Hallucinations tended to occur early in therapy in patients with longer durations of disability and in patients taking concomitant medications also reported to cause hallucinations. The hallucinations were not associated with psychoses and resolved upon withdrawal or reduction in dosage of tizanidine or withdrawal of the concomitant medication. There was one case where hallucinations persisted after tizanidine withdrawal and were accompanied with delusions.

Animal studies signaled a possibility for untoward ophthalmologic events. However, ophthalmologic evaluations of patients in the primary trials were not conducted adequately to provide information regarding evidence of tizanidine-related ophthalmologic changes.

Extensive review of vital sign data collected during the well-controlled trials indicated that tizanidine did not produce a consistent lowering of blood pressure or increase the incidence of orthostatic hypotension relative to placebo. However, clinically relevant reductions in supine systolic (3%) or diastolic (35%) blood pressure was more frequent in the tizanidine

group than in the placebo group (24% and 13%, respectively).

There were three tizanidine-treated deaths in the clinical trial database, two in an extension trial and one in a long term trial. One was attributable to long-standing cardiac failure. The other two deaths are not well documented, one after 46 weeks of treatment and one in a compassionate use trial. Six deaths were reported from spontaneous surveillance.

Considering the number of patients estimated to have been exposed to the drug it can be concluded that, when administered within the recommended dose range and for the approved indications, tizanidine is generally well-tolerated, although the hepatotoxicity is worrisome and needs close monitoring..

To summarize, adverse events seen with tizanidine are frequent but generally mild. Most of the side effects reported can be related to the pharmacological actions of the drug and are non-serious, dose-dependent and reversible. Serious adverse events hallucinations and transaminase elevations occur at a rate of 2-5% and 10% respectively. Most cases abate with withdrawal of tizanidine. The risk/benefit ratio favors tizanidine for the patient with significant spinal spasticity.


Janeth Rouzer-Kammeyer, M.D.

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REVIEW AND EVALUATION OF CLINICAL DATA

ORIGINAL NDA 20-397 December 3, 1993 Vol 1.1-1.214

DRUG: Zanaflex® (tizanidine HCl)
4 mg Tablets

INDICATION: Spasticity of Spinal Cord Origin

SPONSOR: Athena Neurosciences, Inc.

DATE OF REVIEW: September 7, 1994

RELATED INDs: Athena IND #
Sandoz USA IND #

1.0 INTRODUCTION

Development of tizanidine as an antispastic agent was undertaken initially by Sandoz Pharma, Ltd., the company that discovered the compound. Zanaflex (tizanidine.HCl) is licensed from Sandoz Pharma, Ltd., Basel, Switzerland and was first approved for marketing in December 1983 in Switzerland. The initial market introduction also took place in Switzerland in May 1984 under the registered trademark name, Sirdalud. At the time of initial approval and market introduction, three doses were included: 2mg, 4mg, and 6mg. To date tizanidine has been approved in 30 countries and introduced into the market in 27. Available doses include 1, 2, 4, 6, and 12mg; 6 mg in both immediate and modified release (MR) forms, and 12mg in MR form only.

Tizanidine was not approved by the Committee on Safety of Medicine (United Kingdom) in October 1984 nor by the Canadian Food and Drug Association in September 1989 for inadequate evidence of efficacy. Since then, two new efficacy studies have been performed.

A multicenter, randomized, double-blind, placebo-controlled study of tizanidine in patients with spasticity due to multiple sclerosis (Study DS0502) was conducted in the United Kingdom from July 1989 to March 1991 under the sponsorship of Sandoz Pharma Ltd.. U.S. rights to tizanidine were acquired by Athena Neurosciences, Inc. in 1991. Athena has undertaken a clinical development program for the drug in the treatment of spasticity of spinal cord origin. An IND was filed by Athena in September 1991 under which a second study was proposed in patients with MS to be conducted in the U.S. using a study design similar to that of Study DS0502. The U.S. study (Study 021-001) was conducted from February 1992 to June 1993. Due to concerns by the Division for a potentially narrow interpretation of the spasticity indication for tizanidine since only patients with spasticity associated with MS were included in the primary studies, a third placebo-controlled study was initiated in patients with spasticity secondary to spinal cord injury (Study 021-003) to broaden the indication to spasticity of spinal cord origin. Study 021-003 was conducted in North America from March 1993 to August 1993.

In this submission, Athena presents data from 933 patients in Table 1 (attached Vol 103 p 11-), evaluated after treatment with tizanidine in Athena- or Sandoz-sponsored clinical efficacy and safety trials to demonstrate the clinical effectiveness of tizanidine in the treatment of spasticity of spinal cord origin. The trials include well-controlled comparisons of tizanidine with placebo (including 3 primary and 2 supportive studies), supportive active-controlled comparisons and uncontrolled studies, including assessments of long-term effectiveness.

2.0 IDENTIFICATION OF THE NEW DRUG SUBSTANCE

Tizanidine hydrochloride, a centrally acting alpha2-adrenergic agonist, is a muscle relaxant and antispastic agent.

Structural formula:

Molecular formula: $C_9H_8ClN_5S.HCl$

Molecular weight: 290.2

Chemical name: 5-Chloro-4-(2-imidazolin-2-ylamino)-2, 1, 3-benzothiadiazole hydrochloride

3.0 CHEMISTRY, MANUFACTURING, AND CONTROLS

The manufacture of the new drug substance and the new drug product, tizanidine HCl is described in the . For more complete information, please consult the Chemistry review.

Proprietary name: Zanaflex (Athena)

Proprietary names: Sirdalud
(ex-U.S.) Ternelin (Sandoz, Ltd.)

4.0 PHARMACOLOGY

Tizanidine HCl (Zanaflex) is an imidazoline compound which demonstrates α_2 adrenergic activity at the α_2 binding α_2 -adrenergic and imidazoline (I) receptor sites, resembling the imidazoline antihypertensive drug clonidine. Tizanidine is a full α_2 -adrenergic agonist unlike clonidine which has been shown to be a partial agonist at alpha2-receptors. Tizanidine prefers I2 sites although the physiologic significance of the I2 site is not understood.

The imidazoline chemical structure of tizanidine is related to that of the antihypertensive drug clonidine. Pharmacologic studies in animals show similarities between the two compounds, however, tizanidine was found to be 10-50 times less potent than clonidine in antihypertensive effect.

Preliminary evidence indicates that tizanidine acts at both spinal and supra-spinal α_2 -adrenergic sites. At the supra-spinal level tizanidine acts at autoreceptor sites on noradrenergic cells in the locus coeruleus and subcoeruleus. This action effectively reduces the firing rates of the noradrenergic cells and the resultant release of norepinephrine. Noradrenergic terminals in spinal cord are known to produce facilitation of motoneurons. The data indicate that, in the spinal cord, tizanidine may have both pre- and post-synaptic effects. There is evidence that the release of aspartate and glutamate from synaptic elements in vitro is reduced by tizanidine. The postsynaptic effects of excitatory amino acids were either reduced or unaffected depending upon the model and amino acid used.

Neurophysiologic studies of reflex activity also suggest that tizanidine produces postsynaptic effects. Both the supraspinal and spinal actions of tizanidine are blocked by the α_2 -adrenergic antagonist, yohimbine.

Tizanidine has no significant effects directly on the muscle, the neuromuscular junction or on monosynaptic reflexes. When considered overall, animal and in vitro studies indicate that tizanidine suppresses activation of motor neurons produced by polysynaptic pathways either by reducing the effectiveness of excitatory synapses, by increasing presynaptic inhibition or by both mechanisms.

4.1 PHARMACOKINETICS

Tizanidine is rapidly absorbed with a bioavailability of approximately 34%. The plasma half-life of unchanged drug is approximately 2 hr and very little accumulation in plasma occurs during chronic dosing on a 4mg q 8hr regimen. Tizanidine is extensively metabolized and 15 metabolites have been identified in plasma and urine but none are expected to have biological activity. The molecular structures were determined for 14 of the metabolites and 4 of them were measured at concentrations of approximately 10ng/ml or greater in plasma at 2hr after a single oral dose.

4.2 PHARMACODYNAMICS

A single 2 mg dose of tizanidine reduces the central excitability of the lower motor neurons of healthy, non-spastic subjects, while a single 4 mg dose of tizanidine produces a modest but significant increase in central inhibition in patients with spasticity. A single 4 mg dose of tizanidine has been shown to increase presynaptic inhibition on Ia afferents when measured 60 minutes after dosing.

The relationship between plasma levels and antispastic effects of tizanidine were assessed after administration of an 8 mg dose to 5 quadraplegic and 5 paraplegic patients. Spasticity was measured using the Ashworth Scale. Lower limb spasticity was rapidly reduced following tizanidine administration with peak reductions occurring between 1 and 1.5 hours after dosing coincident with peak plasma levels which were observed at 1 hour. Spasticity returned to baseline levels by 4 hours after dosing.

The dose-response relationship for the antispastic efficacy of tizanidine was assessed in 16 patients with spasticity secondary to MS who received single doses of placebo, 2, 4, or 8mg in a 4-way crossover study. Plasma tizanidine concentrations were determined up to 8 hours after dosing. There was a significant linear dose-effect relationship for reduction in muscle tone as measured by the pendulum test (expressed as the log of the amplitude of the first swing from the most spastic limb) over the dose range of 2 mg to 8 mg. Assessment of muscle tone based on Ashworth score revealed a significant reduction only with the 8 mg dose at 1-hour post-dosing. Plasma concentrations increased linearly with dose and antispastic efficacy increased with increasing plasma concentrations.

5.0 CLINICAL DEVELOPMENT PROGRAM

Athena Neurosciences, Inc. has undertaken a clinical development program of tizanidine for the treatment of spasticity of spinal cord origin. The following three placebo-controlled studies are identified as pivotal sources of efficacy:

PROTOCOL	TITLE
DS 0502	A Multicenter, Double-blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity due to MS.
021-001	A Multicenter, Double-blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity Due to MS.
021-003	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity resulting from Spinal Cord Injury.

Study DS 0502 was sponsored by Sandoz and was conducted in the United Kingdom; Studies 021-001 and 021-003 were sponsored by Athena and were conducted in the US and Canada. Two of the trials (Studies DS-502 and 021-001) enrolled patients with spasticity secondary to multiple sclerosis; the other trial (Study 021-003) enrolled patients with spasticity due to spinal cord injury. A total of 284 patients received tizanidine in these trials and 277 received placebo.

An original protocol, study report, case report tabulations, and data sheets were submitted for each pivotal trial. For all three studies, double-blind medication was administered during a 3-week titration phase followed by a plateau phase of 9 weeks (Studies DS-0502 and 021-001) or 4 weeks (study 021-003) in duration concluded by a one week withdrawal. The target symptom is spasticity of spinal cord etiology resulting from multiple sclerosis or spinal cord injury.

The following placebo-controlled studies are identified by the firm as supportive of efficacy:

PROTOCOL	TITLE
DS-2N #S-1	LaPierre Y. Double-blind study comparison between tizanidine and placebo in patients with spasticity related to multiple sclerosis. Montreal. May 1987.
DS103-282	U.K.Rinne. A comparative trial of DS103-282 and placebo in patients with spasticity due to multiple sclerosis or chronic myelopathy. Turku, Finland. May 1980

There are also 21 Sandoz-sponsored randomized, double-blind trials comparing the efficacy and safety of tizanidine with that of baclofen (15 studies) or diazepam (6 studies) conducted in Europe and South America.

6.0 PIVOTAL CONTROLLED CLINICAL TRIALS GENERAL REMARKS

Patient Population

The patient population selected for the three trials were male and female inpatients or outpatients, 18 years or older, with established spasticity secondary to multiple sclerosis (Studies DS-0502, 021-001) or to spinal cord injury between neurologic levels cervical-5/6 and thoracic-12 with a Frankel rating of A, B, or C (Study 021-003).

In the MS studies, spasticity had to be associated with significant discomfort or functional impairment and reach a minimum score of 2 in the Ashworth scale for spasticity or a minimum score of 2 in muscle spasm and automatism type and frequency score in the most severely affected muscle group. In the spinal cord injury study, a minimum score of 2 in the Ashworth scale was required in at least one lower extremity muscle group at baseline. Patients were required to discontinue all previous antispastic drug therapy prior to study entry.

Study Design

The three primary efficacy trials were conducted using the same randomized, parallel group, placebo-controlled multicenter study design. The study consisted of four phases: Phase I- Screening and Washout (Weeks -1 to 0 [baseline]), Phase II- Titration (Weeks 1 through 3), Phase III - Plateau (Weeks 4 through 12, Studies DS0502 and 021-001 or Weeks 4 through 9 Study 021-003) followed by Phase IV- a 1-week dose tapering and a final visit (Week 14) 1 week after cessation of the study drug. During the Titration Phase, each patient was individually titrated up from a dose of 2 mg (Studies DS0502 and 021-001) or 4mg (Study 021-003) to a maximum dose of 36 mg daily (12 mg TID). The individual doses reached at the end of the Titration Phase were maintained without any changes (except where intolerable adverse events occurred) during the Plateau Phase. Patients were examined weekly during the Titration Phase and every 3 weeks during the Plateau Phase. At the end of 12 weeks of treatment (or 9 weeks in the spinal cord study), the drug dose was tapered over 1 week and then discontinued. This taper was included in order to protect the blind. The last examination was performed 1 week after treatment was discontinued. At the end of the drug taper phase, patients who wished to do so were entered into a long-term open-label study.

Efficacy Measures

All protocols employed the same core efficacy measures. The primary outcomes consisted of evaluation of spasticity by the 5-point Ashworth Scale and evaluation of spasms by a frequency scale. All remaining variables were considered secondary.

For all three trials, change from baseline in muscle tone was assessed using the Ashworth Scale. The scores obtained for each of the muscle groups evaluated for muscle tone were summed to obtain the total Ashworth score. For the two MS studies, total Ashworth score summed across all muscle groups was based on bilateral evaluation of ten specified upper and lower body muscle groups, while total Ashworth score in the spinal cord injury study was based on bilateral evaluation of three lower body muscle groups. In the two MS studies (DS0502 and 021-001) muscle tone was assessed at each visit during the titration and plateau phases, while in the spinal cord injury study (021-003), assessments of muscle tone were made only at the final titration and final plateau visits. These assessments were performed at approximately the same time of day, and in the same body position.

ASHWORTH SCALE	MUSCLE GROUPS EVALUATED	
	MS STUDIES	SCI STUDY
Muscle Tone 0=no increase in tone 1=slight increase in tone, giving "catch" when limb is flexed or extended 2=more marked increase in tone but limb easily flexed 3=considerable increase in tone; passive movement difficult 4=limb rigid in flexion or extension	Both sides: elbow flexors elbow extensors elbow pronators elbow supinators wrist flexors finger flexors hip adductors knee flexors knee extensors foot flexors	Both sides: hip adductors knee flexors knee extensors

In two of the three trials (021-001 and 021-003), changes from baseline in the number of daily spasms (daytime plus nighttime spasms or awakening from spasms) were obtained from diary cards completed by patients daily during the study. For the DS-0502 study, the spasm data was obtained during the investigator's examination at each visit.

Scale for Muscle spasms and automatisms**Type and Frequency**

- 0= Absent
- 1= Provoked by painful stimuli only
- 2= Provoked by touch, light pressure and/or occasionally spontaneous (<5 per day and/or <2 per night)
- 3= Provoked by passive movements (during physiotherapy or nursing care) and/or frequently spontaneous (>5 per day, >2 per night)
- 4= Provoked by attempts to perform active movements, continuously spontaneous during day and/or more than 5 times in the night, or both

Pain and disability due to muscle spasms and clonus

- 0= Not interfering with function, causing no discomfort or pain
- 1= Making function (writing, eating, dressing, transfer or walking) difficult or causing moderate discomfort or pain or awakening 1-2 times in the night
- 2= Preventing the function or causing severe discomfort or severe pain or awakening more than 2 times a night

In all three studies, changes from baseline in muscle strength were assessed using the British Research Council Scale or a modification of this scale. In the two MS studies, muscle strength score was based on bilateral evaluation of nine muscle groups, while in the spinal cord injury study, evaluation of muscle strength was based on bilateral evaluation of the biceps and quadriceps.

Muscle Strength			
BMRC Scale	MODIFIED BMRC SCALE	MUSCLE GROUPS EVALUATED	
5=normal muscle strength 4=voluntary movement against mild resistance 3=voluntary movement against gravity but not resistance 2=voluntary movement present but not able to overcome gravity 1=contraction of muscle detected by palpation but without effect on limb 0=absence of voluntary movement	5=normal muscle strength 4.5=voluntary movement against major resistance but not normal 4=voluntary movement against moderate resistance 3.5=voluntary movement against mild resistance 3=voluntary movement against gravity but not resistance 2=voluntary movement present but not able to overcome gravity 1=contraction of muscle detected by palpation but without effect on limb 0=absence of voluntary movement	Both sides: arm abduction elbow flexion hand grip hip flexion hip extension knee flexion knee extension dorsal flexion plantarflexion	Both sides: biceps brachii quadriceps

For the spinal cord injury study (021-003), a pendulum test was performed as an additional primary assessment of spasticity in these patients. Angular displacement (degrees) in the arc of the first swing of the pendulum test was recorded for the right leg only.

Secondary measures of antispastic efficacy included deep tendon reflexes and clonus (based on a 7-point scale where 0=normal and 7=limb rigid so that reflexes are not elicitable), assessment of functional capacity (tests for walking and activities of daily living), changes in patient comfort (patient's self assessment of overall disability and discomfort, sleep quality, easiness of active and/or passive physiotherapy and easiness of nursing care). All three studies included global evaluations of efficacy and/or tolerability of study medication as assessed by the patient and investigator. In Study DS0502, the patient and clinician (assessor) rated overall efficacy on a 5-point scale of "very good" to "very poor". In study 021 003, the patient, physician-prescriber and physician-assessor each evaluated overall efficacy and tolerability on a single bipolar analog scale ranging from "spasticity does not interfere with any functions" to "spasticity interferes with all functions". The physical therapist (assessor) rated functional capacity on a similar scale ranging from "normal functional and interactive capacity" to "minimal functional and interactive capacity". It should be noted that an addendum to the protocol allowed the same person to act as the assessor of efficacy as well as the prescriber.

Statistical Methodology

An integrated review of efficacy is based on the following primary efficacy parameters: change from baseline in total Ashworth score, percent of patients with improvement in Ashworth score, and change from baseline in daily counts of spasms. Change from baseline in muscle strength was analyzed to indicate that tizanidine does not exert its antispastic effects at the expense of limb strength.

In each of the three studies, the change from baseline in total Ashworth score (summed across muscle groups) was compared for the two treatment groups based on the F-test for treatments from the analysis of variance model. The number and proportion of patients with an improvement from baseline in muscle tone (decrease in total Ashworth score) were also summarized; treatment comparisons were made using the Cochran Mantel Haenszel test stratified by center (Studies DS0502 and 021-001) or Fisher's Exact test (Study 021-003). Pooling of data across studies was not considered appropriate since different numbers of muscle groups were evaluated in the multiple sclerosis and spinal cord injury studies. However, a global test of the null hypothesis of no treatment difference between placebo and tizanidine was carried out using Fisher's inverse chi-square method (Hedges L, Olkin I. *Statistical Methods for Meta-analysis*. Academic Press, 1985) applied to the probabilities for the test for treatment effect at endpoint from each of the three trials. The percent of patients with improvement in Ashworth score was summarized by study and for the three studies combined without application of formal statistical inference.

For Studies 021-001 and 021-003, the change from baseline in daily counts of spasms and clonus was compared for the two treatment groups. In order to satisfy assumptions of the analysis of variance, count data were normalized by calculating a response ratio relative to baseline for each patient at each visit; treatment comparisons were based on the F-test for treatments from the analysis of variance model used in the analysis of total Ashworth score. For these two studies, daytime counts of spasms and clonus were pooled for analysis. The comparison of treatments was based on the response ratio relative to baseline for daytime counts using an analysis of variance model with study and treatment effects.

For Study 021-003, the change from baseline in degrees of displacement on the first swing of the pendulum test was compared for the two treatment groups based on the F-test for treatments from the analysis of variance model used in the analysis of total Ashworth score. Because of a markedly non-normal distribution in the change from baseline in the pendulum test, a secondary, nonparametric rank analysis was also applied to this parameter.

For the two MS studies (DS0502 and 021-001), the change from baseline in total muscle strength (summed across muscle groups) was compared for the two treatment groups using the F-test for treatments from the analysis of variance model used to analyze total Ashworth score. For Study 021-003, the planned parametric inferential analysis of treatment group differences in change from baseline in muscle strength was not completed due to the discrete nature of the distribution; alternatively, the distribution of change from baseline was summarized by category, Improved (increase), No change, or Worsened (decrease), without inferential statistics. A pooled analysis of muscle strength was not considered appropriate since scores were based on different numbers of muscle groups for the multiple sclerosis and spinal cord injury studies. Therefore, change from baseline in muscle strength was summarized separately for the three trials.

In the analysis of individual studies, no treatment by center or treatment by strata interactions were found. Consequently, the interaction terms were dropped and main effects models were used.

All treatment comparisons were two-sided at the 0.05 level of significance unless otherwise noted.

7.0 Protocol DS-0502: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity due to Multiple Sclerosis

This study was initiated July 7, 1989 and completed on March 29, 1991.

Design

The treatment period consisted of a titration phase (Weeks 1 through 3) and a plateau phase (Weeks 4 through 12). Procedures and ratings were scheduled weekly during titration and then at 3-week intervals (Weeks 6, 9, and 12) during the plateau phase. All patients had their study medication dose tapered over 1 week (Week 14), then discontinued. Final assessments (primarily to evaluate the presence of rebound phenomena) were performed 1 week after discontinuation of study medication. At the end of the study patients were queried if they preferred study drug to prestudy treatment (if any). Study drug was supplied as 2.0 and 4.0 tablets by Sandoz Ltd, Basel, Switzerland.

Assessments included

- Muscle tone by the Ashworth scale
- Muscle spasms and automatisms: type, frequency, pain & disability
- Deep tendon reflexes and clonus
- Muscle strength by the BMRCS

At the end of Week 3 and Week 12 and Final visit:

Assessment of functional capacity, including

- Walking time
- Activities of daily living (based on Kurtzke ISS)

Assessment of patient comfort, including

- Patient self assessment of overall disability and discomfort
- Sleep quality
- Easiness of active and/or passive physiotherapy
- Easiness of nursing care

Patient and Physician global assessment of tolerability and efficacy using a 5-point scale for each (very good to none) for efficacy; (very good to very poor) for tolerability.

The prospectively identified primary endpoint as stated in the protocol was the decrease in mean total muscle tone measured using the Ashworth scale on ten muscle groups over a 12 week period.

An addendum to the protocol allowed the same person to act as the assessor of efficacy as well as the prescriber.

Patient Population

After qualifying for the study, patients were stratified to one of three severity groups according to the score of the most severely spastic muscle (independent of the severity of spasticity in other muscles) using the Ashworth scale (1 and 2=mild; 3=moderate; 4=severe). Patients within each stratum were then randomized to one of the two treatment groups to ensure that equal numbers of patients in each stratum were randomized to both treatments. Each study center was given a separate randomization list.

Statistical Issues

Sample size

Under the assumption that the standard deviation of the changes from baseline in total Ashworth score for muscle tone is 6.5, it was determined that a sample size of 106 patients per treatment arm would provide 80% power to detect a difference of 2.5 between treatment groups with a two-tailed asymptotically normal test at $\alpha=0.05$.

The data from this trial had previously been analyzed by Sandoz UK. Differences in statistical methods include: In the ANOVAs, some centers with small sample sizes were pooled for the factor "Center". Specifically, Centers 1, 6, and 15 and Centers 10 and 7 were pooled into one level each for this factor because each center had less than four subjects per treatment. Bio-Pharm obtained a significant interaction of treatment with baseline severity that was further investigated by an outlier analysis. There was no evidence of treatment by center interaction.

The supportive variables change from baseline in deep tendon reflexes and clonus, best walking time, type and frequency of spasms, Kurtzke ISS (ADL) were summarized by visit and treatment group using descriptive statistics. No statistical inference procedures were carried out on these parameters. The final global assessment of efficacy was also summarized descriptively.

Results

Patient Demographics

No significant differences were observed between the two treatment groups for any demographic characteristics. Sixty-eight (68) were males and 119 were females, such that the ratio of females to males was 2:1 in both treatment groups. All patients were caucasian. Mean age was 46 years for both groups. The majority of patients had a severity score of 2 or 3 based on stratification class definition where 1 to 2=mild, 3-moderate and 4=severe. Mean Ashworth Score at Baseline was 16.84 (PBO) v. 18.47 (tizanidine).

Study Drug Administration

No meaningful treatment group difference (tizanidine v. placebo) was observed for the duration of exposure to treatment (76 v. 80 days) and the average duration of the Plateau Phase (55 v. 61 days). The mean daily prescribed dose during the Plateau Phase was 28.8 mg for tizanidine-treated patients compared with 34.8 mg for placebo-treated patients.

Patient Disposition

187 patients were randomized at sixteen (16) centers ranging in size from one (1) subject to twenty-two (22) subjects and received double-blind treatment. 94 patients received tizanidine and 93 patients received placebo. 134 patients (64 tizanidine, 70 placebo) completed the study and 53 (27%) patients (30 tizanidine, 23 placebo) discontinued prematurely as summarized in the sponsor's Table 2 (vol 41 pg 46) following.

Table 2 Patient Disposition by Treatment Group	Treatment Group	
	Placebo N (%)	Tizanidine N (%)
<u>Number of Patients:</u>		
Randomized	93	94
Treated ^a	93	94
Completed Study	70 (75)	64 (68)
Discontinued ^b		
Adverse Events	4 (4)	16 (17)
Illness not related to study drug	1 (1)	1 (1)
Uncooperative	1 (1)	4 (4)
Protocol Violation	1 (1)	0 (0)
Study Medication Ineffective	14 (15)	12 (13)
Other	2 (2)	1 (1)

a Patients who received at least one dose of study medication. Percents are based on the number of treated patients in each treatment group.

b Patients may have had multiple reasons for discontinuation.

A summary of patients on study by visit and treatment group is presented in Sponsor's Table 3 (vol 41 pg 47).

Table 3 Patients on Study by Visit and Treatment Group	Treatment Group			
	Placebo		Tizanidine	
	N (%)	Analyzable Data N (%)	N (%)	Analyzable Data N (%)
<u>Number of Patients:</u>				
Randomized	93	0	94	0
Randomized, Not Treated	0	0	0	0
Treated ^a	93 (100)	0	94 (100)	0
Baseline ($\leq$ Day 1)	93 (100)	93 (100)	94 (100)	94 (100)
Titration 1 (Days 2-10)	93 (100)	88 (95)	93 (99)	84 (89)
Titration 2 (Days 11-17)	93 (100)	80 (86)	90 (96)	79 (84)
Titration 3 (Days 18-24)	89 (96)	83 (89)	87 (93)	83 (88)
Plateau 1 (Days 25-52)	83 (89)	79 (85)	84 (89)	78 (83)
Plateau 2 (Days 53-73)	79 (85)	71 (76)	73 (78)	67 (71)
Plateau 3 (Days 74-94)	78 (84)	71 (76)	65 (69)	65 (69)
Follow-up ($>$ Day 94)	24 (26)	0	18 (19)	0

a Patients who received at least one dose of study medication. Percents are based on the number of treated patients in each treatment group.

When the proportion of patients who discontinued from the study were compared with visit and treatment group, a higher proportion of tizanidine-treated patients were discontinued due to adverse events at Visits 5 and 6 (Plateaus 1 and 2, respectively) as compared with placebo-treated patients. A higher proportion of placebo-treated patients discontinued due to ineffective study medication at visits 4 and 7 (Titration 3 and Plateau 3, respectively) as compared with tizanidine-treated patients. At Visit 6 (plateau 2), a higher proportion of tizanidine treated patients discontinued as a result of ineffective study medication when compared with placebo-treated patients.

Sponsor's Efficacy Results

In the analysis of muscle tone (Ashworth Score), the mean scores were comparable for the two treatment groups at baseline, although a slightly higher score was observed for the tizanidine group (18.47) as compared with the placebo group (16.84). During the titration phase, the decrease from baseline in the mean score in muscle tone was larger for the tizanidine group as compared with the placebo group, and became significant ($p=0.0017$) at the start of the Plateau Phase (Visit 5) with a mean decrease from baseline in muscle tone score for the tizanidine group of 4.69 compared with a mean decrease of 1.99 for the placebo group. The mean decrease from baseline in muscle tone score was consistently larger for the tizanidine group as compared with the placebo group throughout the Plateau Phase. At the endpoint evaluation, the difference was significant ($p=0.0072$) with a decrease in the tizanidine group of 3.88 compared with a decrease of 1.53 in the placebo group. Antispastic effect of tizanidine was still evident at the final visit, 1 week after the end of taper. Mean decrease from baseline in muscle tone score was 3.08 for tizanidine compared with 1.08 for the placebo group. These scores indicate that there is no evidence of rebound in muscle tone after discontinuation of tizanidine.

Table 10 (Vol 41 pg 59)

Mean Scores and Changes from Baseline in Muscle Tone (Ashworth Score) by Visit and Trtmnt. Grp.-All Trtd. Pt. Pop.	Treatment Group		
	Placebo	Tizanidine	p-value ^a
Plateau 1 (Visit 5: 25 to 52 days)			
N ^b	79	78	0.0017
Visit Mean ^c	13.75	13.83	
Change from Baseline ^b			
Mean	-1.99	-4.69	
Median	-1.00	-4.00	
SD	5.34	5.26	
Plateau 2 (Visit 6: 53 to 73 days)			
N ^b	71	67	0.0005
Visit Mean ^c	13.68	12.64	
Change from Baseline ^b			
Mean	-1.68	-5.52	
Median	-1.00	-4.00	
SD	5.53	5.92	
Plateau 3 (Visit 7: 74 to 94 days)			
N ^b	71	65	0.0000
Visit Mean ^c	13.75	12.91	
Change from Baseline ^b			
Mean	-1.20	-5.00	
Median	0.00	-4.00	
SD	4.32	5.00	
Endpoint^d			
N	93	94	0.0072
Visit Mean	15.31	14.59	
Change from Baseline			
Mean	1.53	-3.88	
Median	0.00	3.00	
SD	5.38	4.99	
Final (Visit 8: >94 days)			
N ^b	71	62	0.0326
Visit Mean ^c	14.85	13.77	
Change from Baseline ^b			
Mean	1.08	1.08	
Median	0.00	2.00	
SD	4.40	5.04	

^a p values for between treatment comparisons were calculated by using the F test for treatment of a 1 way ANOVA model with strat. center and treatment effects

^b Based on patients with values both at baseline and at the visit

^c Includes all patients with data at the visit

^d Last study visit while on, or at the end of study medication prior to taper

When the sponsor also analyzed muscle tone in the lower extremities, significantly larger mean decreases from baseline were observed in tizanidine-treated patients as compared with placebo patients at the first and second titration visits ($p=0.0311$ and 0.0085 , respectively); at plateaus 1, 2, and 3 ($p=0.0032$, 0.0067 and 0.0002 , respectively); at study endpoint ($p=0.0006$); and at the final visit ($p=0.0484$).

In the analysis of percent of patients with improvement in muscle tone, comparable proportions of patients in the tizanidine and placebo groups had improvement during the titration phase. Significant treatment group differences in the percent of patients with improvement were observed at the start of the Plateau phase [visit 5] ($p=0.01$) and at the endpoint evaluation ($p=0.003$). Similar results were seen at all other plateau visits.

Table 11 (vol 41 pg 61)

Count and Percent of Patients Who Achieved Improvement ^a in Muscle Tone (Ashworth Score) By Visit and Treatment Group - All Treated Patient Population	Treatment Group		
	Placebo n/N (%)	Tizanidine n/N (%)	p-value ^b
First Plateau (Visit 5)			
Improved	44/93 (47)	58/94 (62)	0.0100
Not Improved	35/93 (38)	20/94 (21)	
Not Assessed	14/93 (15)	16/94 (17)	
Endpoint			
Improved	46/93 (49)	67/94 (71)	0.0030
Not Improved	47/93 (51)	27/94 (29)	

a Improved muscle tone defined as a decrease in total Ashworth Score.

b p-values were calculated by using the Cochran Mantel Haenszel test. The "not assessed" patients were considered as "not improved" for the purpose of the analysis.

c Last study visit while on, or at the end of study medication prior to taper.

A summary of the count and percent of patients who achieved improvement in muscle tone (Ashworth Score) by demographic subgroup and treatment group is presented in Sponsor's Table 12.

Count and Percent of Patients Who Achieved Improvement ^a in Muscle Tone (Ashworth Score) at the Endpoint by Demographic Subgroup and Treatment Group-All Treated Patient Population	Treatment Group	
	Placebo n/N (%)	Tizanidine n/N (%)
Endpoint ^b Number of Patients	46/93 (49)	67/94 (71)
By Gender		
Males	16/33 (48)	23/35 (66)
Females	30/60 (50)	44/59 (75)
By Ethnic Group		
Caucasian	46/93 (49)	67/94 (71)
By Age (years)		
≥65	1/2 (50)	3/3 (100)
40-64	39/71 (55)	51/69 (74)
<40	6/20 (30)	13/22 (59)
By Stratification Class ^c		
A	24/48 (50)	26/40 (65)
B	19/39 (49)	37/48 (77)
C	3/6 (50)	4/6 (67)

a Improved muscle tone was defined as a decrease in total Ashworth Score.

b Last study visit while on, or at the end of study medication prior to taper.

c Stratification class definition based on baseline Ashworth Score for the most severely affected muscle group at baseline: A=(1-2), B=(3), C=(4)

Supportive Efficacy Variables

In the analysis of the type and frequency of muscle spasms and automatisms, slightly larger mean decreases from baseline were observed for the tizanidine group compared with the placebo group at Visits 2, 3, 5, 6 and 7. The mean decrease from baseline to the end of the study including the endpoint evaluation ranged from 0.78 to 2.24 for the tizanidine group compared with a decrease ranging from 0.57 to 1.25 for the placebo group. However, the effects were not significant.

Type and Frequency of Spasms and Automatism by Visit and Treatment Group - All Treated Patient Population	Treatment Group	
	Placebo	Tizanidine
Baseline (Visit 1)		
N	93	94
Visit Mean	5.11	6.30
First Plateau (Visit 5)		
N ^a	77	78
Visit Mean ^b	3.34	
Change from Baseline ^c		
Mean	-1.00	4.73
Median	0.00	
SD	3.26	-1.22
Endpoint ^c		0.00
N		4.47
Visit Mean		
Change from Baseline	93	
Mean	4.40	94
Median		5.52
SD	-0.71	
	0.00	
	3.53	-0.78
		0.00
		4.27

- a Based on patients with values both at baseline and at visit.
b Includes all patients with data at this visit.
c Last study visit while on, or at the end of study medication prior to taper.

With regard to supportive efficacy assessments deep tendon reflexes, pain and disability due to muscle spasms, walking time (time to walk 8 meters), activities of daily living (Kurtzke ISS) muscle strength-generally slightly larger mean decreases from baseline were observed for the tizanidine group compared with the placebo group but were not significant. No consistent treatment-related effect was evident in these results.

For the global assessment of efficacy, a slightly better efficacy score (lower score is better) was observed for the tizanidine group as compared with the placebo group when assessed by both the clinician and the patient. In the tizanidine group the clinician rated the efficacy with a mean score of 3.80 v. 4.30 for the placebo group. Similar scores for the tizanidine (3.81) and placebo (4.08) groups were observed when efficacy was rated by the patient. A slightly better tolerability was seen in the placebo group compared with the tizanidine group when assessed by both the clinician and patient.

Summary

EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSES
Change from baseline in total Ashworth Score	F test (ANOVA) visit 5 - endpoint (p = .0072)
Proportion of patients with improvement from baseline in muscle tone	Mantel-Haenszel visit 5 (p = 0.01) endpoint (p = .003)
Change from baseline frequency of spasm	Visit 1,5, endpoint (NS)
Mean changes from baseline muscle strength	Visit 1,4,5,7, endpoint (NS)

2° Efficacy Variable	
Change from baseline deep tendon reflex & clonus	NS
Pain & disability due to muscle spasm	NS
Walking time	NS
ADL-Kurtzke ISS	NS
Global efficacy: Physician\patient	p = .002\N S

Comment

This study provides evidence of the efficacy of tizanidine in the treatment of spasticity associated with MS. The prospectively identified primary outcome measure of spasticity as measured by the Ashworth scale was statistically significant in favor of tizanidine from the start of the Plateau Phase throughout to the endpoint evaluation. Results for the lower extremities were very similar to the results for all muscle groups with a statistically significant treatment difference of about 2 throughout the plateau phase and at endpoint. Likewise, the proportion of patients with improvement from baseline in muscle tone was also significant. Overall assessment of efficacy at endpoint as rated by the physician (physician's global) was significantly better for the tizanidine group. However, this outcome is tempered by the lack of significance in the frequency of spasm data and the other secondary measures. It may be recalled that spasm frequency was assessed by the investigator during his examination which may have reduced some of the variance in this measure.

8.0 Protocol 021-001 A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity due to Multiple Sclerosis

The study was initiated February 2, 1992 and completed June 8, 1993.

Design

The study consisted of four phases: a Baseline Phase (Weeks 0 and 1), a Titration Phase (Weeks 2,3 and 4) and a Plateau Phase (Weeks 5 through 13) followed by one week of dose tapering and a final visit (Week 15). During the Titration Phase, each patient was individually titrated from a dose of 2 mg up to a maximum dose of 36 mg daily (12 mg TID). The individual doses reached at the end of the Titration Phase were maintained without any changes (except where intolerable adverse events occurred) during the Plateau Phase. Patients were assessed weekly during the Titration Phase and every 3 weeks during the Plateau Phase. Diary cards for recording the number of daily spasms and clonus were completed by the patients and collected at Visits 3 through 9. Week 0 data was used to establish a baseline incidence of spasms. At the end of 12 weeks of treatment, the drug dose was tapered over 1 week and then discontinued. The last examination was performed 1 week after treatment was discontinued.

Assessments included

- Muscle tone by the Ashworth scale
- Muscle spasms and automatisms: type, frequency, pain & disability
- Deep tendon reflexes and clonus
- Muscle strength by the BMRCs

At the end of Week 3 and Week 12 and Final visit:

Assessment of functional capacity, including

- Walking time
- Activities of daily living (based on Kurtzke ISS)

Assessment of patient comfort, including

- Patient self assessment of overall disability and discomfort
- Sleep quality
- Easiness of active and/or passive physiotherapy
- Easiness of nursing care

Patient and Physician global assessment of tolerability and efficacy on a single bipolar analog scale ranging from "very satisfied with treatment" to "not at all satisfied with treatment".

NDA-020397

FIRM: ATHENA NEUROSCIENCES

3 OF 7

TRADE NAME: ZANAFLEX ORAL TABS. 4MG

GENERIC NAME: TIZANIDINE HCL

The prospectively identified primary outcome measure(s) was muscle tone as graded by the Ashworth scale and the counts of flexor spasms and automatism excluding tendon jerks (day and night counts), from diary cards. For the count of flexor spasms and automatism, which is based on diary data, the baseline is defined as the mean (day/night) count obtained over the week (Week 0) prior to the start of the titration phase. All other assessments were considered as supportive evidence of efficacy.

Patient Population

After qualifying for the study (patient must have a minimum score of 2 in the Ashworth scale or a minimum score of 2 in muscle spasm type and frequency in the most severely affected muscle), patients were stratified to one of three severity groups according to the score of the most severely spastic muscle (independent of the severity of spasticity in other muscles) using the Ashworth scale (1 and 2 = mild; 3 = moderate; 4 = severe). Patients within each stratum were then randomized to one of the two treatment groups to ensure that equal numbers of patients in each stratum were randomized to both treatments. Each study center was given a separate randomization list.

Statistical Issues

After conclusion of the study, upon review of the drug accountability records, multiple drug administration irregularities were discovered at Center #4. Identity testing of patient returns from this center revealed that some placebo patients received at least some active medication. Data from this center were excluded from all efficacy and safety analyses unless specifically stated otherwise. All treated dataset includes all patients including Center #4; All analyzed dataset includes all patients excluding Center #4.

There was no evidence of treatment by center interaction.

In the analysis of muscle tone (Total Ashworth) a higher mean score was observed for the placebo group as compared with the tizanidine group at baseline for all patient datasets. These differences were not significant. However, plots of the changes from baseline in Ashworth score v. baseline total Ashworth score revealed a significant inverse linear relationship indicating that more severely disabled patients had greater improvement. Consequently, the baseline Ashworth score was included as a covariate in this analysis.

The analysis of the lower body Ashworth score was included after review of the data revealed that most patients had little or no spasticity in the upper body. In the analysis of muscle tone for the lower body, a significantly lower mean score was observed for the tizanidine group as compared with the placebo group at baseline for all patient datasets. Therefore, treatment comparisons were based on the F-test from an analysis of covariance model with center, treatment and baseline lower body Ashworth score.

The distribution of the changes from baseline in the total count of spasms and clonus did not satisfy the assumptions of the analysis of variance due to a markedly skewed distribution, due to extrapolation of total counts from high frequency rates occasionally reported in patient diaries. In addition, the treatment groups were not well-balanced at baseline. The response ratio, a transformation used to normalize count data, is defined as:

$$\text{Response ratio} = \frac{\text{count at visit (or endpoint)} - \text{count at baseline}}{\text{count at visit (or endpoint)} + \text{count at baseline}}$$

The response ratio is centered around 0 with extremes of -1 and +1. A response ratio of -0.33 is equivalent to a 50% reduction. The response ratio was chosen for inferential statistical analysis because of the better distributional properties and was analyzed by visit and treatment group using the analysis of variance for all visits and endpoint.

Other supportive efficacy variables (deep tendon reflexes, type and frequency of muscle spasms and clonus, pain and disability due to muscle spasms and clonus, walking time and activities of daily living) were summarized with descriptive statistics. No statistical inference procedures were performed.

Results

Patient Demographics

No significant differences were observed between the two treatment groups for demographic characteristics. Mean age was 44.5 (tizanidine) and 46.1 (placebo). The ratio of females to males was 2:1 and the proportion of patients in mild, moderate, and severe stratification classes were comparable between the two treatment groups.

Patient Disposition

Two hundred and fifty seven (257) patients were randomized to receive double-blind treatment at seventeen centers ranging from two (2) to thirty-six (36) subjects. All patients except one who was randomized to tizanidine received study medication (tizanidine 4 mg tablets and matching placebo). One hundred and thirty-one (131) patients received tizanidine and 125 patients received placebo. This dataset represents the intention to treat analysis.

Patients enrolled at Center #4 were ineligible for sponsor's analysis due to dosing irregularities. This excluded 20 patients who were randomized to tizanidine and 16 patients who were randomized to placebo. Therefore, 111 patients randomized to tizanidine and 109 patients randomized to placebo were analyzed. This population represents the sponsor's all analyzed dataset. One hundred fifty-nine (159) patients (83 tizanidine, 76 placebo) completed the study and 61 patients (28 tizanidine, 33 placebo) were prematurely discontinued (27%).

Table 2 Patient Disposition by Treatment Group	Treatment Group	
	Placebo N (%)	Tizanidine N (%)
Number of Patients:		
All Treated ^a	125	131 (100)
Ineligible	16(13)	20 (15)
All Analyzed	109 (100)	111 (100)
Completed Study	76 (70)	83 (75)
Discontinued ^b		
Lost to Follow-up	33 (30)	28 (25)
Adverse Events	1 (<1)	1 (1)
Protocol Violation	4 (4)	8 (7)
Patient Request (adverse event)	4 (4)	2 (2)
Patient Request (other)	3 (3)	6 (5)
	21 (19)	11 (10)

a All patients (including center #4) who received at least one dose of study medication. One patient was randomized but not treated. Percents are based on the number of treated patients in each treatment group.

b Patients may have had multiple reasons for discontinuation.

No meaningful difference was observed between the two treatment groups for the proportion of patients on study during the Titration Phase, Plateau Phase and Followup.

When the proportion of patients who discontinued from the study was compared by visit and treatment group, a larger proportion of tizanidine subjects as compared with placebo subjects was discontinued due to adverse events at Visit 4 (Titration 1) and Visit 7 (Plateau 1). In contrast, a larger proportion of placebo-treated patients discontinued due to patient's request (other) at Visit 8 (Plateau 2) and Visit 9 (Plateau 3) as compared with the tizanidine-treated patients. Overall, the highest discontinuation rate was observed for the tizanidine group at Visit 7 (Plateau 1) and for the placebo group at Visit 8 (Plateau 2). At these visits, the majority of tizanidine-treated patients discontinued due to adverse events and patient's request and the majority of placebo-treated patients discontinued due to patient's request.

Study Drug Administration

No significant difference was observed in the duration of exposure to treatment between the tizanidine and placebo groups. For all analyzed patients, tizanidine-treated patients were exposed to the study drug for an average of 77.8 days and placebo-treated patients were exposed to study drug for an average of 76.5 days. Additionally, no meaningful treatment group difference was observed in the average

duration of the Plateau Phase. For all analyzed patients, the average duration of the Plateau Phase was 54.1 days for the tizanidine patients and 54.9 for the placebo-treated patients. During the Plateau Phase (Visits 7, 8, and 9) a lower prescribed mean daily dose of study medication was observed for the tizanidine-treated patients (26.7 mg) as compared with the placebo-patients (33.0 mg).

Sponsor's Efficacy Results

The primary efficacy parameters included mean score in muscle tone (Ashworth score) and mean score in average daily spasms and clonus.

For All Analyzed dataset, during the Titration Phase and throughout the Plateau Phase, slightly smaller mean decreases from baseline in muscle tone score were observed for the tizanidine group as compared with the placebo group. At the endpoint, significant decreases in Ashworth score were observed in both treatment groups. The mean decrease from baseline was 1.66 (covariate adjusted mean decrease from baseline = 2.03) for the tizanidine group compared with a mean decrease of 2.84 (covariate adjusted mean decrease from baseline = 2.73) for the placebo group. However, between group differences in the mean total Ashworth score at baseline and changes from baseline in total Ashworth scores were not significant at any timepoint (All analyzed).

Table 10 (vol 41 pg 180)

Mean Scores and Changes from Baseline in Muscle Tone (Total Ashworth Score) by Visit and Treatment Group - ALL ANALYZED Patients	Treatment Group		
	Placebo	Tizanidine	p-value ^a
Baseline (Visit 2) N	108 ^b	111	0.152
Visit Mean	14.95	12.99	
Titration 1 (Visit 4) N ^b	99	96	
Visit Mean ^c	11.91	11.81	
Change from Baseline			
Mean	-3.01	-1.22	
Least square mean ^c	-2.84	-1.38	0.116
S.D.	6.42	7.03	
Titration 2 (Visit 5) N ^b	96	96	
Visit Mean ^c	11.69	10.17	
Change from Baseline			
Mean	-3.69	-3.09	
Least square mean ^c	-3.55	-3.33	0.807
S.D.	6.74	6.10	
Titration 3 (Visit 6) N ^b	89	86	
Visit Mean ^c	10.19	9.91	
Change from Baseline			
Mean	-5.12	-3.59	
Least square mean ^c	-4.91	-3.86	0.292
S.D.	7.12	7.37	
Plat 1 (Visit 7) N ^b	93	90	
Visit Mean ^c	11.02	9.40	
Change from Baseline			
Mean	-4.53	-3.37	
Least square mean ^c	-4.13	-4.07	0.955
S.D.	7.06	8.15	
Plateau 2 (Visit 8) N ^b	75	82	
Visit Mean ^c	11.87	9.00	
Change from Baseline			
Mean	-3.77	3.28	
Least square mean ^c	-2.82	-3.80	0.425
S.D.	8.61	8.39	
Plateau 3 (Visit 9) N ^b	76	83	
Visit Mean ^c	11.99	10.46	
Change from Baseline			
Mean	-2.59	-2.18	
Least square mean ^c	-2.43	-2.44	0.921
S.D.	7.83	7.30	
Endpoint ^d N ^b	104	105	
Visit Mean ^c	12.12	11.33	
Change from Baseline			
Mean	-2.84	-1.66	
Least square mean ^c	-2.73	-2.03	0.460
S.D.	7.17	7.22	

^a P-values for between treatment comparisons from the F-test for treatments of a 2-way ANCOVA model adjusted for center and Total Ashworth score at baseline.

^b Based on patients with data both at baseline and at the visit.

^c Least square mean = covariate adjusted mean

^d Last study visit while on, or at the end of study medication prior to taper.

^e One patient did not have a total Ashworth score due to hand surgery prior to study start.

For the lower body Ashworth Score, at baseline, a significant ($p=0.004$) lower mean score was observed for the tizanidine group (10.41) as compared with the placebo group (12.75). During the Titration Phase (excepting the first titration visit, Visit 4) and throughout the Plateau Phase, the mean and covariate adjusted mean decrease from baseline in lower body muscle tone score were slightly smaller for the tizanidine group as compared with the placebo group. No significant treatment group difference was observed at any timepoint after Visit 4 (Titration 1).

In the analysis of the percent of patients who achieved improvement in muscle tone, no significant treatment differences were observed throughout the study.

For the intention to treat analysis, with respect to total muscle tone (total Ashworth score) a significant ($p=0.039$) baseline difference was observed such that a lower mean score was observed for the tizanidine group as compared with the placebo group (tizanidine: 15.59; placebo: 17.68) indicating that the placebo group was the more severely affected. No other significant difference was observed between the tizanidine and placebo treatment groups.

For the intent to treat analysis, a significantly ($p=0.002$) lower mean score for lower body muscle tone was observed for the tizanidine group (11.92) as compared with placebo group (13.82) at baseline. At the first titration visit (Visit 4), a marginally significantly ($p=0.054$) smaller covariate mean decrease from baseline in lower body muscle tone score was observed for the tizanidine group (mean=0.47, covariate adjusted mean=0.91) as compared with the placebo group (mean=2.09, covariate adjusted mean 2.13). During the remaining part of the Titration Phase and throughout the Plateau Phase, no significant difference was observed between the tizanidine and placebo groups.

For all treated patients, no significant treatment effect was observed throughout the titration and Plateau Phases and at endpoint for the count and percent of patients who achieved improvement in muscle tone.

When the total Ashworth score was summarized by demographic subgroup (gender, ethnic group and age) and treatment group, no difference was observed except as follows: larger decreases in muscle tone score were generally seen in the tizanidine group for females with severe disease. For the placebo group, larger decreases were generally seen for males with moderate disease.

Spasm Data

The spasm data were normalized by transformation to the response ratio, defined as $\frac{\text{count}(\text{visit}) - \text{count}(\text{baseline})}{\text{count}(\text{visit}) + \text{count}(\text{baseline})}$.

There was a greater reduction in the frequency of spasms and clonus as indicated by the response ratio (negative or lower ratio is better) in the tizanidine group compared with the placebo group. Analyses of variance of the mean response ratio were significant ($p=0.048$) at the endpoint in favor of the tizanidine group. The Wilcoxon test was also significant ($p=0.033$). During the Titration Phase, no meaningful difference in response ratio was observed between the tizanidine and placebo groups. During the Plateau Phase, a greater reduction in the frequency of spasms and clonus was observed for the tizanidine group as compared with the placebo group at all visits. However, these differences were not significant.

With respect to percent change from baseline for count of daily spasms and clonus a less favorable median percent change (negative or lower score is better) was observed for the tizanidine group as compared with the placebo group at Visit 5 (Titration 2). A more favorable median percent change from baseline was observed for the tizanidine group as compared with the placebo group at Visit 5 (Titration 2). A more favorable median percent change from baseline was observed for the tizanidine group as compared with the placebo group at all other visits. At the endpoint, a median percent change from baseline of -57.14 was observed for the tizanidine group compared with -40.81 for the placebo group.

A summary of the response ratio and percent change from baseline for the count of daytime and nighttime spasms and clonus by visit and treatment group from patient diaries for ALL TREATED patients is presented for Visits 6 and 9 and endpoint in Table 19 (vol 41 pg 202)

Response Ratio and Percent Change from Baseline of the Daily Average Spasms and Clonus by Visit And Treatment Group From Patient Diary - ALL TREATED Patients	Treatment Group		
	Placebo	Tizanidine	p-value
Daily Count of Spasms and Clonus:			
Baseline			
N	116	120	
Mean	129.38	45.65	
Median	8.88	8.57	
S.D.	846.49	265.98	
Response Ratio:			
Titration 3 (Visit 6) N ^b	110	110	
Visit Mean ^b	67.48	16.34	
Response ratio:			
Mean	-0.16	-0.20	
Median	-0.16	-0.21	0.505
S.D.	0.38	0.41	
Plateau 3 (Visit 9) N ^b	85	91	
Visit Mean ^b	52.24	16.66	
Response ratio:			
Mean	-0.24	-0.38	
Median	-0.31	-0.46	0.064
S.D.	0.46	0.46	
Endpoint	114	120	
Visit Mean ^b	53.33	17.88	
Response ratio:			
Mean	-0.20	-0.33	0.048 ^c
Median	-0.26	-0.40	0.033 ^d
S.D.	0.44	0.048	
Percent change from Baseline:			
Titration 3 (Visit 6) N ^b	110	110	
Visit Mean ^b	67.48	16.34	
Percent change:			
Mean	4.77	19.73	
Median	-27.72	-34.81	
S.D.	199.94	318.55	
Plateau 3 (Visit 9) N ^b	85	91	
Visit Mean ^b	52.24	16.66	
Percent change:			
Mean	114.36	-20.49	
Median	-48.08	-63.18	
S.D.	1103.0	125.00	
Endpoint	114	120	
Visit Mean ^b	53.33	17.88	
Percent change:			
Mean	85.06	7.69	
Median	-40.81	-57.14	
S.D.	949.94	315.98	

a Daytime and nighttime spasms and clonus.

b Based on patients with data both at baseline and at the visit.

c p-values were calculated from ANOVA model with strata, center and treatment effects.

d p-values from Wilcoxon Sum of Ranks procedure.

Note: The effective N for the Response Ratio maybe slightly lower at some visits because the Response Ratio is not defined if baseline and the visit were both=0 Response Extracted from Table D.2.5.1.

There were no clinically meaningful differences between the tizanidine and placebo groups with regard to mean change from baseline in muscle strength.

For the supportive efficacy parameters, no clinically significant treatment group difference was observed for deep tendon reflexes and clonus, type and frequency of muscle spasm and clonus, pain and disability due to muscle spasm and clonus and functional capacity (walking time and activities of daily living [minimum activity status score]).

In the global assessment of efficacy and tolerability, a significantly better score was observed for the tizanidine group as compared with the placebo group when assessed by the physician-prescriber ($p=0.043$) and the patient ($p=0.011$). When assessed by the physician-assessor, a better efficacy and tolerability score was also observed for the tizanidine group as compared with the placebo group. However, this difference was not significant.

Summary

EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSES
Change from baseline in total Ashworth Score	F test (ANOVA) (NS)
Proportion of patients with improvement from baseline in muscle tone	Mantel-Haenszel (NS)
Change from baseline frequency of spasm	Response Ratio endpoint ($p=0.053$)
Mean changes from baseline muscle strength	Visit 1,4,5,7,endpoint (NS)

Treatment differences in the mean total Ashworth score at baseline and changes from baseline in total Ashworth scores were not significant at any timepoint. Similar results were obtained for lower body muscle tone with the exceptions that differences at Visit 4 (Titration 1) favored placebo. The statistical reviewer examined this outcome by either including or excluding Center 4; no significant treatment effects were seen regardless of these maneuvers.

In the same manner, no significant treatment effect was observed throughout the Titration and Plateau Phases and endpoint for the percent of analyzed patients who achieved improvement in muscle tone. At the endpoint, 58% of the patients in the tizanidine group improved as compared with 60% of patients in the placebo group.

Because the data for daily spasms and clonus were not normally distributed, these data were converted to a response ratio. During the Titration Phase, no significant difference was observed between tizanidine and placebo groups. During the Plateau Phase, a better response ratio but not significant was observed for the tizanidine group as compared with the placebo group at all visits. By endpoint, the difference between the tizanidine and the placebo groups approached significance ($p=0.053$) for the mean response ratios for daily spasms.

There were no clinically meaningful differences between the tizanidine and placebo groups with regard to mean change from baseline in muscle strength.

2° Efficacy Variable	
Change from baseline deep tendon reflex & clonus	NS
Pain & disability due to muscle spasm	NS
Walking time	NS
ADL-Kurtzke ISS	NS
Global efficacy: Physician-prescriber\patient	.043\011
Physician-assessor	NS

For the supportive efficacy parameters, no clinically significant treatment group difference was observed excepting the physician-prescriber (who was not blinded) and the patient' global which were both significant.

Comment

This study does not provide significant evidence of the efficacy of tizanidine in the treatment of spasticity due to MS. There was no difference between treatment groups for the primary outcome Ashworth score; for the other primary outcome of spasm frequency, there was a trend present during the plateau which approached significance only at the endpoint. Of the supportive efficacy parameters, the physician prescriber and patient global were significant. It is difficult to account for the lack of activity of tizanidine in this study other than a large placebo response or, as the sponsor has suggested, that tizanidine has a time-dependent response. The inclusion or exclusion of center 4 does not change the outcome of the study.

9.0 Protocol 021-003 A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Tizanidine Tablets in Patients Suffering from Spasticity Resulting from Spinal Cord Injury.

The study was initiated February 23, 1993 and completed September 8, 1993.

Design

Patients were randomized to one of 15 centers ranging from 1 to 19 subjects. The treatment period consisted of a Titration Phase (Weeks 0 to 3) during which time doses (4 mg tablet) were adjusted and a Plateau Phase (Weeks 4 through 7) during which time doses were generally fixed at the dose administered at the end of the Titration Phase, Day 21. Procedures and ratings were scheduled weekly during the Titration Phase and at the end of Week 5 and Week 7 during the Plateau Phase.

Assessments on Day 1, at the end of week 3 by a physical therapist included

- Muscle tone by the Ashworth scale
- Muscle tone using the Pendulum Test
- Muscle strength by the BMRCs

Global evaluation of patient's capacity

Activities of Daily Living using the modified Klein-Bell scale

At the end of Week 5 and Week 7 and Final visit:

- Muscle tone by the Ashworth scale
- Muscle tone using the Pendulum Test
- Muscle strength by the BMRCs
- Overall assessment of efficacy by patient interview by the physician

Patient and Physician global assessment of tolerability and efficacy using a bipolar analog scale ranging from "spasticity does not interfere with any functions" to "spasticity interferes with all functions". The physical therapist (assessor) rated functional capacity on a similar scale ranging from "normal functional and interactive capacity" to "minimal functional and interactive capacity".

The prospectively identified primary outcome measure(s) per protocol were the change from baseline in total Ashworth score for lower extremities, the counts of spasms (day and night counts) from diary cards, and the Pendulum test.

Patient Population

Adult patients of either sex suffering from established (i.e. a stable clinical course for at least 18 months) spasticity secondary to spinal cord injury were eligible.

The spinal cord injury was between cervical-6 and thoracic-12 with Frankel ratings of A, B, or C and may have been the result of trauma or other causes. The level of spasticity was associated with significant discomfort or functional impairment with a minimum score of 2 in the Ashworth scale for muscle tone in at least one lower extremity muscle group at the time of Baseline evaluations. Included were

patients who have not experienced relief from symptoms with other antispastic medication due to lack of efficacy or tolerability, or patients untreated for spasticity, or patients willing to discontinue their present antispastic drug. No other muscle relaxants were permitted during the study. The concomitant use of all other drugs which a patient was receiving for concomitant conditions was allowed, provided the dosage was kept constant. Patients who were receiving physiotherapy were allowed to continue without changes in the frequency of sessions and the methods used.

Patient Disposition

One hundred and twenty-four (124) patients were randomized to receive double-blind treatment in the study. All except six patients (two randomized to tizanidine and four randomized to placebo) received study medication. Fifty-nine (59) patients received tizanidine and 59 received placebo. Patients received study drug daily for up to 8 weeks (3 weeks of Titration Phase and 4 weeks of Plateau Phase and one week of dose tapering). Seventy-eight (78) patients (38 tizanidine, 40 placebo) completed the study and 40 patients (33%; 21 tizanidine, 19 placebo) were prematurely discontinued. The most common reasons for discontinuation among patients in the tizanidine and placebo groups were adverse events and insufficient therapeutic effect, respectively.

Table 2 (vol 41 pg 328)

Patient Disposition by Treatment Group	Treatment Group	
	Placebo N (%)	Tizanidine N (%)
<u>Number of Patients:</u>		
Randomized	63	61
Randomized, Not Treated	4	2
Treated ^a	59	59
Completed Study ^b	40 (68)	38 (64)
Discontinued ^c	19 (32)	21 (36)
Adverse Experience	5 (8)	14 (24)
Insufficient Therapeutic Effect	9 (15)	2 (3)
Failed Selection Criteria/Non-compliant	4 (7)	3 (5)
Other (adverse event/insufficient therapeutic effect)	0	1 (2)
Other (antispasticity medications, administrative error, personal reasons)	5 (8)	3 (5)

a Patients who received at least one dose of study medication.

b According to investigator's definition of study completion. Note: Due to an administrative error, 6 patients were considered to have completed the study after completion of the first two weeks of the Plateau Phase and are noted as completers in this table.

c Patients could have more than one reason for premature discontinuation.

Note: Percents are based on number of treated patients in each group.

Table 3 (vol 41 pg 329)

Patients on Study By Visit and Treatment Group	Treatment Group	
	Placebo N (%)	Tizanidine N (%)
<u>Number of Patients:</u>		
Randomized	63	61
Randomized, Not Treated	4	2
Treated ^a	59 (100)	59 (100)
Completed Study ^b	40 (68)	38 (64)
On Study At ^c :		
Titration 1 (Visit 4)	55 (93)	55 (93)
Titration 2 (Visit 5)	54 (92)	54 (92)
Titration 3 (Visit 6)	53 (90)	47 (80)
Plateau 1 (Visit 7)	45 (76)	41 (69)
Plateau 2 (Visit 8)	38 (64)	38 (64)

a Patients who received at least one dose of study medication.

b Number of patients who completed the study according to the investigator's definition of study completion. Note: Due to an administrative error, 6 patients were considered to have completed the study after completion of the first two weeks of the Plateau Phase and are noted as completers in this table.

c Number of patients who were on study at each visit.

Note: The relative study day windows for each visit are summarized detail in Section 5.6 (Statistical Methods).

Note: Percents are based on the number of treated patients in each group.

Patient Demographics

No significant differences were observed between the two treatment groups for demographic characteristics. The patients were aged 15 to 69. The ratio of males to females and the proportion of patients with Frankel ratings of A, B, or C were comparable between the two treatment groups. The majority of patients were male, white, with a Frankel rating of A. The cause and duration of spinal cord injury were also comparable between the two treatment groups.

Study Drug Administration

No clinically meaningful difference was observed between the tizanidine and placebo groups for the average duration of exposure to treatment. In the all treated patient population, patients were exposed to tizanidine for an average of 45.6 days and placebo for an average of 48.0 days. Additionally, no meaningful difference was observed between the two treatment groups for the average duration of the Plateau Phase. In the all treated patient population, the average duration of the Plateau Phase was 25.1 days for the tizanidine-treated patients and 25.7 days for the placebo-treated patients.

No differences were seen between the two treatment groups for the average daily dose of study medication taken during the Titration Phase or during the Plateau Phase. During the Titration Phase, the average daily doses of study medication were 19.4 mg/day in the tizanidine group and 20.1 mg/day in the placebo group. During the Plateau Phase, the average daily dose of study medication was 31.1 mg/day in the tizanidine group and 33.4 mg/day in the placebo group.

Statistical Methods

Two datasets were defined for efficacy analyses. The first dataset, called the "all treated" dataset, included all patients who received blinded study drug. The second dataset, termed the "evaluable" dataset, included those patients who met all criteria.

Centers with 3 or fewer evaluable patients per treatment group were pooled, pairwise largest (based on the total number of evaluable patients) with smallest among this set, until at least 4 evaluable patients per treatment group were obtained.

The scores obtained for each of the 6 muscle groups evaluated for muscle tone were summed to obtain the total Ashworth score (range from 0 to 24).

Sponsor's Efficacy Results

The primary outcome criteria included the mean scores in muscle tone as measured by the Ashworth scale and Pendulum Test.

Tizanidine produced significantly ($p < 0.0001$) greater decreases in muscle tone, based on the Ashworth score across six muscle groups, from baseline to the end of titration, end of plateau and endpoint, as compared with placebo. Additionally, for all treated patients, the proportion of patients who improved (defined as decrease from baseline in total Ashworth score) were significantly ($p < 0.05$) higher in the tizanidine group than in the placebo group at the end of titration (T3, Visit 6), end of plateau (P2, Visit 8) and endpoint (P).

Table 10 (vol 41, pg 342)

Mean Scores and Changes form Baseline in Muscle Tone (Total Ashworth Score) by Visit and Treatment Group - All Treated Patients	Treatment Group		
	Placebo	Tizanidine	p-value ^a
Baseline (B Visit 3)			
N	59	59	
Visit Mean	10.71	11.83	0.1841
End of Titration (T3, Visit 6)			
N	50	47	
Visit Mean	10.48	8.11	
Change from Baseline			
Mean	0.30	-3.70	<0.0001
S.D.	3.15	4.60	
End of Plateau (P2, Visit 8)			
N	38	37	
Visit Mean	10.11	7.57	
Change from Baseline			
Mean	-0.55	-4.35	<0.0001
S.D.	3.63	3.98	
Endpoint (EP)^b			
N	55	49	
Visit Mean	10.25	7.47	
Change from Baseline			
Mean	-0.44	-4.41	<0.0001
S.D.	3.55	4.01	

A p-values for between treatment group comparisons from ANOVA F-test.

b Last visit while on, or at the end of study medication prior to taper.

Note: Total Ashworth muscle tone score ranged from 0 to 24.

For all treated patients, the proportion of patients who achieved improvement was significantly ($p < 0.05$) higher in the tizanidine group than in the placebo group at the end of titration (T3, Visit 6), end of plateau (P2, Visit 8) and endpoint.

Subset analyses of the proportion of patients who achieved improvement in muscle tone suggest that gender, ethnicity, and duration of spinal cord injury had no influence on the therapeutic effect of tizanidine. The results suggest that younger patients and severely spastic patients may be more responsive to tizanidine than older or less spastic patients.

As the data for daily count of spasms were not normally distributed, the data were transformed to a response ratio scale which had a more normal distribution. At all visits, there were greater reductions in the frequency of daytime spasms as indicated by the response ratios (negative or lower ratio is better) in the tizanidine group as compared with the placebo group at all visits. The analysis of variance used to test for treatment differences in the mean response ratios for the average daily count of daytime spasms showed significance at the end of the first (T1, Visit 4, $p = 0.0038$), second (T2, Visit 5, $p = 0.0005$) and third weeks of titration (T3, Visit 6, $p = 0.0097$) and at the end of the first two weeks of plateau (P1, Visit 7, $p = 0.0026$). At the end of the plateau (P2, Visit 8), the frequency of daytime spasms in the tizanidine group were no longer significantly different from placebo. The differences seen between the two treatment groups in the mean response ratios for the average daily count of daytime spasms were significant at the end of the first (Visit 4, $p = 0.0038$), second (Visit 5, $p = 0.0097$) and at the end of the first two weeks of plateau (Visit 7, $p = 0.0026$). At the end of plateau (Visit 8), although the frequency of daytime spasms in the tizanidine group continued to decrease at a greater rate than in the placebo group, the differences between the treatments was not significant. By the end of the Plateau Phase, the average daily count of daytime spasms in the tizanidine group was reduced by nearly 50% that at baseline.

Response Ratios of the Average Daily Count of Daytime Spasms by Visit and Treatment Group - All Treated Patients	Treatment Group		
	Placebo	Tizanidine	p-value ^a
Response Ratio:			
Titration 1 (T1, Visit 4)			
N	56	56	
Visit Mean	61.24	24.16	
Response Ratio:			
Mean	-0.06	-0.17	0.0038
S.D.	0.22	0.17	
Median	-0.08	-0.15	
Titration 3 (T3, Visit 6)			
N	51	49	
Visit Mean	45.35	21.65	
Response Ratio:			
Mean	-0.09	-0.25	0.0005
S.D.	0.34	0.29	
Median	-0.04	-0.29	
Plateau 1 (P1, Visit 7)			
N	50	45	
Visit Mean	32.50	19.82	
Response Ratio:			
Mean	-0.05	-0.28	0.0026
S.D.	0.37	0.32	
Median	-0.03	-0.36	
Plateau 2 (P2, Visit 8)			
N	45	39	
Visit Mean	43.37	18.34	
Response Ratio:			
Mean	-0.17	-0.28	0.3445
S.D.	0.38	0.33	
Median	-0.12	-0.33	
Endpoint (EP)^b			
N	58	56	
Visit Mean	47.12	22.57	
Response Ratio:			
Mean	-0.13	-0.21	0.1902
S.D.	0.34	0.30	
Median	-0.12	-0.22	

There were no differences between the two treatment groups with regard to the mean change from baseline in muscle strength. The majority of patients in both groups had no change in muscle strength from baseline to any timepoint throughout the study.

The global evaluations of spasticity and functional capacity (rated on a scale of 1 to 10 at baseline and endpoint by a physical therapist and patient) were not sensitive to any changes in patient status. However, when the activities of daily living (ADL) were assessed, the increases in mean scores in the tizanidine group were greater than in the placebo group throughout the study. These differences were attributed to increases in a minority of patients in the tizanidine group, as the majority of patients had no change from baseline in their ADL Assessment scores.

Significant differences in favor of tizanidine were also observed between the two treatment groups for the change from baseline in the median degrees of angular displacement of the right leg (first swing) during the Pendulum Test at the end of titration, end of plateau and endpoint using the rank analysis test ($p=0.0135$, $p=0.0401$ and $p=0.0038$, respectively).

9.0 Summary

EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSES
Change from baseline in total Ashworth Score	F test (ANOVA) baseline-end of plateau ($p=.0001$)
Proportion of patients with improvement from baseline in muscle tone	Mantel-Haenszel (T3 Visit 6)(P2Visit 8) endpoint ($p=.05$)
Change from baseline frequency of spasm	Response Ratio T1,T2,T3,P1 ($p=0.0026$)
Mean changes from baseline muscle strength	NS

2° Efficacy Variable	
Change from baseline deep tendon reflex & clonus	NS
Pain & disability due to muscle spasm	NS
ADL-modified Klein-Bell	NS
Global evaluation of spasticity: Therapist\patient	NS\NS

This study provides statistically significant evidence of the effect of tizanidine in the treatment of spasticity of spinal cord origin. The study was well conducted and yielded significant results for the prospectively defined primary outcome measures of spasticity as assessed by the Ashworth score and frequency of muscle spasms throughout the plateau phase. It is notable, however, that the global scores were not sensitive to these effects.

10.00 Summary

The sponsor identified the preceding three studies as pivotal in establishing the efficacy of tizanidine in spasticity of spinal cord origin. The sponsor performed an integrated review of efficacy across the three primary efficacy trials based on change from baseline in total Ashworth score, percent of patients with improvement in Ashworth score, change from baseline in daytime count of spasms and clonus, and change from baseline in muscle strength. Global assessments of efficacy and tolerability differed for the three trials and therefore could not be pooled for analysis. Where pooling of data across studies was considered appropriate, treatment comparisons were carried out for baseline, first plateau visit and endpoint.

Within each of the three primary efficacy trials, there were no significant differences between the tizanidine and placebo groups with respect to demographic variables and spasticity at baseline. More than 60% of the patients enrolled in the two MS trials were female, while nearly 90% of the patients enrolled in the spinal cord study were male. The spinal cord injury patients were generally 10 years younger than the MS patients. Among the MS patients (n=407), 47% had an Ashworth score of 1-2 for their most severely affected muscle group at baseline, 43% had a score of 3, and 9% had a score of 4. Among the spinal cord injury patients (n=118), 39% had an Ashworth score of 2 for their most severely affected muscle group at baseline, 52% had a score of 3, and 9%

had a score of 4. The majority of spinal cord injury patients (56%) had a Frankel rating of A, 24% had a rating of B, and 19% had a rating of C.

TABLE 8- Mean and Mean Change from Baseline in Total Ashworth Score In Study DS0502, decreases from baseline in total Ashworth score, indicating improvement in spasticity, were significantly greater for the tizanidine group than for the placebo group at the first plateau visit ($p=0.0017$) and at endpoint ($p=0.0072$). In Study 021-001, there were no significant differences between tizanidine and placebo in the change from baseline in total Ashworth score. In Study 021-003, decreases from baseline in total Ashworth score were significantly greater for the tizanidine group than for the placebo group both at the end of titration ($p=0.0001$) and at endpoint ($p=0.0001$). The 95% confidence intervals for the change from baseline in total Ashworth score at endpoint are displayed by treatment group for each of the three studies in Figure 1.

TABLE 9-Number and Percent of Patients with Improvement in muscle tone (Ashworth). The results are consistent with those observed for change from baseline in total Ashworth score. In Studies DS0502 and 021-003, the rate of improvement at endpoint was significantly greater for patients in the tizanidine group ($p=0.003$ and 0.0253 , respectively) than for those in the placebo group, while no significant difference between tizanidine and placebo was observed in Study 021-001. When the results from the three studies were combined, 65% of patients in the tizanidine group were improved at endpoint compared to 35% who were not improved or not assessed, while 53% of patients in the placebo group were improved and 47% were not improved or assessed. The percent of patients with improvement in Ashworth score at endpoint is displayed by treatment group for the three studies separately and combined in Figure 2.

TABLE 10-Mean Daily Count of Spasms and Clonus and Mean Response Ratio Mean daily counts of spasms and clonus at baseline are shown by treatment group in Table 10 along with effects of study medication displayed as a response ratio relative to baseline. A decrease in counts relative to baseline was observed for both treatment groups in each of the studies (021-001 and 021-003) with greater decreases in the tizanidine group than in the placebo for both studies. In Study 021-001, the difference between tizanidine and placebo was not significant at the first plateau visit, but reached significance at endpoint ($p=0.0346$). In Study 021-003, differences between tizanidine and placebo were significant at the first plateau visit ($p=0.0026$) but were no longer significant at endpoint ($p=0.1902$). Between treatment comparisons for the combined data indicated a significant difference favoring tizanidine over placebo at the first plateau visit ($p=0.026$) and at endpoint ($p=0.0077$). The 95% confidence intervals for the response ratio at endpoint are displayed by treatment group for the two studies separately and combined in Figure 3.

TABLE 12-Mean Change from Baseline in Total Ashworth Score for Three Lower Body Muscle Groups. The change from baseline in Ashworth Score based on a subtotal of the three lower body muscle groups common to all three primary efficacy trials (knee extensors, knee flexors, and hip adductors) was compared for all placebo- and tizanidine-treated patients. A favorable effect of tizanidine was observed in Study DS0502, while the changes induced by tizanidine in Study 021-001 were less than those observed for placebo. When the data from the three studies were combined, the lower body Ashworth scores for the two treatment groups were shown to be comparable at baseline. At the first plateau visit, the mean decrease from baseline was greater for patients receiving tizanidine than for those receiving placebo; however, the difference was not significant ($p=0.2028$). At endpoint, the difference between the two treatment groups was significant ($p=0.0099$). A two-way ANOVA model with terms for study, treatment, and study by treatment interaction was fitted to the changes from baseline for the pooled data at each visit. At endpoint, there was a significant treatment by study interaction ($p=0.0001$) due to the difference in the results observed for Study 021-001 v. Studies DS0502 and 021-003; there was no evidence of a treatment by study interaction for the Plateau 1 data. The 95% confidence intervals for the change from baseline in lower body Ashworth score at endpoint are displayed by treatment group for each of the three studies separately and combined in Figure 5.

TABLE 14-Mean Change from Baseline in Lower Body Ashworth Score by Population Subset in Combined Primary Efficacy Trials First Plateau Visit and Endpoint

At Endpoint, between treatment comparisons were statistically significant for males ($p=0.0514$) and for patients <40 years ($p=0.0018$). These findings probably reflect the highly significant results in spinal cord injury patients, most of whom were younger males. A significant difference between tizanidine and placebo was observed among patients whose lower body Ashworth score at baseline was above the median for the population ($p=0.01$). Within this subgroup, the mean change from baseline observed for tizanidine patients (-3.08) was almost twice that observed for placebo patients (-1.64). For patients whose lower body Ashworth score at baseline was below the median, the changes from baseline were much smaller (-0.84 TIZ; -0.38 PBO).

The sponsor's analysis suggests that these findings may in part explain the failure to demonstrate a significant effect of tizanidine on total Ashworth score in Study 021-001. The mean baseline Ashworth scores (12.99 TIZ; 14.95 PBO) were lower than those in Study DS0502, also in MS patients (18.47 TIZ; 16.84 PBO). Also, the placebo effect on change from baseline in total Ashworth score was greater in Study 021-001 than in either of the other two efficacy studies. A significant

reduction in daily counts of spasm relative to placebo was observed for tizanidine patients in Study 021-001, yet no improvement in Ashworth score was demonstrated.

The sponsor also suggests that time of evaluation relative to dosing may have diminished the change in Ashworth score. To this end, the time of the last dose received prior to study evaluations at the endpoint visit was collected for 120 patients treated in the study (57PBO; 63 TIZ). For tizanidine patients who received their last dose of study medication less than 3 hours prior to evaluation (n=29), the mean change from baseline in total Ashworth score at endpoint was -3.69, while those who were dosed >3 hours prior to evaluation (n=34) had a mean change from baseline at endpoint of -0.12. In contrast, for placebo patients who received their last dose of study medication less than 3 hours prior to evaluation (n=26), the mean change from baseline in Ashworth score (-4.50) was similar to that of patients who were dosed >3 hours prior to evaluation (-3.81; n=31). The action of tizanidine on Ashworth score was measurable at peak plasma levels in these patients; however, there is no explanation for the large placebo response in Study 021-001.

The dose-response relationship for tizanidine with respect to antispastic efficacy was evaluated based on the pooled efficacy data from all tizanidine treated patients in the three primary efficacy studies. Correlation analyses were performed for change from baseline in Ashworth score for the three lower body muscle groups common to all three studies and for the response ratio relative to baseline in daytime counts of spasms and clonus (Studies 021-001 and 021-003 only) v. estimated dose in mg. There were no correlations found between the mg dose of tizanidine and either change from baseline in lower body Ashworth score or response ratio for daily counts of spasm and clonus.

The average plateau dose for all tizanidine-treated patients in the three primary efficacy studies combined was 26.5 mg (0.40 mg/kg). The average plateau dose for patients with improvement in Ashworth score and/or daytime counts of spasms was 26.8 mg (0.40 mg/kg). Among the patients with improvement in these efficacy parameters, the interquartile range (25th to 75th percentile) of tizanidine plateau doses was 19.3 to 35.1 mg. The efficacy of tizanidine in these studies was demonstrated at daily doses of 19mg or greater for the majority of patients who responded to treatment.

The Sandoz-sponsored trial DS-0502 demonstrated statistical significance for the primary efficacy parameter change from baseline in total Ashworth scale, lower extremity muscle tone and proportion of patients with improvement in muscle tone. There was no significant result demonstrated for frequency of muscle spasm nor for physician/patient global. Study 021-001 was essentially a negative study, the only positive contrast being an endpoint p-value of p=0.053 for the response

ratio for frequency of spasm and a physician prescriber/patient global. A large placebo response is the only explanation for the study outcome. Study 021-003 has statistically significant results for the Ashworth score, the proportion of patients with improvement in muscle tone, and spasm frequency. Physician and patient globals were negative. It appears that it is easier to show a difference in a spinal cord population, as the spasticity is more purely spinal in origin than that of MS which probably has supraspinal contribution. All three studies were negative regarding change in muscle strength, which suggests that tizanidine does not have a weakening effect on spastic muscles.

11.0 Supportive Placebo-Controlled Trials

11.1 Study S-1 LaPierre Y. Double-blind study comparison between tizanidine and placebo in patients with spasticity related to multiple sclerosis. Montreal. May 1987 (Sandoz)

This was a double-blind, parallel, placebo-controlled study to assess the efficacy and safety of tizanidine in patients suffering from spasticity due to multiple sclerosis.

Patients included in the study were male or female outpatients, aged between 18 and 60 years, with a confirmed diagnosis of multiple sclerosis with at least a moderate degree of spasticity, severe enough to interfere with functional performance in daily life. Their spasticity had to have been stable for at least two months prior to the study. In the tizanidine group, duration of M.S. was 15.2 ± 1.2 years, and the duration of spasticity was 7.7 ± 0.7 year (both means). In the placebo group, the duration of M.S. was 11.6 ± 1.3 years; that of spasticity was 6.4 ± 0.8 years (means).

The study had a 10-week duration with 2 phases: 1) a 2-week washout period during which patients who were already treated for spasticity had their antispastic medication withdrawn; and 2) an 8-week active treatment period including a 3-week dose titration and a 5-week dose maintenance period. Patients under regular physiotherapy prior to beginning the study were permitted to continue without any change during the trial. At the study's conclusion, patients had the option of continuing treatment with tizanidine for up to one year.

Treatment was initiated with 2 mg tizanidine for the first day, and 6 mg/day on the second to fifth days (t.i.d.). Thereafter the dose was increased by 6 mg at 4-day intervals until the patient's spasticity was satisfactorily controlled or intolerable side effects appeared, or to a maximum dose of 32 mg/day (q.i.d.) The equivalent number of capsules was given to the placebo group. The mean daily dose of tizanidine was 18.4 ± 1.2 mg, and of placebo was 22.5 ± 1.2 mg, a difference that was statistically significant.

Three types of assessments were used in the study:

1. Assessment of overall neurological status. This was done to determine the record of the course of muscle sclerosis throughout the study and the effect of treatment on the neurological functions of the patient. The Kurtzke neurological status and clinical neurological examinations were used.
2. Assessment of efficacy. This was done to determine the specific effects of treatment on spasticity due to M.S. The Kurtzke and Hauser indices for functional disability, neurological evaluations for limb weakness, muscle tone and stretch reflexes were performed. Electrophysiological and overall evaluations by the investigator were also done.
3. Assessment of safety and tolerability. Physical examination, vital signs, laboratory screening, ophthalmological examinations and side effects reporting were performed.

Assessments were made by one of the four neurologists in the study.

A primary outcome was not specified prospectively in the protocol. However, the study report states that the parameters limb power and tone, deep tendon reflexes and functional disability score were used for the assessment of efficacy, whereas cerebral functions, sensory functions, vision and brainstem functions were assessed for completeness of the neurological exam and for screening of possible drug effects on the other CNS functions. These were also used as control of the natural course and activity of MS during the study.

Only data for completers was used in the analysis of efficacy. When muscle tone, strength and deep tendon reflexes were analyzed, patients with normal scores at baseline through day 56 for a given muscle group were excluded from that analysis. These exclusions were carried through to the total scores, so that each patient was variably represented in these totals.

Results

Patient Disposition

Sixty-six patients enrolled in the study and 59 completed it. Four patients on tizanidine withdrew because of lack of efficacy and/or unwanted effects (stiffness, gait instability, dry mouth) and one dropped out because of a relapse of M.S. Two placebo patients dropped out because of intercurrent illness and unwanted effects (weakness, shortness of breath).

Patient #		Treatment Duration	Reason for Discontinuation
Sirdalud	Placebo		
#8		2 weeks	Lack of efficacy-side effects: stiffness, spasms
#19		2 weeks	Relapse of M.S.
#24		3½ weeks	Side effects: stiffness
	#26	5½ weeks	Intercurrent illness: seizure
#40		3½ weeks	Side effects: gait instability
	#51	7 weeks	Side effects: weakness, shortness of breath
#52		5 weeks	Lack of efficacy - Side effects: dry mouth

Patient Demographics

Both treatment groups were comparable with regard to all demographic parameters. Fifty percent of patients were females in each treatment group. Mean age was 47 with range 27-56 in the tizanidine group and 44 years with range 22-55 in the placebo group. History of multiple sclerosis in the two treatment groups was comparable: disease duration was 12 (placebo) to fifteen (tizanidine) years. Spastic paraparesis was the chief complaint for all patients (91% tizanidine; 97% placebo). The history of spasticity is described in sponsor's table IV. Patients had had spasticity for 6 to 8 years, which was moderate (66% in tizanidine and 61% in placebo) to severe (25% in tizanidine and 33% in placebo) and mainly located in the legs (88% in tizanidine and 84% in placebo). Most patients had been previously treated with baclofen (48% in tizanidine and 76% in placebo; $p < 0.05$ between the two groups) or had not been on any antispastic medication previously (52% in tizanidine and 24% in placebo; $p < 0.05$ between the two groups). In most patients the disease was classified as relapsing progressive (35% in tizanidine and 30% in placebo) or chronic progressive (45% in tizanidine and 58% in placebo).

At the end of the maintenance phase (day 56), the mean daily dosage was 18.4 ± 1.2 mg of tizanidine (range 4 to 24 mg) and 22.5 ± 1.2 mg of placebo (range 6 to 32 mg). The difference between the doses of each treatment group was statistically significant ($p < 0.05$). Most patients were receiving a daily dose of 24mg (46% of tizanidine and 57% of patients on placebo).

Efficacy Assessment

Efficacy was assessed in terms of functional assessment, limb tone, limb weakness, alteration of stretch reflexes, and electrophysiology.

Sponsor's Table 15 shows the means for total limb tone, deep tendon reflexes and limb weakness at baseline and after 10, 21, and 56 days of treatment with tizanidine or placebo. The improvements in overall limb tone and deep tendon reflexes with tizanidine were significantly greater than those observed with placebo. The mean baseline scores for total limb tone differed significantly between the treatment groups ($p = 0.015$; Wilcoxon test). The mean improvement in total limb tone from baseline at Day 56 was statistically larger in the tizanidine group than in the placebo group ($p < 0.05$; Welsh nonparametric test). Also, the mean deep tendon reflex at Day 56 was significantly lower in the tizanidine group than in the placebo group ($p = 0.006$; Wilcoxon test).

Treatment with tizanidine also resulted in a statistically significant decrease in the severity of ankle clonus ($p < 0.05$; Tukey's pairwise comparison) [9.5% improvement v. 0% change in placebo group]. The number of patients with ankle clonus who exhibited an improvement (10/23, or 36%) was significantly greater than the number of placebo patients with improved clonus [4/30, or 13%] ($p = 0.001$; Wilcoxon test). There were no significant differences in the rated limb weakness scores between the tizanidine and placebo groups.

The improvements in muscle tone, stretch reflexes and clonus with tizanidine were not accompanied by significant changes in functional disability scores. Sponsor's Table X presents descriptive statistics for **Functional Disability** assessment scores. The upper extremity index reflecting the ability to write and eat, and the ambulation index based on the ability to walk, were improved in the group treated with tizanidine, whereas disability status remained unchanged. No change was observed in the placebo group in any of these variables. No statistical significance was found within and between groups.

	SIRDALUD			PLACEBO		
	Day 0	Day 56	Change from baseline ▲	Day 0	Day 56	Change from baseline ▲
Disability Status	5.07±0.29	5.07±0.28	0.00	4.90±0.34	4.90±0.34	0.00
Ambulation Index	4.22±0.40	4.11±0.41	0.11	4.61±0.43	4.61±0.44	0.00
Upper extremity Index	0.52±0.14	0.48±0.14	0.04	0.52±0.14	0.52±0.14	0.00

Table Xa shows the total number of patients in whom a change in functional disability was observed during the treatment. Five patients in the tizanidine group and two patients in the placebo group had an improvement in either their disability status, ambulation or upper extremity index, whereas a deterioration was observed in the ambulation index of one patient treated with tizanidine and two patients on placebo.

Index	SIRDALUD		PLACEBO	
	Improvement	Deterioration	Improvement	Deterioration
Disability Status	1	1	0	0
Ambulation	3	1	2	2
Upper extremity	1	0	0	0
TOTAL	5	1	2	2

According to the neurological status assessment, there was no significant difference between groups in cerebral and brainstem parameters, cerebellar function, sensory parameters, and Kurtzke parameters, suggesting that the two treatments had no effects on general neurological functioning of the patients.

Limb Tone

The evaluation of limb tone was assessed at each visit on 11 parameters (right and left sides) and on the total score with the following rating scale:

- 0 = No movement
- 1 = Severely spastic
- 2 = Moderate increase of spasticity
- 3 = Slight increase of spasticity
- 4 = Normal

(It should be noted that this scale is the inverse of the Ashworth scale where 0=no increase in tone and 4 indicates limb rigid.)

While the tizanidine group demonstrated significant improvement within treatment group in seven muscle groups, significant difference between groups was found only in right ankle dorsiflexion and the total score ($p=0.015$) at day 56, with mean values of 23.8 for tizanidine and 29.9 for placebo.

Stretch Reflexes

Clonus was examined in the knee and ankle. There was a statistically significant difference in the frequency of ankle clonus between the two groups in favor of tizanidine. In the rating of severity of clonus, clonus in the ankles was improved in the tizanidine group, but there was no statistically significant difference between the two groups.

Electrophysiological Evaluation

No statistically significant differences between the two treatment groups were observed with regard to the H max/M max ratio, the H rest/H Jendrassick ratio or the H 120/150 ratio. The F wave amplitude /M max ratio on the left side was significantly more improved ($p < 0.05$) in the placebo than in the tizanidine group. A statistically significant difference was also found in favor of the placebo group with regard to the H rest/H vibration 120 Hz ratio on the right side.

Global Evaluation

At the study's conclusion, overall evaluation of tizanidine and placebo was assessed by both the physician and the patient. The rating scale and frequency distributions are presented in sponsor's Table 2.15.1. A log-likelihood ratio test was performed to compare the groups. Significant difference was found for both physician ($p=0.035$) and patient ($p=0.022$) tolerance. Patients and investigators considered tolerance to be good to excellent in 85% of the patients on placebo as compared to 60% for tizanidine. A significant difference ($p=0.033$) was also found for physician's rating of treatment relative to the previous treatment. Thirty-three percent of the tizanidine patients found the pre-trial therapy better, compared to 12% for placebo. The investigator judged the overall evaluation as good to excellent in 27% of the tizanidine patients and 10% of placebo patients. The corresponding values of the patients's own overall evaluation were 22% and 19%, respectively.

TABLE XIX

VARIABLE	EVALUATION	PHYSICIAN'S ASSESSMENT			PATIENT'S ASSESSMENT		
		SURDALLUD n (%)	PLACEBO n (%)	COMPARISON BETWEEN GROUPS (P value)	SURDALLUD n (%)	PLACEBO	COMPARISON BETWEEN GROUPS (p value)
Antispasmodic Efficacy	Excellent	1 (4)	0 (0)	0.003	2 (7)	1 (3)	0.582
	Good	6 (23)	3 (10)		4 (15)	5 (16)	
	Fair	11 (42)	8 (28)		10 (37)	8 (25)	
	Poor	8 (31)	18 (62)		11 (41)	18 (56)	
Toleranc	Excellent	10 (36)	23 (72)	0.035*	8 (30)	22 (69)	0.022*
	Good	4 (15)	4 (13)		8 (30)	5 (16)	
	Fair	10 (39)	3 (9)		8 (30)	3 (9)	
	Poor	2 (8)	2 (6)		3 (10)	2 (6)	
Comparisons to previous treatment	Better	5 (33)	2 (12)	0.033*	8 (47)	4 (19)	0.166
	Equal	30 (67)	11 (66)		7 (41)	12 (57)	
	Worse	0 (0)	4 (23)		2 (12)	5 (24)	

Summary

EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSES
Change from baseline in limb tone R Ankle dorsiflexion, total score	Wilcoxon $p=0.015$ Day 56
Change from baseline stretch reflexes Ankle reflex (L); total DTR	$p < 0.05$; $p \leq 0.01$ Wilcoxon
Frequency of Clonus: Ankle	$p < 0.01$
Mean change from baseline Limb Weakness	NS

2° EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSES	
Functional Disability: Disability Status	NS	
Ambulation Index	NS	
Upper Extremity Index	NS	
Electrophysiological Index	NS	
Global:	Physician	Patient
Antispastic Efficacy	.083	0.582
Tolerance	.035*	.022*
Comparison to previous Rx	.033 *	.166

The efficacy of tizanidine was evaluated in terms of functional assessment, limb tone, limb weakness, alteration of stretch reflexes, and electrophysiology. In functional abilities, there was no statistical significance within and between groups. Regarding limb tone, comparison between treatment groups showed a significant difference only in ankle dorsiflexion and total limb tone in favor of tizanidine. There were no significant between group contrasts for limb weakness. Change from baseline stretch reflexes showed a significant contrast for left ankle reflex and total deep tendon reflexes; frequency of clonus was significant only at the ankle.

However, global evaluation performed by the investigators demonstrated efficacy in 69% of patients on tizanidine and 38% on placebo ($p=0.08$), while 59% and 44% of

patients considered tizanidine and placebo as efficacious, respectively. Tizanidine was considered moderately to excellently tolerated in 90-92% of patients by both the investigators and the patients.

Comment

Although the statistical analysis of this study found several significant differences between the tizanidine and placebo groups, these differences can only be viewed as qualitative. There was no primary outcome designated prospectively. There were baseline differences for limb tone which were unadjusted. Only data for completers was used in the analysis of efficacy. When muscle tone, strength, and deep tendon reflexes were analyzed, patients with normal scores at baseline through Day 56 for a given muscle group were excluded from that analysis. These exclusions were carried through to the total scores, so that each patient was variably represented in these totals. The actual differences between tizanidine and placebo were such a small magnitude as to be clinically insignificant.

This study may provide some evidence of efficacy of tizanidine, as the primary outcome of total limb tone showed a significant difference in favor of tizanidine. However, the magnitude of effect is small and not supported by the individual parameters which comprise the total.

11.2 U.K.Rinne. A comparative trial of DS103-282 and placebo in patients with spasticity due to multiple sclerosis or chronic myelopathy. Turku, Finland. May 1980

31 patients (18 females, 13 males, between 18 and 66 years) 20 with multiple sclerosis, 11 with chronic myelopathy (7-chronic myelopathy, 2-tetraparesis spastica, 2-amyotrophic lateral sclerosis), were treated in a double-blind cross-over study comparing tizanidine with placebo. The study was 8 weeks, 4 weeks of active treatment and 4 weeks of placebo. There was no wash-out period between treatment phases. For 16 patients, the initial treatment was tizanidine. Patients were titrated up to a maximum daily dose of 18 mg taken in 3 divided doses. A primary outcome was not specified prospectively in the study protocol, although it is stated the main clinical features will include spasticity, spasms, and clonus. Assessments included the Ashworth spasticity scale and the Northwestern University Disability Scale, as well as a physician and patient global.

32 patients were randomized to therapy; however, there was one premature discontinuation after 3 days of treatment with tizanidine due to severe weakness in the lower legs. This patient was not included in the evaluation, as only baseline values were available. Mean age of the patients was 44 years; there were 18 females and 13 males. Type of spasticity was spinal in 16 patients, cerebral in 6, and localization not evaluable in 9. Spasticity was localized to the upper extremity (1-right sided, 3-left sided, 10-bilateral) or to the lower extremity (right sided-2, left sided-1, 27-bilateral).

Duration of symptoms was 2 > 1 year and 29 > 2 years. Regarding previous therapy, 17 had had none, 13 had previous treatment, and there was no data for one patient.

Fifteen patients suffered from spasticity in the lower limbs and 16 from spasticity in the upper and lower limbs. Spasticity was severe in 19 patients, moderate in 10 and mild in 2. Nine patients were non-ambulatory and the rest could walk with various degrees of difficulty.

Results

Spasticity was measured using the Ashworth Scale and functional disability was rated using the Northwestern Disability Scale at baseline and at 2-week intervals throughout the study. Global assessments of efficacy were made by the physician and patient at the end of each treatment period.

Ashworth Scale

The investigator states in the study report: "This scale seems to be not sensitive enough; only for a very few patients a change in the symptomatology could be found".

<u>Spasticity</u>	<u>No Change</u>	<u>TIZ > PBO</u>	<u>TIZ < PBO</u>
upper extr R	30	1	-
L	30	1	-
lower extr R	20	7	4
L	19	8	4
<u>Reflexes</u>			
upper extr R	31	-	-
L	31	-	-
lower extr R	29	2	-
L	28	3	-
Ankle Clonus R	26	3	2
L	27	3	1
Mobility	30	1	-

Again, for the Northwestern University Disability Scale (NUDS), the investigator states in his study report "Again this scale is not sensitive enough; only a few patients had changes in the symptomatology. A statistical analysis is not meaningful."

<u>Item</u>	<u>No Change</u>	<u>TIZ > PBO</u>
Walking	24	7
Dressing	30	1
Hygiene	31	-
Eating	31	-
Feeding	29	1
Speech	31	

The subjective assessment by investigator, patient and nurse was in favor of tizanidine (2 p < 0.05; the overall efficacy showed a "slight improvement" for tizanidine in 9 patients (2 patients with placebo) and a "moderate improvement" for tizanidine in 4 patients (0 PBO). No change in 18 TIZ, 27 PBO, 2 deterioration with PBO.

After 4 weeks of treatment with tizanidine or placebo there were no noticeable changes in the functional performance. Spasticity of the lower limbs was reduced in 5 out of 15 patients

SUMMARY

EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSES
Change from baseline limb tone Ashworth Scale	NS
Northwestern University Disability Scale	NS
Global: Investigator	2p < 0.01
Patient	2p < 0.05
Nurse	2p < 0.01

Comment

This study does not provide evidence of efficacy of tizanidine in MS patients with spasticity. A primary outcome was not specified in the protocol; the data collected for the Ashworth and NUDS score showed no statistically significant change for tizanidine treatment. The trial was reported in insufficient detail to assess the design and conduct of the study. The crossover design was flawed due to lack of a washout between the two treatment periods and no titration phase. The patient sample was a mixed population with severe spasticity (9 nonambulatory) including myelopathies as well as MS. The maximum dose was limited to 18mg; the outcome may have been improved if larger doses were permitted.

12.0 Clinical Effectiveness of Long-Term Tizanidine Therapy

The results of Athena- and Sandoz-sponsored trials involving a total of 313 tizanidine-treated patients indicate that the effectiveness of tizanidine in chronic spasticity is maintained over long-term therapy.

12.1 Study 021-002: Athena-Sponsored Long-term extension Trial

Study 021-002 is an open extension trial of long-term tizanidine therapy in patients with spasticity secondary to MS which is yet in progress. (Note: No data will be reported for Open-label Study 021-004, a follow-on to Study 021-003, as enrollment had just begun at the time of data cut-off). Patients enrolled in Study 021-001 were eligible to enroll in Study 021-002 if they had successfully completed Study 021-001 or if they were withdrawn due to insufficient therapeutic effect after week 5. In order to protect the study blind, patients were to undergo tapering of double-blind study medication in Study 021-001 prior to enrollment in Study 021-002. All patients enrolled in Study 021-002 were then re-titrated to a maximum tolerated dose up to 36 mg daily. During the plateau phase, antispastic efficacy (change from baseline in Ashworth score) was evaluated at months 1, 4, 8, and 12 and at endpoint (last visit prior to tapering and discontinuation of study medication). Baseline data were collected prior to dose titration.

161 patients from Study 021-001 were enrolled in Study 021-002. Of these, 73 patients had received tizanidine in Study 021-001 and 88 had received placebo. As of August 16, 1993, 112 patients were still receiving tizanidine in Study 021-002. For all patients treated, the median duration of therapy as of the clinical cut-off date was 134 days. The median tizanidine dose was 28 mg/day.

Significant decreases from baseline in total Ashworth score were observed at Months 1, 4, 8, and at endpoint (Sponsor's Table 24). A nonsignificant decrease was observed at Month 12. To account for differences in the numbers of patients evaluated at each successive visit, separate cohort analyses were performed for the subset of patients who had data available up to Months 1, 4, 8, or 12. Decreases from baseline were observed within 1 month after the end of titration and were maintained for up to 8 months of therapy. Results for the 8 month cohort (n=43, or one fourth of the 161 total patients) are included in Table 24. For the subset of patients who completed 12 months of therapy, the changes from baseline in Ashworth score were not significant at any timepoint, however, the number of patients in this subset (n=15) is very small.

12.2 Sandoz-Sponsored Supportive Long-Term Trials

Eight Sandoz-sponsored trials examined the long-term efficacy and safety of tizanidine in patients with chronic spasticity (Table 25). Three of the trials were open-label extensions of double-blind, active-controlled trials (S-16A; S-26; S-86); four were primary long term open-label trials (S-24; S-25; S-27; S-28). Study S-16B was an extension of a 6-week comparative trial with baclofen (S-16); 20 of the original 33 patients who participated in the double-blind study (9 tizanidine; 11 baclofen) received open-label treatment with tizanidine for 12 months. Eight of the 14 patients enrolled in the 36-month open-label study S-26 had previously participated in a 1-week double-blind comparison of tizanidine and diazepam (S-40). Results of this open extension trial are presented in three reports: one reporting the findings after one year of treatment in 12 patients; one reporting results over two years of treatment in 11 patients (9 of whom were also included in the one-year report plus 2 patients not included in the one year report) and one reporting findings during the third year of treatment in 10 patients (all of whom were included in the combined 1-2 year report). The third open extension trial was a 1-year study in 6 patients (S-86). Tizanidine was administered for at least 12-14 months in each of the long-term Sandoz trials, with some patients receiving the drug for 3 years in two of the trials. In three of the long term trials, daily dose of tizanidine averaged between 5 and 8 mg (S-27, S-28, S-86) while in the other five studies it ranged from 16 to 20 mg/day. Efficacy was assessed by ratings of muscle tone, spasms, clonus and muscle strength, patient and investigator globals. The results for these parameters have been combined for all tizanidine-treated patients from the 8 long-term trials (Table 27)

There was no evidence of development of tolerance to the antispastic effects of tizanidine within the first year for those patients who continued tizanidine treatment. Treatment with tizanidine for more than 1 year was limited to two studies (S-26, S-28). Although the number of patients treated in these studies was relatively small, improvements in muscle tone and spasms and clonus appeared to be maintained for the duration of therapy.

12.3 Long-Term Active-Controlled Trial (S-17)

The long-term efficacy and safety of tizanidine was evaluated in a 12-month double-blind, parallel group trial with baclofen. Thirty patients suffering from spasticity due to cerebrovascular or spinal lesions were randomized to either tizanidine or baclofen. The dosage of study medication was individually titrated for each patient within the first two study weeks to a maximum dose of 20 mg/day tizanidine or 50 mg/day baclofen; this dosage was to be maintained throughout the 52 week study. Efficacy was assessed at baseline, at monthly intervals during the first 6 months and every other month thereafter. Efficacy assessments included muscle tone by the Ashworth scale, spasm, clonus, muscle strength, functional disability and global ratings of

antispastic effectiveness. There were improvements from baselines in the mean sum of scores for muscle tone, muscle spasms, clonus however, the magnitude of improvement did not differ statistically between the two treatments (p.0.05; Mann Whitney-Wilcoxon U-test).

13.0 Active-Controlled Trials

Twenty-one Sandoz-sponsored trials comparing the efficacy and safety of tizanidine with that of baclofen (15 studies) or diazepam (6 studies) were conducted in Europe and South America over the interval from 1977 to 1987. Seven hundred ten (710) patients, 400 of whom received tizanidine, with spasticity due to various neurological states, primarily in MS, but also including cerebrovascular lesions, cerebral palsy, and amyotrophic lateral sclerosis were enrolled in these trials. These trials were conducted under randomized, double-blind conditions; all but two used a parallel design. Multiple outcome measures were employed.

With the exception of one study, study drugs were administered for 6 to 8 weeks; in the one remaining trial, study drugs were administered for 52 weeks. Tizanidine was administered over a dosage range of 2 to 32 mg/day while dosages of baclofen and diazepam ranged from 10 to 90 mg/day and 5 to 40 mg/day, respectively.

These studies have been reviewed firstly for protocol-specified outcome measures and then for those where tizanidine is superior to the active control.

- 13.1 Eysette M. Multicentre double-blind trial in spasticity associated with multiple sclerosis. Unpublished Sandoz Research Report. May 1985. S-3.

This study report is lacking an original protocol. There was no statistically significant difference between the efficacy of the two antispastic treatments.

- 13.2 Ebers G.C. Tizanidine v. baclofen in the treatment of spasticity related to multiple sclerosis

This study is accompanied with a protocol however no primary outcome measure is specified. No differences were shown for muscle tone, spasms, muscle strength.

- 13.3 Chrzanowski K. A comparative trial of tizanidine and baclofen in the treatment of spasticity due to multiple sclerosis. Unpublished Sandoz Research Report. September 1981. S-6.

There is a study report but no original protocol. No statistical analysis of the single parameters of spasticity were performed due to the small sample size (8 v. 7 patients)(sic), global assessments of efficacy was statistically significant in favor of tizanidine..

- 13.4 Wickstrom J. A double-blind, parallel group, therapeutical comparative study to assess the efficacy and tolerability of tizanidine (Sirdalud) vs. baclofen in the treatment of spasticity due to multiple sclerosis. Unpublished Sandoz Research Report. October 1987. S-4.

This study report is provided with a 2 page "Summary of the Trial Protocol", however, it fails to specify a primary outcome measure. There were no statistically significant differences between the two groups for muscle tone, spasms, physician and patient global.

- 13.5 Newman P.K. A double-blind, comparative trial of tizanidine and baclofen in the treatment of chronic spasticity in patients with multiple sclerosis (Study No. 27). Unpublished Sandoz Research Report. October 1981. S-7.

This study is provided with an original protocol which sets forth multiple clinical parameters of efficacy, however, a primary outcome measure is not specified. The crossover design was flawed in that there was a baseline differential at the start of the first and second treatment period. The sponsor concludes that tizanidine had a better effect on muscle tone and strength while baclofen was slightly more effective against muscle spasms.

- 13.6 Rinne U.K. Comparative double-blind trial between DS 103-282 and baclofen in the treatment of spasticity due to multiple sclerosis or chronic myelopathy (Study No. 28). Unpublished Sandoz Research Report. March 1979. S-8.

The study is accompanied with "Summary of the Trial Protocol" which sets forth multiple parameters for assessment, however, a primary outcome is not specified. Tizanidine and baclofen had a comparable effect on spasticity.

- 13.7 Smolenski Ch. A double-blind comparative trial of a new muscle relaxant tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Current Medical Research and Opinion 1981; 7:373-383. S-9.

The study report is furnished with a single page "Summary of the Trial Protocol" which fails to specify a primary measure. No significant differences were found between the two treatments.

- 13.8 Stien R., Slettebo M., Oftedal S., Nordal H. A comparative trial of DS 103-282 and baclofen in the treatment of spasticity due to multiple sclerosis (Study No. 30). Unpublished Sandoz Research Report. May 1981. S-10.

The study report includes an original protocol which itemizes multiple clinical criteria of efficacy (Ashworth, muscle strength, spasms, clonus, DSS) however, none is specified as the primary outcome. The results were in favor of baclofen although statistically significant differences were never reached.

- 13.9 Wuthrich R. A comparative trial of tizanidine and baclofen in the treatment of spasticity due to multiple sclerosis (Study No. 31). Unpublished Sandoz Research Report. September 1981. S-11.

The study report includes a two page "Summary of the Trial Protocol" which outlines multiple efficacy criteria but specifies no primary outcome criteria. No statistically significant differences were shown between the two treatments.

- 13.10 Banessy H. A comparative trial of DS 103-282 and baclofen in the treatment of spasticity due to multiple sclerosis (Study No. 32). Unpublished Sandoz Research Report. October 1981. S-12.

The study included a two page "Summary of the Trial Protocol" which outlined the efficacy assessments but without specifying a primary outcome criterion. There were no statistically significant differences between the two treatment groups regarding spasms, stretch reflexes, muscle strength, functional status, and global ratings.

- 13.11 Rinne U.K. Comparative double-blind trial between DS 103-282 and baclofen in the treatment of spasticity due to cerebrovascular lesions (Study No. 36). Unpublished Sandoz Research Report. December 1979. S-13.

There was no original protocol provided in the study report. The clinical population of spasticity of cerebral origin is outside that of the indication sought for tizanidine, that is, spasticity of spinal cord origin. There were no statistically significant results between treatments in muscle tone, spasms, clonus, mobility, reflexes, and disability status.

- 13.12 Rinne U.K. Comparative double-blind trial between DS 103-282 and baclofen in the treatment of amyotrophic lateral sclerosis and spasmodic torticollis (Study No. 37). Unpublished Sandoz Research Report. September 1980. S-14.

There was no protocol provided in the study report. Neither tizanidine nor baclofen demonstrated efficacy in the treatment of spasmodic torticollis and no difference was shown between treatments for ALS, both disorders outside the proposed indication.

- 13.13 Rinne U.K. Comparative double-blind trial between DS 103-282 and baclofen in the treatment of spasticity due to cerebral palsy (Study No. 38). Unpublished Sandoz Research Report. May 1980. S-15.

The study report includes a two-page "Summary of the Protocol" itemizing multiple efficacy assessments without specifying a primary outcome. This patient population with spasticity of cerebral origin is outside the proposed indication of spasticity of spinal cord origin. There was no statistically significant changes between treatments in muscle tone, spasms, clonus, mobility, reflexes, and disability status. There was a

statistically significant difference in patient self assessment of disability in favor of tizanidine after 4 assessments.

- 13.14 Medici M. A comparative trial of tizanidine and baclofen in patients with spasticity due to various neurological disorders (Study No. 39). Unpublished Sandoz Research Report. Undated. S-16A.

This study report is provided with an original trial protocol which identifies the clinical criteria of response to treatment are changes in the following parameters: muscle strength, muscle tone, flexor or extensor spasms, clonus. There were 14 MS patients (7 per group), 12 with cerebrovascular disease (5 on tizanidine and 7 on baclofen), 3 with congenital encephalopathy (2 on tizanidine and 1 on baclofen), 2 with cervical myelopathy, 1 with syphilis and 1 with familial spastic paraplegia. The optimal daily dose of tizanidine was in the majority of patients 20mg and that of baclofen 50 mg. There were no statistically significant differences in antispastic efficacy between the two treatments (muscle strength, muscle tone, muscle spasms, functional assessment, Kurtzke neurological examination); the trend was in favor of tizanidine.

- 13.15 Medici M. A double-blind, parallel group, long-term study to assess efficacy and tolerability of tizanidine (DS 103-282, Sirdalud®) compared to baclofen during chronic administration in patients with spasticity due to cerebrovascular lesions (Study No. 39). Unpublished Sandoz Research Report. January 1983. S-17.

No study protocol is provided. The patient population (cerebrovascular spasticity) is outside the proposed indication of spinal spasticity. The criteria of therapeutic response (muscle strength, muscle tone, muscle spasms, clonus) did not show statistically significant differences between the two treatments.

- 13.16 Jellinger K. A controlled, chewable-blind, clinical therapeutic, comparative study with two parallel groups (tizanidine and diazepam) in ambulant/hospitalized patients with multiple sclerosis. Unpublished Sandoz Research Report. August 1983. S-18.

The study report is accompanied by a two page "Summary of the Trial Protocol" which itemizes multiple efficacy criteria but without specifying a primary outcome. There was no significant difference between treatments for muscle tone, muscle spasm, clonus, patient global while muscle strength and walking ability showed a statistically significant difference in favor of tizanidine.

- 13.17 Rinne U.K. A comparative trial of DS 103-282 and diazepam in the treatment of spasticity due to multiple sclerosis (Study No. 33). Unpublished Sandoz Research Report. March 1978. S-19.

This study report provides an original protocol that identifies the target symptoms as spasticity, reflexes, ankle clonus, and mobility, along with patient and investigator global. 30 patients with MS were randomized to tizanidine or diazepam in a 6 week double blind trial. There were no statistically significant changes in spasticity, reflexes, ankle clonus and mobility.

- 13.18 Chantraine A., van Ouvealler Ch. A double-blind comparative trial of tizanidine and diazepam in the treatment of chronic spasticity in patients with hemiplegia (Study No. 34). Unpublished Sandoz Research Report. February 1981. S-20.

The study report was accompanied by a two page "Summary of the Protocol" which itemized multiple efficacy assessments but without identifying a primary outcome. The patient population is outside of the proposed indication. There were no statistically significant treatment differences for Kurtzke neurological functions, EDSS, muscle strength, muscle tone, ADL. Patient assessment of overall antispastic efficacy was statistically significant in favor of tizanidine.

- 13.19 Martinez-Lage J.M. A comparative trial of DS 103-282 and diazepam in patients with spasticity due to cerebrovascular accidents (Study No. 35). Unpublished Sandoz Research Report. September 1981. S-21.

The study report was accompanied by a "Summary of the Protocol" which itemized the efficacy assessments without designation of a primary outcome. The patient population is outside the proposed indication. There was no difference shown between treatments on all components of spasticity.

- 13.20 Vetter G. A comparative trial of DS 103-282 and diazepam in patients with spasticity due to neurological disorders (Study No. 40). Unpublished Sandoz Research Report. January 1981. S-22.

No protocol was provided. There were no statistically significant differences between the two trial drugs.

- 13.21 Geyer N., Ladurner G. Final clinical report of a double-blind comparative study in two parallel groups of patients (cooperative study at two trial centers). Unpublished Sandoz Research Report. May 1982. S-99.

No protocol was provided. There was no difference in efficacy between the two drugs.

- 13.22 McLellan D.L., Hassan N. Double-blind comparison of single doses of DS 103-282, baclofen and placebo for suppression of spasticity (Study No. 47). Journal of Neurology, Neurosurgery and Psychiatry, 1980;43:1132-1136. S-60.

12 spastic patients received single oral doses of tizanidine 6 mg, baclofen 20 mg, and placebo on three separate days. Passive stretch responses (EMG) were measured before administration and for 4h afterwards. Tizanidine was more effective than baclofen, and both drugs were more effective than placebo.

14.0 Uncontrolled Supportive Trials, including Long Term Use

Tizanidine, dosage range of 1 to 32 mg/day, was administered under open-label conditions in 8 Sandoz-sponsored trials conducted in South America and Europe. All excepting one of these trials assessed the efficacy and safety of tizanidine for 12 to 36 months. The one remaining trial assessed 1-5 mg/day of open-label tizanidine for 7 to 8 weeks. These trials were conducted in 165 patients who had spasticity due to paraparesis, multiple sclerosis, cerebral lesions, various neurological states or strokes. The antispastic efficacy of tizanidine was maintained over long-term therapy and the drug was well-tolerated in these trials.

15.0 Efficacy and Safety in Acute Musculoskeletal Spasms

Nineteen Sandoz-sponsored studies in patients with acute musculoskeletal spasms were conducted in Europe in 680 patients, 331 of whom received treatment with tizanidine 2 to 4 mg tid. Five Sandoz-sponsored trials in this patient population were conducted in the U.S.; these five trials involved a total of 1076 patients, 476 of whom were treated with tizanidine (1 to 6 mg tid). Treatment was administered for 7 days in all but two trials; in two trials, study medication was given for 10 or 14 days. In acute conditions the antispastic efficacy of tizanidine was equal to that of the reference treatments and was superior to that of placebo.

16.0 Summary

The efficacy of tizanidine in the treatment of symptoms of spasticity was assessed in three primary double-blind, placebo-controlled efficacy trials involving 525 patients, 407 with spasticity secondary to MS and 118 with spasticity secondary to spinal cord injury. A total of 264 patients received tizanidine in these trials, 205 patients with MS and 59 with spinal cord injury. An additional 65 patients received tizanidine in two supportive, placebo-controlled trials of spasticity secondary to MS or chronic myelopathy; 386 patients received tizanidine in 20 active-controlled trials of spasticity secondary to MS (12 trials) or cerebrovascular lesions or other neurologic disorders (8 trials); and 10 patients with spinal cord lesions received tizanidine in an open, uncontrolled trial. Long term tizanidine treatment was assessed in 313 patients.

The effectiveness of tizanidine in the treatment of spasticity was demonstrated in three randomized, double-blind, placebo-controlled clinical trials. In the assessment of muscle tone (Ashworth score), tizanidine was significantly superior to placebo in one MS study (DS 0502) and in the spinal cord injury study (021-003).

In the combined analysis of the three studies, decreases in spasticity were demonstrated with tizanidine administration without any decreases in muscle strength. Improvement in muscle tone was most pronounced in patients with greater severity of spasticity at baseline and was not accompanied by a decrease in muscle strength. The effects of tizanidine on muscle tone did not appear to differ among subsets of patients according to race or gender, but may be more pronounced in younger patients.

In active-controlled trials, the efficacy of tizanidine was comparable to that of baclofen or diazepam. The efficacy of tizanidine is maintained during long-term treatment. Significant improvements in muscle tone are observed for up to 8 months of therapy. Experience in smaller numbers of patients treated for 1 to 3 years suggests that these improvements are maintained for the duration of therapy.

In the primary efficacy studies, tizanidine doses were titrated to a maximum of 36 mg daily, limited primarily by the development of side effects. No clear linear dose-response trend was observed. The majority of patients who responded to treatment were receiving daily doses of 19 mg or greater.

For Study DS-0502, the results for the prospectively identified primary efficacy variable Ashworth Total Score as well as the Physician's Global were statistically significant for tizanidine.

The failure of tizanidine to demonstrate significance against placebo in the treatment of spasticity in the 021-001 trial is hard to dismiss. Among other factors, it is the largest study, and the design and study population is identical to Study DS-0502, a highly positive study. There is some positive spasm and global data in 001. The failure of the study is attributed by the sponsor to delays in Ashworth assessment with respect to time of study drug dosing (assessments performed more than three hours after drug administration). However, this reviewer does not feel that the sponsor's case showed this. The sponsor also attributes the failed outcome to an unusually large placebo response. The severity of the muscle tone at baseline may also be involved, as the Ashworth scores of the patients in Study 021-001 were not as severe as those in the other studies, and the placebo group was more severe than the tizanidine treated group.

Study 021-003 provides statistically significant evidence of the effect of tizanidine in the treatment of spasticity of spinal cord origin. Highly significant results were demonstrated for the prospectively identified primary outcome measures of spasticity as assessed by the Ashworth score and frequency of spasms throughout the plateau phase.

Of the two supportive placebo-controlled trials, only the Lapierre study contributes to the efficacy claim. The Rinne study is excluded by crossover design; even first period analysis had no significant findings. For the LaPierre study, data transformation of the Ashworth scores yielded treatment effects of comparable magnitude to those seen in Study DS-0502 and Study 021-003. These results provide supportive evidence of the efficacy of tizanidine v. placebo for the treatment of spasticity.

To conclude, there is some consistency across the primary outcome measures of the pivotal studies to support the efficacy of tizanidine in the treatment of spasticity of spinal cord origin.

16 0 Recommendation

NDA 20-397 Tizanidine for treatment of spasticity of spinal cord origin is approvable.


Janeth Rouzer Kammeyer, M.D.

cc: ORIG NDA 20-397

Div. File HFD-120/

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Statistical Review

Statistical Review and Evaluation

DEC 23 1994

NDA #: 20-397 / 1-S

Name of Drug: Zanaflex (tizanidine HCL)

Applicant: Athena Neurosciences, Inc.

Indication: Treatment of spasticity of spinal cord origin

Documents Reviewed: Volumes 1.1 and 1.2 and 1.113 to 1.159

Medical Input: Janeth Rouzer-Kammeyer, M.D. (HFD-120) was consulted during the review process.

Introduction

The sponsor has presented the results of 5 placebo-controlled studies to establish the efficacy and safety of tizanidine for the treatment of spasticity. Table 1 below presents an overview of the studies which are the focus of this review; studies S-1 and S-2 are considered by the sponsor to be supportive and will be only briefly reviewed here.

Table 1. SUMMARY OF PLACEBO-CONTROLLED TRIALS

Study Number	Number of Centers	# of Placebo Patients	# of Tizanidine Patients	Patient Population	Design	Duration of Treatment
DS-0502	16	93	94	MS	double-blind, randomized, parallel groups	13 weeks
021-001	15	125	131	MS	same as above	13 weeks
021-003	14	59	59	spinal cord injury	same as above	7 weeks
S-1	1	33	33	MS	same as above	8 weeks
S-2	1	31	31	MS or chronic myelopathy	double-blind, crossover	4 weeks

Table 2 below lists the efficacy parameters measured in each of the 3 main studies (DS-0502, 021-001 and 021-003). The outcomes for the primary efficacy variables will be reviewed in detail. The results for the Physician's Global Assessment will also be presented. For more details regarding other secondary variables, see Dr. Rouzer-Kammeyer's clinical review.

Table 2. Efficacy Variables Measured in 3 Main Trials

	DS-0502	021-001	021-003
Ashworth Score	Primary	Primary	Primary
Count of Spasms and Clonus (Diary)		Primary	Primary
Global Assessment (Physician)	X	X	X
Global Assessment (Patient)	X	X	X
Pendulum Test			Primary
Muscle Strength	X	X	X
Tendon Reflexes	X	X	
Type and Frequency of Spasms	X	X	
Walking Abilities	X	X	
Pain	X	X	
Activities of Daily Life	X	X	X

The Ashworth Total is the sum of muscle tone scores at 10 body sites on both the left and right side of the body. (For Study 021-003, 3 lower body sites on both sides were assessed.) The scale is defined as follows:

- 0 = No increase in tone
- 1 = Slight increase in tone giving a "catch" when the limb is moved in flexion or extension
- 2 = More marked increase in tone but limb easily flexed or extended
- 3 = Considerable increase in tone, passive movement difficult
- 4 = Limb rigid in flexion or extension.

Spasms and clonus experienced during the day and night were recorded in diaries by the patients in Studies 021-001 and 021-003. The response measure was the mean count for the week on study where the mean was computed as the total number of spasms and clonus for the week divided by the total number of days on which data was recorded.

The Physician's Global Assessment was measured only at the final visit in Studies DS-0520 and 021-001. For Study 021-003, the global assessment was performed at baseline and at several timepoints. For Study DS-0502, the physician was asked to assess efficacy on a scale of 1 (Very Good) to 5 (None). In the other 2 studies, the global was measured by a visual analogue scale where the lowest value corresponded to "not at all satisfied" or "minimal function" and the highest value to "very good" or "normal function".

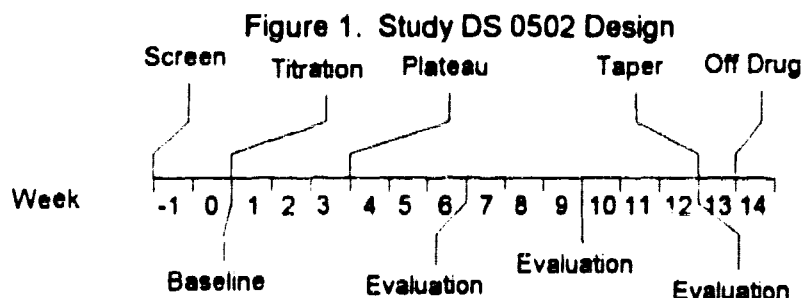
The sponsor analyzed data for both evaluable patients and all patients (intent-to-treat population); the ITT results will be the main focus of this review.

The analysis model generally used by the sponsor included main effect terms for treatment, center and baseline strata. Three baseline strata were defined based on the Ashworth score for the most severely affected muscle group; scores of 1 or 2 defined one stratum, 3 defined the second stratum and 4 the third. This reviewer used an analysis of covariance model to confirm the sponsor's results if the assumptions for ANCOVA were satisfied. In general, baseline (as a continuous measure) and response were found to be positively correlated and the model fit was good ($r^2 > .7$).

Study DS 0502 (Conducted 7/89 to 3/91)

1. Design

Patients diagnosed with spasticity secondary to multiple sclerosis at 16 centers (all in England) were randomized to tizanidine or placebo stratifying on the Ashworth score for the most severely affected muscle group. The schematic below shows the design used. During the first week of the titration phase, each patient's dose was titrated from 2 mg per day (1 tablet for placebo) to 16 mg (5 tablets). Dosing was TID and both 2 mg and 4 mg tablets were used. During the second and third weeks of the titration phase, the dose could be titrated up to a maximum of 36 mg (9 tablets). Titration could be discontinued and doses below 36 mg used if spasticity was considered controlled (based on weekly visits) or adverse events occurred. Patients were to be maintained on their final titration dose during the 9-week plateau phase; this dose could be lowered if not well-tolerated. The dose was tapered during Week 13 and a final efficacy assessment was made after 1 week off treatment.



2. Patient Sample

2.1 Demographics

About two-thirds of the patients were female; all patients were white. The average age of the sample was about 46 years. The mean duration of illness was 13 years; 90% of the patients had an Ashworth score of 2 or 3 at baseline for the most severely affected muscle .

2.2 Patient Disposition

A total of 187 patients were enrolled in this study; 94 on tizanidine and 93 on placebo (the protocol called for a sample size of 250). The number of patients on study (where 'on study' refers only to those patients available for assessment) at each timepoint is shown below in Table 3. (These numbers were derived from the sponsor's Appendices B.1.2 and B.1.3.)

Table 3. Study DS-0502
Patients on Study by Week

	PLA	TIZ
Randomized	93 (100%)	94 (100%)
Baseline	93 (100%)	94 (100%)
Week 1 (Titration)	93 (100%)	90 (96%)
Week 2 (Titration)	89 (96%)	87 (93%)
Week 3 (Titration)	83 (89%)	84 (89%)
Weeks 4-6 (Plateau)	79 (85%)	78 (83%)
Weeks 7-9 (Plateau)	78 (84%)	67 (71%)
Weeks 10-12 (Plateau)	71 (76%)	65 (69%)

From the table below, it can be seen that a larger percentage of tizanidine-treated patients dropped due to adverse events than placebo patients ($p = .03$). The groups were comparable for the other reasons listed. (These numbers were derived from the sponsor's Appendix C.26.)

Table 4. Study DS-0502
Reasons for Discontinuation While on Treatment

	PLA	TIZ
Randomized	93	94
Reason for Discontinuation		
Adverse Event	4 (4%)	12 (13%)
Lack of Efficacy	13 (14%)	12 (13%)
Other	5 (5%)	5 (5%)
Completers	71	65

4. Results for the Total Ashworth Score

4.1 Sponsor's Results

The results of the sponsor's analysis of variance on the change from baseline scores for the Total Ashworth are given below. The model for the analysis included main effect terms for treatment, center and baseline strata. Three baseline strata were defined based on the Ashworth score for the most severely affected muscle group; scores of 1 or 2 defined one stratum, 3 defined a second stratum and 4 the third. In separate models, the sponsor tested the significance of the interaction of treatment with center and treatment with baseline strata. The former interaction was not statistically significant ($p > .15$) while the latter was significant ($p = .02$). Dropping one outlier rendered the treatment by stratum interaction nonsignificant.

Table 5. Study DS-0502
Sponsor's Total Ashworth Score Results
Change from Baseline

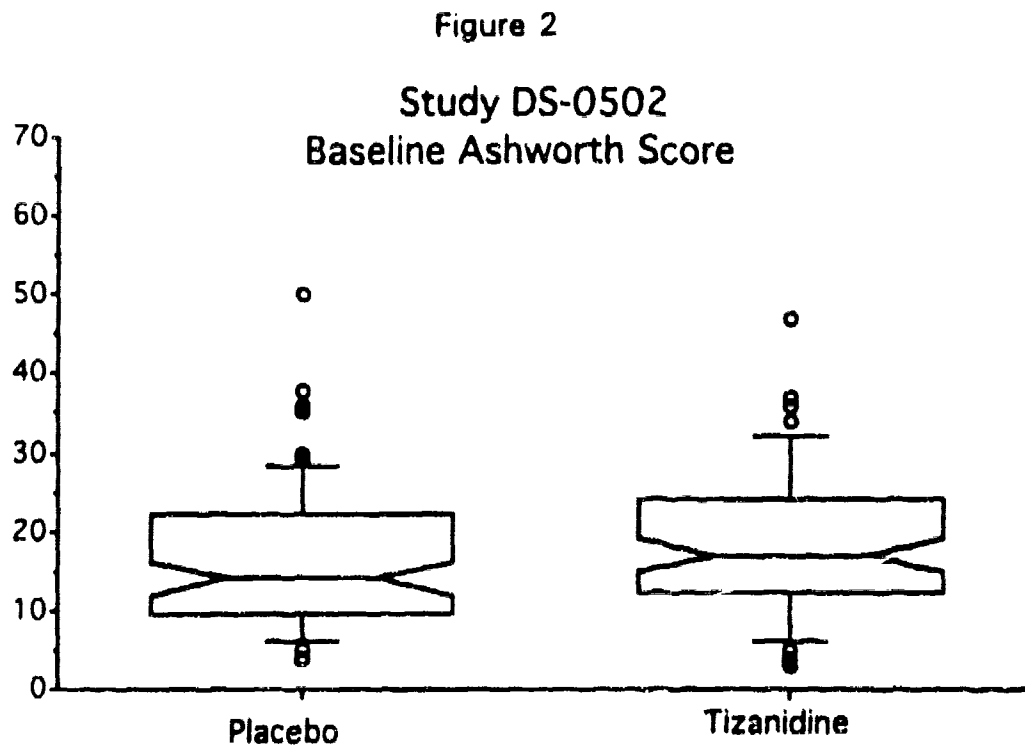
	Placebo Mean (SD)	Tizanidine Mean (SD)	p-value
Baseline	16.3	18.5	.90
Titration 1	-0.8 (3.6)	-1.8 (3.8)	.12
Titration 2	-1.7 (5.7)	-3.8 (5.0)	.07
Titration 3	-2.5 (5.0)	-3.9 (5.8)	.19
Plateau 1	-2.0 (5.3)	-4.7 (5.3)	.002
Plateau 2	-1.7 (5.5)	-5.5 (5.9)	.0005
Plateau 3	-1.2 (4.3)	-5.0 (5.0)	<.0001
LOCF	-1.5 (5.4)	-3.9 (5.0)	.007
Last Visit Off Treatment	-1.1 (4.4)	-3.1 (5.0)	.03

The results for the Total Ashworth Score clearly show the groups to be statistically significantly different during the entire plateau phase.

Results for the lower extremities were very similar to the results for all muscle groups with a statistically significant treatment difference of about 2 at each plateau visit and at endpoint (LOCF). The sponsor also compared the percentage of patients showing improvement on the Ashworth score and found the groups significantly different (49% of placebo patients vs. 71% of tizanidine patients, $p = .003$). In addition, stratification on age, race and gender revealed consistent treatment differences across the strata.

4.2 Reviewer's Results and Comments

According to the sponsor's analysis, the baseline treatment comparison (see box plots below) of the total Ashworth score was nonsignificant with a p-value of .90. Analyses by this reviewer revealed a smaller p-value ($p < .3$)¹ and a strong relationship between baseline and endpoint ($R^2 = .75$).

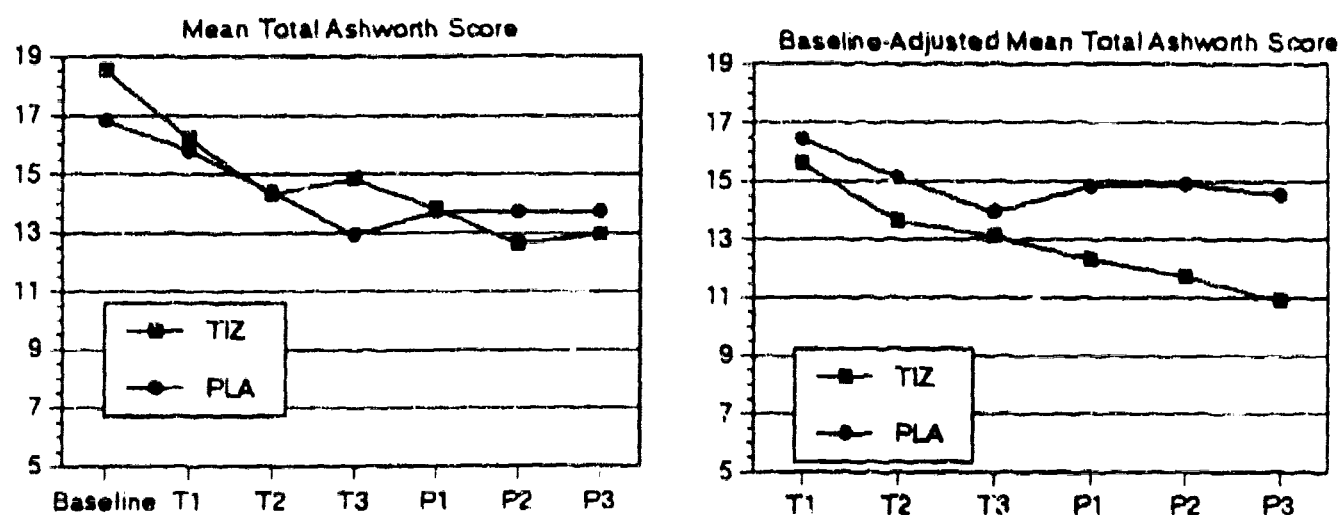


¹ The difference between the results was due to the inclusion of strata (the Ashworth score for the most severely affected muscle site) in the sponsor's model but not in this reviewer's model. Since strata is highly correlated with baseline, it did not seem appropriate to this reviewer to adjust for strata when making baseline comparisons.

As an alternative analysis to the sponsor's analysis of variance on the change scores, this reviewer performed an analysis of covariance (ANCOVA) using the total Ashworth baseline as the covariate. Plots of the mean total Ashworth over time and the least squares means (LSM, means adjusted for baseline) are shown below (Figure 3). Both plots are of the observed cases data (more than 70% of the patients completed the study). The ANCOVA results showed a significant treatment effect at each plateau visit ($p \leq .003$) and at endpoint (placebo LSM = 15.4 vs. tizanidine LSM = 13.4, $p = .008$).

To confirm that the treatment effect was statistically significant over the whole plateau phase (this is visually obvious from the LSM plots of Figure 3), I averaged the plateau values and performed an ANCOVA with the average as the response variable and baseline as the covariate. This analysis yielded a significant p-value for the treatment effect of .0002 and a treatment difference of about 3 in favor of tizanidine.

Figure 3. Study DS-0502



The results by strata (Table 6) show consistent results in favor of tizanidine for baseline strata mild and moderate (more than 90% of the patients). The large change (-7) seen for placebo patients in the severe stratum is due to one patient with a score of 80 at baseline and a score of 50 at endpoint. The median score for that group was -2.5.

Table 6. Study DS-0502
Ashworth Mean Change from Baseline By Baseline Strata

Baseline Strata	Placebo		Tizanidine	
	N	Mean (SD)	N	Mean (SD)
Mild	48	-1.3 (3.8)	40	-3.3 (4.2)
Moderate	39	-0.9 (5.4)	48	-5.0 (5.7)
Severe	6	-7.0 (12.0)	6	-2.7 (3.4)

5. Results for the Physician's Global Score

5.1 Sponsor's Results

At the final visit, both the patient and the physician were asked to give an overall assessment of efficacy and of tolerability. The physician was asked to assess efficacy according to the following scale:

- 1 = Very good
- 2 = Good
- 3 = Moderate
- 4 = Slight
- 5 = None.

About 1/4 of the patients were not assessed on this measure. The mean efficacy response given by physicians is shown below. The sponsor performed no statistical analysis of this data.

PLACEBO MEAN 4.3 (SD = 1.0) TIZANIDINE MEAN 3.8 (SD = 1.1)

5.2 Reviewer's Results and Comments

Overall assessment of efficacy at endpoint as rated by the physician was significantly better for the tizanidine group compared to the placebo group (Table 7 $p = .002$, Cochran-Mantel-Haenszel test adjusting for center). Twice as many tizanidine patients (16%) as placebo patients (7%) were given an overall rating of "very good" or "good". About one-third of the tizanidine patients compared to more than half of the placebo patients showed no improvement. The results for completers were similar ($p = .014$). (Note that about one quarter of the patients were not rated at endpoint.)

The right 2 columns of Table 7 show the mean Ashworth change score for each global score. The correlation between the global and the Ashworth change from baseline at endpoint was significant in each treatment group ($R = .31$, $p = .01$ for tizanidine and $R = .38$, $p = .0009$ for placebo). It is interesting to note that the Ashworth changes indicate greater improvement in the tizanidine group than the placebo group even for those patients not considered improved at endpoint. (For Study 021-001 (Table 18), we will see that this is not the case.)

Table 7. Study DS-0502
Physician's Global Assessment at Endpoint

Overall Efficacy Rating	Number and Percentage of Patients by Rating		Mean Change from Baseline Ashworth by Rating	
	PLA	TIZ	PLA	TIZ
Very Good	3 (4%)	1 (1.6%)	-6.0	-16.0
Good	2 (3%)	9 (14%)	-8.0	-4.1
Moderate	6 (8%)	12 (19%)	-4.0	-7.4
Slight	22 (30%)	22 (34%)	-1.7	-3.8
None	41 (55%)	20 (31%)	+0.2	-2.2

6. Reviewer's Overall Comments on DS-0502

The results for the Ashworth Total Score (the primary efficacy variable) and the Physician's Global Score show statistically that tizanidine is more effective at decreasing spasticity than placebo. Of the secondary variables listed in Table 2, only muscle strength was analyzed showing no difference between the groups. For the other variables, only descriptive statistics by treatment group were presented; these results did not offer evidence of efficacy for tizanidine over placebo.

Study 021-001 (Conducted 2/92 to 6/93)

1. Design

A total of 15 centers enrolled patients into Study 021-001. The sponsor excluded the data of one center (Center 4) from their analyzable database due to "multiple drug administration irregularities". This reviewer requested further information from the sponsor regarding Center 4 and was told the following;

1. The sponsor noted upon completion of the trial that some placebo patients in Center 4 exhibited side effects usually associated with the drug.
2. Vials returned by patients in each center were assayed to determine if patients were receiving drug as randomized. These vials contained medication returned by the patient. Vials from about 2 to 4 patients in each center except Center 4 were tested; vials from all 16 placebo patients and 4 tizanidine patients enrolled in Center 4 were tested.
3. From the assays it was found that 3 placebo patients enrolled in Center 4 received some tizanidine tablets.

The sponsor chose to exclude Center 4 from their main analyses because the sponsor could not ascertain how many placebo patients actually may have taken tizanidine or the reason for the presence of both drugs within the same vial. This reviewer thinks it is reasonable to look at the data for this study including and excluding Center 4 since it is not clear that the drug mixup occurred for a large number of patients. Also Center 4 had the largest enrollment (36 patients).

Patients diagnosed with spasticity secondary to multiple sclerosis were randomly assigned to receive tizanidine or placebo stratified on the Ashworth score of the most severely affected muscle group. The design for this study was the same as for Study DS-0502 (see Figure 1); a 3-week titration phase was followed by a 9-week plateau phase where dosing was maintained and then drug was tapered for one week. The dosing titration scheme was the same as the scheme used for Study DS-0502.

Two physicians were involved with patient evaluation; the primary investigator (referred to as the assessor by the sponsor) performed the efficacy measurements and the secondary investigator (the prescriber) managed the dose titration and patient care.

2. Patient Sample

2.1 Demographics

About 60% of the patients enrolled in Study 021-001 were female. More than 90% of the patients were Caucasian. The average age of the sample was about 45 years. About 80% of the patients had a score of 2 or 3 at baseline for the most severely affected muscle group.

2.2 Patient Disposition

The retention rate in this study was high with about 3/4's of the patients completing the third plateau visit (Table 8). (The numbers in the table below were computed by the reviewer from the database provided by the sponsor.) Table 8 shows patient disposition by study phase with Center 4 patients included while Table 9 shows patient disposition excluding Center 4 patients.

Table 8. Study 021-001
Patient Disposition
Center 4 Included

	PLA	TIZ
Randomized	125 (100%)	132 (100%)
Baseline	125 (100%)	131 (99%)
Week 1 (Titration)	123 (98%)	130 (98.5%)
Week 2 (Titration)	118 (94%)	121 (92%)
Week 3 (Titration)	117 (94%)	121 (92%)
Weeks 4-6 (Plateau)	112 (90%)	115 (87%)
Weeks 7-9 (Plateau)	101 (81%)	104 (79%)
Weeks 10-12 (Plateau)	92 (74%)	101 (77%)
Followup (Completers)	90 (72%)	100 (76%)

Table 9. Study 021-001
Patient Disposition
Center 4 Excluded

	PLA	TIZ
Randomized	109	112
Completed Phase 3 (Weeks 10-12)	77 (71%)	84 (75%)
Completed Followup	75 (69%)	83 (74%)

The major reason for discontinuation in the tizanidine group was experiencing an adverse event; while in the placebo group lack of efficacy was the major reason for dropping out. More than 80% of the adverse events experienced by the tizanidine patients occurred during the first 6 weeks of the study. (The data in Table 10 was extracted from Vol 126, Appendix C.3.)

Table 10. Study 021-001
Reasons for Discontinuation
Center 4 Included¹

	PLA	TIZ
Randomized	125	132
Reason for Discontinuation		
Adverse Event	9 (9%)	16 (12%)
Lack of Efficacy	14 (11%)	8 (6%)
MS Exacerbation	5 (4%)	4 (3%)
Other	7 (6%)	4 (3%)
Completers	90	100

The sponsor analyzed 3 different groups of patients:

1. "analyzable patients" = all patients with at least one measurement on treatment excluding Center 4 patients;
2. "evaluable patients" = protocol compliers excluding Center 4 patients;
3. "all-treated patients" = the analyzable patients including the Center 4 patients.

The sponsor's presentation emphasized the results for dataset 1 above. Due to the large number of patients in Center 4 and the uncertainty about the breadth of the drug-mixup problem, this reviewer will comment on the results for the third dataset also.

¹Only 4 patients in Center 4 discontinued the study. One placebo patient and 2 tizanidine patients dropped due to an adverse event and one tizanidine patient dropped due to lack of efficacy.

3. Results for the Total Ashworth Score

3.1 Sponsor's Results

The analysis of all treated patients excluding Center 4 was considered the primary analysis by the sponsor; the results for that patient sample are shown below. The sponsor's results for the evaluable patients and all treated patients including Center 4 were consistent with the results in Table 11.

Table 11. Study 021-001
Sponsor's Total Ashworth Score Results
Change from Baseline
Center 4 Excluded

	Placebo Mean (SD)	Tizanidine Mean (SD)	p-value
Baseline	14.95	13.0	.15
Titration 1	-3.0 (6.4)	-1.2 (7.0)	.12
Titration 2	-3.7 (6.7)	-3.1 (6.1)	.81
Titration 3	-5.1 (7.1)	-3.6 (7.4)	.29
Plateau 1	-4.5 (7.1)	-3.4 (8.2)	.96
Plateau 2	-3.9 (8.6)	-3.3 (8.4)	.43
Plateau 3	-2.6 (7.8)	-2.2 (7.3)	.99
LOCF	-2.8 (7.2)	-1.7 (7.2)	.48

The sponsor's results for the Ashworth score of the lower body also showed no significant treatment differences (Table 12).

Table 12. Study 021-001
Ashworth Total Score for the Lower Body
Center 4 Excluded

	PLA		TIZ		P-value
	Mean (SD)	LSM ¹	Mean (SD)	LSM	
Baseline	12.8		10.4		
Plateau 3	-1.9 (6.6)	-1.9	-0.9 (6.0)	-1.2	.47
LOCF	-2.0 (5.9)	-2.0	-0.4 (6.0)	-0.9	.19

The analysis of percentage of patients showing improvement in tone (a decrease in

¹Least Squares Mean

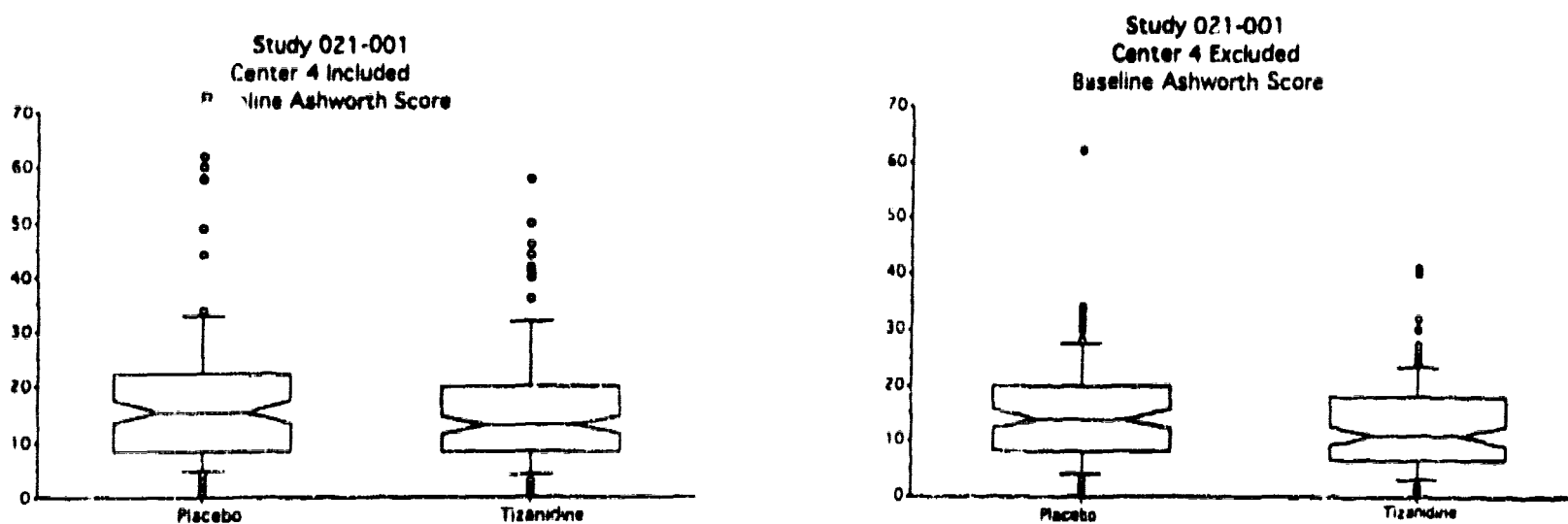
the Ashworth score) showed no significant difference between the groups ($p > .4$).

Subgroup analyses of the Ashworth score revealed no improvement for tizanidine patients over placebo patients in any subgroup based on age, gender or race.

3.2 Reviewer's Results

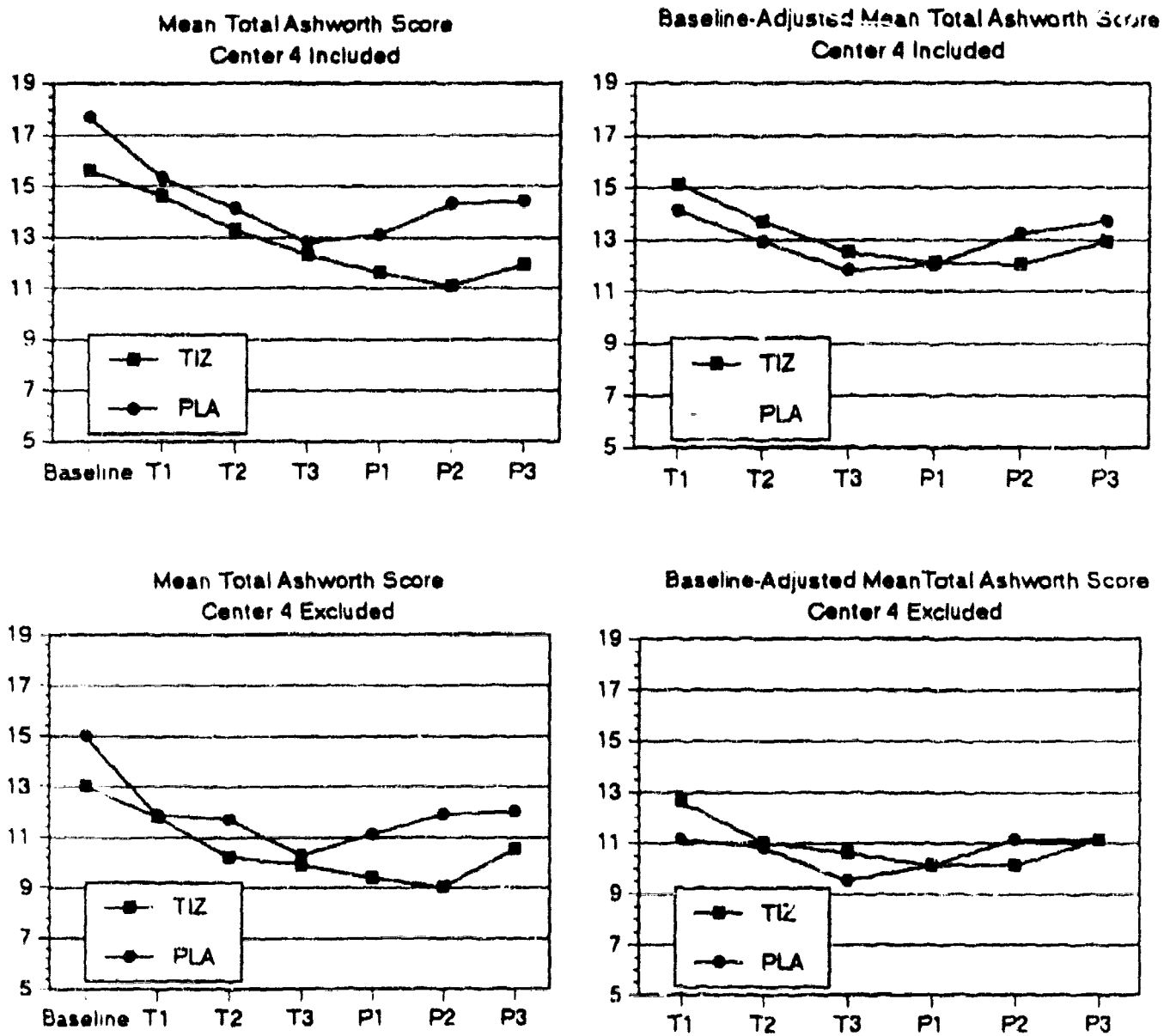
Baseline distributions by treatment group are shown below (Figure 4). Note that the inclusion of Center 4 shifts the baselines upward.

Figure 4



This reviewer's analyses confirmed the sponsor's results shown in Table 11. ANCOVA and blocked Wilcoxon tests adjusting for baseline at each timepoint and endpoint showed no significant treatment effects ($p > .40$) including or excluding Center 4 (Figure 5). In addition, an ANCOVA of the mean plateau response adjusting for baseline revealed no significant treatment differences ($p > .70$).

Figure 5. Study 021-001



The results for Center 4 alone (Table 13 below) show that the magnitudes of the baselines and the changes from baseline are larger than what was observed in the other centers combined (Table 11). From the baseline scores it appears that the patients in Center 4 had more severe spasticity at baseline than the patients in the other centers; this may explain the large changes shown here. (These changes are not significantly different with $p > .30$.)

Table 13. Center 4 Ashworth Total Results

	PLA (N = 16)		TIZ (N = 20)	
	Mean (SD)	LSM	Mean (SD)	LSM
Baseline	36.1 (17)		30.0 (14.7)	
LOCF	-9.9 (17.6)	-8.3	-11.2 (14.1)	-12.6

By center results showed about half of the center results favored tizanidine over placebo. Of the 4 largest centers (which encompasses about half the patient sample), 3 centers showed a treatment difference of about 1 in favor of tizanidine while the fourth center's results favored placebo.

The sponsor found a significant strata by treatment interaction at endpoint; the results by strata are given in Table 14 below. In the mild and moderate strata, the means favor placebo over tizanidine. The small number of patients and the small difference between the groups suggest no positive treatment effect for patients with severe spasticity at baseline. (The results with Center 4 included were similar for the mild and moderate strata; for the severe stratum, the mean changes were about double those shown here.)

Table 14. Study 021-001
Ashworth Mean Change from Baseline at Endpoint by Baseline Strata
Center 4 Excluded

Baseline Strata	PLA Mean (n)	Tizanidine Mean (n)
Mild	-0.7 (49)	-0.3 (53)
Moderate	-5.1 (41)	-2.8 (42)
Severe	-3.6 (14)	-4.1 (10)

4. Results for the Total Number of Daily Spasms and Clonus

4.1 Sponsor's Results

The count of spasms and clonus was not normally distributed. To normalize the data, the sponsor used the following transformation:

$$\text{RESPONSE RATIO} = (\text{COUNT} - \text{BASELINE COUNT}) / (\text{COUNT} + \text{BASELINE COUNT})$$

The response ratio results show that the tizanidine patients consistently show a greater decrease in daily spasm counts and clonus than the placebo patients from Week 3 (Titration 3) to Week 12 (Plateau 3) (see Table 15 below). At endpoint the groups are statistically different regardless of the inclusion or exclusion of Center 4. However the treatment difference is not significant at the last visit for the observed cases ($p > .06$).

Table 15. Study 021-001
Response Ratio for Daily Spasm and Clonus Counts
EXCLUDING CENTER 4

	Placebo Median	Tizanidine Median	p-value
Baseline	8.88	7.86	.31
Response Ratio			
Titration 1	-0.05	-0.09	.44
Titration 2	-0.10	-0.10	.95
Titration 3	-0.15	-0.20	.26
Plateau 1	-0.22	-0.23	.33
Plateau 2	-0.28	-0.39	.07
Plateau 3	-0.33	-0.50	.13
LOCF	-0.26	-0.44	.03

INCLUDING CENTER 4

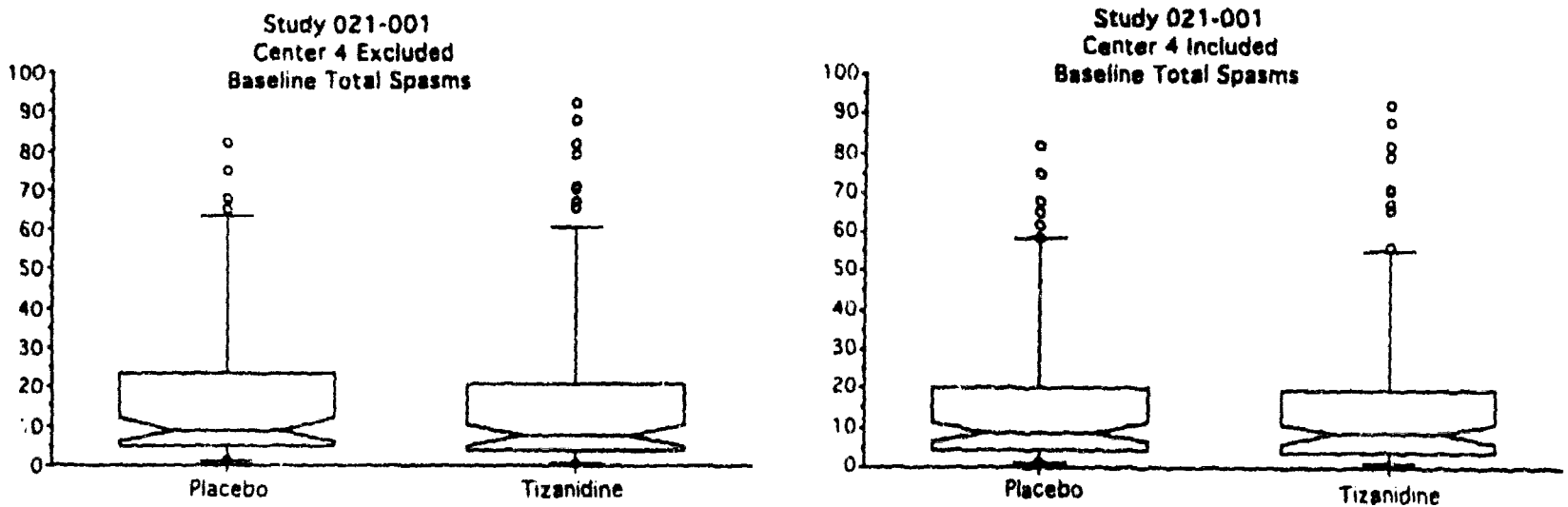
	Placebo Median	Tizanidine Median	p-value
Baseline	8.88	8.57	.31
Response Ratio			
Titration 1	-0.07	-0.08	.68
Titration 2	-0.14	-0.10	.87
Titration 3	-0.16	-0.21	.51
Plateau 1	-0.22	-0.27	.18
Plateau 2	-0.25	-0.34	.03
Plateau 3	-0.31	-0.46	.06
LOCF	-0.26	-0.40	.05

By center results for this variable revealed that about half of the centers (8 out of the 15) showed a larger decrease in count for tizanidine than placebo.

4.2 Reviewer's Results and Comments

The baseline data is not normally distributed (Figure 6) and there are several very large outliers not included in the figure which are listed in the table below. A transformation like the one performed by the sponsor or a rank transform are necessary to produce interpretable results from this skewed data.

Figure 6

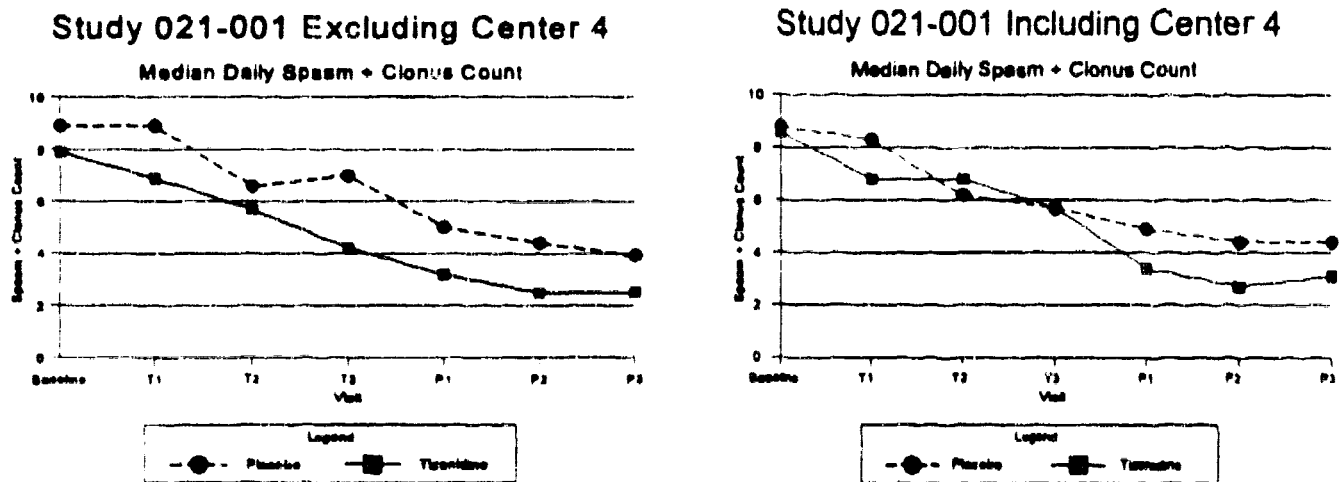


Outliers Excluded from Figure Above

Treatment Group	Baseline Value
Placebo	115, 181, 337, 413, 4176, 8155
Tizanidine	267 (Center 4), 457, 2883

As an alternative analysis this reviewer performed a rank ANCOVA on the total number of spasms and clonus adjusting for baseline and found results similar to those shown in Table 15; the endpoint results were borderline significant ($p = .06$) while the Plateau 3 results were not significant ($p = .08$ with Center 4 and $p = .13$ without Center 4). To see if completers reaped a benefit over the whole plateau phase, analyses of the mean of the plateau responses adjusting for baseline (rank ANCOVA) and strata (blocked Wilcoxon, BW) were performed. The ANCOVA results excluding Center 4 were not significant ($p = .14$) while the BW results were statistically significant ($p = .04$). When Center 4 was included in the analyses, both the BW and ANCOVA results were borderline significant ($p = .07$). These same analyses were repeated for the observed cases data (the data depicted in Figure 7 below) and significant treatment effects were seen for both analyses with or without the Center 4 data. So even though the Plateau 3 results were not positive, the overall results for the plateau phase suggest tizanidine is more effective at decreasing spasm counts than placebo.

Figure 7. Median Daily Spasm and Clonus Count



As for the Ashworth score results shown in Table 14, the data for spasm and clonus count is displayed by baseline strata (Table 16). The tizanidine patients with moderate or severe spasticity at baseline show a benefit over placebo with respect to decrease in number of spasms and clonus. Comparing the results in Table 16 to Table 14, one can see that the relationship between change in Ashworth score and change in daily spasm and clonus count is weak ($R^2 < .1$).

Table 16. Study O21-001
Daily Spasm and Clonus Count
Median Change from Baseline at Endpoint

CENTER 4 EXCLUDED

Baseline Strata	PLA Median (n)	Tizanidine Median (n)
Mild	-2.0 (46)	-1.7 (51)
Moderate	-1.2 (40)	-3.0 (40)
Severe	-6.9 (12)	-8.4 (9)

CENTER 4 INCLUDED

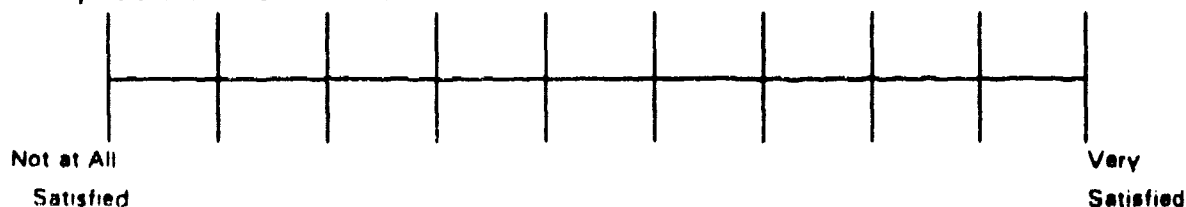
Baseline Strata	PLA Median (n)	Tizanidine Median (n)
Mild	-2.1 (51)	-1.7 (59)
Moderate	-1.2 (47)	-2.9 (45)
Severe	-5.3 (16)	-7.2 (16)

5. Results for the Physician's Global Score

5.1 Sponsor's Results

The prescriber (the physician who manages the dose titration and patient care) and the assessor (the physician who performs the evaluations) were asked to evaluate the overall efficacy of treatment at endpoint. The instructions on the case report form read as follows:

"Place an X on the following 10-point scale to indicate how satisfied you are with the overall effects of the treatment; regarding improvement of symptoms of spasticity along with possible side effects."



Even though the scale indicates a maximum of 10 points the actual recorded scores ranged up to 11.5. The sponsor indicated to this reviewer that the scores were measured in millimeters and the full length of the line was 11.5 (this reviewer measured it as 10 mm).

The sponsor's results are given below (Table 17). The sponsor's analyses of both the assessor's and prescriber's global score including Center 4 (which were confirmed by this reviewer's analyses) yielded significant treatment effects; when excluding Center 4 only the prescriber results are positive.

Table 17. Study 021-001
Global Assessment at Endpoint

	PLA Mean (SD)	TIZ Mean (SD)	p-value (CMH)
Excluding Center 4			
Assessor	4.3 (3.1)	4.9 (3.2)	.28
Prescriber	4.0 (3.6)	5.1 (3.3)	.04
Including Center 4			
Assessor	4.2 (3.1)	5.3 (3.4)	.03
Prescriber	3.8 (3.5)	5.4 (3.4)	.001

The sponsor computed the correlation between the global score and the Ashworth Total score for the whole body and for the lower extremities combining the treatment groups and found a correlation coefficient of about -.30 ($p < .05$).

5.2 Reviewer's Results and Comments

To examine the relationship between the Global rating and the Ashworth Score, the following tables are presented. Only the assessor results are shown because the assessor and prescriber results were similar (paired tests showed no significant differences between the ratings).

Table 18. Study 021-001
Assessor's Global Rating at Endpoint

CENTER 4 EXCLUDED

Global	Number and % of Patients		Mean Change from Baseline Ashworth by Rating	
	PLA	TiZ	PLA	TiZ
Rating < 3	41 (46%)	32 (36%)	-2.0	+0.2
3 ≤ Rating < 6	21 (23%)	26 (29%)	-2.5	-1.5
Rating ≥ 6	28 (31%)	32 (36%)	-4.0	-4.6

	Number and % of Patients		Mean Change from Baseline Ashworth by Rating	
	PLA	TIZ	PLA	TIZ
Global				
Rating < 3	52 (49%)	36 (33%)	-2.4	+0.1
3 ≤ Rating < 6	23 (22%)	28 (26%)	-2.7	-1.8
Rating ≥ 6	31 (29%)	44 (41%)	-7.1	-8.4

Clearly a higher rating is associated with a higher change in Ashworth score in both treatment groups. However, looking at the Ashworth results this way again reveals no significant treatment differences favoring tizanidine.

6.0 Reviewer's Overall Comments on Study 021-001

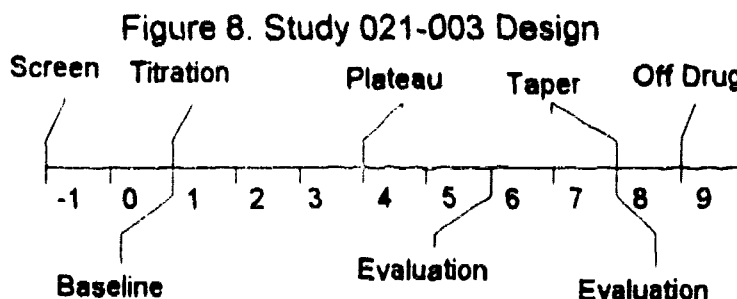
There were no significant decreases in the Ashworth Total score for the tizanidine group compared to the placebo group; in fact the treatment differences at several timepoints favor placebo over tizanidine. Results for the total daily spasm and clonus count (primary efficacy variable) and the physician's global score (secondary efficacy variable) both are favorable for tizanidine but do not offer sufficient evidence of efficacy in the absence of positive results on the Ashworth Total score.

Study 021-003

1. Design

In Study 021-003, 14 centers enrolled patients presenting with established spasticity (observed for a minimum 18 months) secondary to spinal cord injury. Randomization was not stratified on baseline Ashworth as it was in Studies DS-0502 and 021-001. The trial design is shown in the schematic below. After a baseline phase of 2 weeks, dosing was titrated from a starting dose of 4 mg ; 2 mg was the starting dose in Studies DS-0502 and 021-001) to a maximum of 36 mg. Patients then entered a plateau phase of 4 weeks (the plateau phase in the other 2 main studies consisted of 9 weeks) followed by a tapering of drug for 1 week and 1 week off drug. Ashworth score (lower extremities only), pendulum test score and spasm count were named as primary efficacy measures in the protocol. The Ashworth scale and pendulum test were evaluated at the end of titration and the end of plateau while spasm count data was collected weekly by the patient.

Dose adjustments (based on the titration scheme and adverse reactions) were made by a physician while efficacy measures were performed by a physical therapist. The protocol specified that efficacy evaluations be made between 30 and 150 minutes after dosing.



2. Patient Sample

2.1 Demographics

Unlike the MS studies, this sample was made up of predominantly males (88%). About 2/3's of the patients were Caucasian. The average age of the sample was about 36 years. Ninety-two percent of the spinal cord injuries were due to trauma and the median time since injury was about 6 years.

2.2 Patient Disposition

A total of 124 patients were enrolled and randomized in 14 centers. The protocol originally called for a minimum of 15 patients in each center; however, only 1 center enrolled 15 or more patients.

The following tables present the number of patients on study by week (Table 19) and number of dropouts by reason (Table 20). These numbers are different from the ones presented by the sponsor because they are based on patient disposition during the treatment phase only (Baseline to Week 7); the sponsor included patients who dropped after completing Week 7. The database provided by the sponsor and Appendix C.3 were used to create these tables.

Table 19. Study 021-003
Patient Disposition

	PLA	TIZ
Randomized	63 (100%)	61 (100%)
Baseline	63 (100%)	61 (99%)
Week 1 (Titration)	59 (94%)	59 (97%)
Week 2 (Titration)	55 (87%)	53 (87%)
Week 3 (Titration)	53 (84%)	53 (87%)
Week 5 (Plateau)	52 (83%)	47 (77%)
Week 7 (Plateau)	46 (73%)	42 (69%)

Table 20. Study 021-003
Reasons for Discontinuation

	PLA	TIZ
Randomized	63	61
Reason for Discontinuation		
Adverse Event	5 (8%)	11 (18%)
Lack of Efficacy	8 (13%)	3 (5%)
Protocol Violator	4 (6%)	3 (5%)
Other	0 (0%)	2 (3%)
Completed Week 7	46 (73%)	42 (69%)

The major reason for discontinuation in the tizanidine group was experiencing an adverse event while, in the placebo group, the major reason for discontinuation was lack of efficacy. Six of the 11 tizanidine patients who discontinued due to adverse event left the study after the third week (end of titration). In the placebo group, the dropouts due to lack of efficacy predominately (7 out of 8) occurred after the fifth week on study (Plateau 1).

3 Results for Ashworth Total Score

3.1 Sponsor's Results

The results for the sponsor's analyses of the Total Ashworth score are shown in Table 21 below. For this study, the Ashworth score was evaluated only in the lower extremities (3 sites on each side). The ANOVA¹ results clearly show a larger decrease

¹ The sponsor's ANOVA model included terms for treatment and center. Models to test for interaction were performed also and revealed no significant treatment by center effects.

from baseline for the Tizanidine group compared to the placebo group ($p < .0001$). A comparison of percent improved (where improved is defined as a decrease in Ashworth score) showed a significant difference between the treatment groups (46% for placebo versus 68% for tizanidine, $p = .03$).

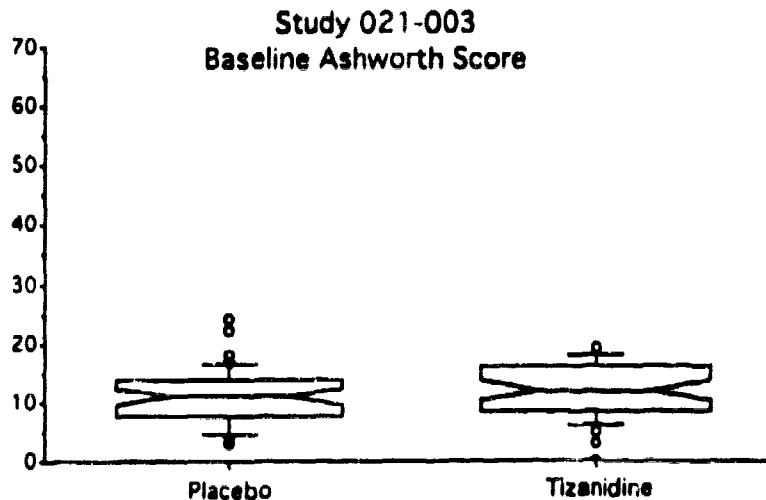
Table 21. Study 021-003
Sponsor's Results for Ashworth Total Score

	Placebo Mean (SD) (n)	Tizanidine Mean (SD) (n)	p-value
Baseline	10.7 (n = 59)	11.8 (n = 59)	.18
Titration 3	+0.3 (3.1) (n = 50)	-3.7 (4.6) (n = 47)	<.0001
Plateau 2	-0.6 (3.6) (n = 38)	-4.4 (4.0) (n = 37)	<.0001
LOCF ¹	-0.4 (3.6) (n = 55)	-4.4 (4.0) (n = 49)	<.0001

3.2 Reviewer's Results and Comments

The distributions for the baseline values of each treatment group are depicted in the boxplots below.

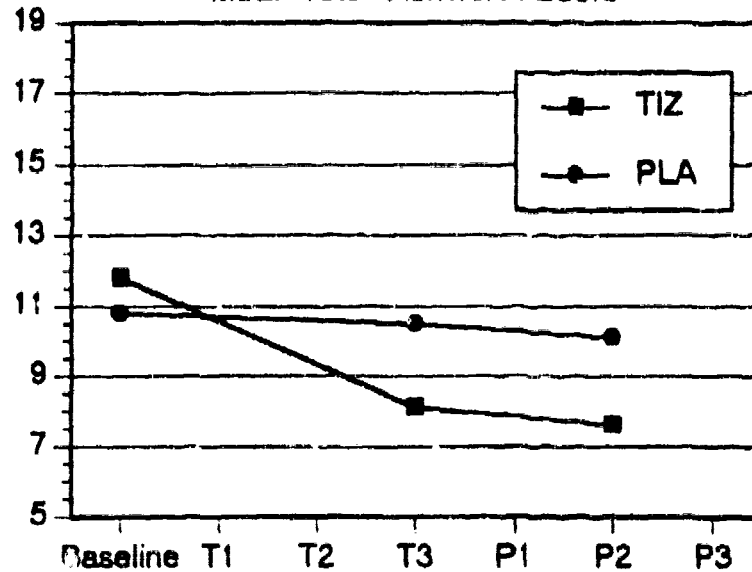
Figure 9



¹ Fourteen patients had baseline data but no Ashworth scores on treatment. 13 of these 14 patients had spasm count data during the plateau phase.

Even though the groups appear comparable at baseline, as an alternative analysis to the sponsor's ANOVA, this reviewer performed baseline-adjusted analyses. ANCOVA analyses adjusting for baseline and blocked Wilcoxon results produced by this reviewer support the sponsor's results (Figure 10); treatment effects were significant for both observed cases data and LOCF data (endpoint) ($p < .01$). At endpoint, the least squares mean (baseline-adjusted) for placebo was 10.8 and for Tizanidine 6.7.

Figure 10. Study 021-003
Mean Total Ashworth Score



For comparison to the other studies, the results by baseline are summarized below (Table 22). Recall that the Ashworth score in this study is a sum of scores for only the lower body extremities so that the total scores at baseline are less than those observed in the other 2 studies. There appears to be no relationship between response and baseline.

Table 22. Study 021-003
Ashworth Mean Change from Baseline by Baseline Score

Baseline Ashworth (Lower Body)	Placebo Mean (n)	Tizanidine Mean (n)
0-9	-0.70 (23)	-4.1 (17)
10-14	-0.09 (22)	-4.8 (16)
15-24	-0.60 (10)	-4.3 (16)

4. Results for Daytime Spasm Counts

4.1 Sponsor's Results

The protocol specified the total number of daytime spasms and nighttime awakenings as a primary efficacy measure. The sponsor analyzed the total as well as daytime spasms and nighttime awakenings separately. Patients had very few nighttime awakenings (about 4-5 per week) and neither group showed a significant decrease over the course of the trial therefore the focus of the sponsor's analysis was the daytime spasms alone. As for Study 021-001, the data was transformed to a response ratio.

For this data, this reviewer discovered while checking the database that the value referred to as "endpoint" in the sponsor's study report does not refer to the last-observation-carried-forward value (which is the definition used for all other variables in this study and all variables in the other studies). Instead the "endpoint" spasm count is the average number of spasms during the taper week plus a few days (the number of days varies from patient to patient) on full dose.

All the significant treatment differences occurred at visits before the second plateau visit (Week 7). The groups are not different at the last taper visit ($p = .19$).

Table 23. Study 021-003
Response Ratio for Daytime Spasms

	Placebo Median (n)	Tizanidine Median (n)	p-value
Baseline	15.0 (59)	19.1 (56)	.18
Response Ratio			
Titration 1	-0.08 (56)	-0.15 (56)	.004
Titration 2	-0.04 (53)	-0.22 (50)	.0005
Titration 3	-0.04 (51)	-0.29 (49)	.01
Plateau 1	-0.03 (50)	-0.36 (45)	.003
Plateau 2	-0.12 (45)	-0.33 (39)	.34
Taper ¹	-0.12 (58)	-0.22 (56)	.19

¹In the sponsor's study report this visit is erroneously called the endpoint (last-observation-carried-forward) visit.

4.2 Reviewer's Results and Comments

The observed cases data presented by the sponsor (Table 23) revealed a difference between the treatment groups at the first plateau visit but not at the second plateau visit. As explained in the previous section, the sponsor did not present LOCF data for this variable so this reviewer computed and analyzed the LOCF values from data provided by the sponsor. Also instead of analyzing the response ratio, this reviewer performed a rank transformation and analyzed the ranks. (The results for both transformations were nearly identical.) The results (Table 24) show no difference between the groups for completers (patients completing Plateau 2) but a statistically significant treatment difference for all patients using the LOCF data suggesting that the patients who drop out in the placebo group are doing appreciably worse than the placebo patients who remain on study. If you compare the last 2 rows of the table below, one can see that this is the case; the 13 placebo patients who did not complete the study showed a small increase in spasm counts while those 46 placebo patients who complete the study show a decrease of nearly 3 daytime spasms. To see if the tizanidine completers reaped some overall benefit over the placebo completers, this reviewer summed the counts for the 2 plateau visits and found no significant difference between the groups ($p = .14$).

Table 24. Study 021-003
Daytime Spasms

	Placebo Median (n)	Tizanidine Median (n)	p-value
All Patients Baseline	15.0 (59)	19.1 (56)	.75
LOCF	-1.5	-5.4	.04
Completers Baseline	14.5 (46)	16.7 (39)	.65
LOCF	-2.5	-5.9	.32
Non-completers Baseline	15.7 (13)	23.1 (17)	.50
LOCF	+0.3	-5.3	.055

5. Results for the Pendulum Test

5.1 Sponsor's Results

Three pendulum tests were performed at each visit and the best one was recorded as the patient's response. Due to the non-normality of the data, the sponsor performed a rank analysis of variance (Table 25).

**Table 25. Study 021-003
Pendulum Test Results**

	Placebo Median (n)	Tizanidine Median (n)	P-value
Baseline	48.2 (57)	40.1 (55)	.30
Plateau 2	56.1 (36)	60.2 (35)	.01
LOCF	46.0 (53)	63.2 (45)	.004

5.2 Reviewer's Results and Comments

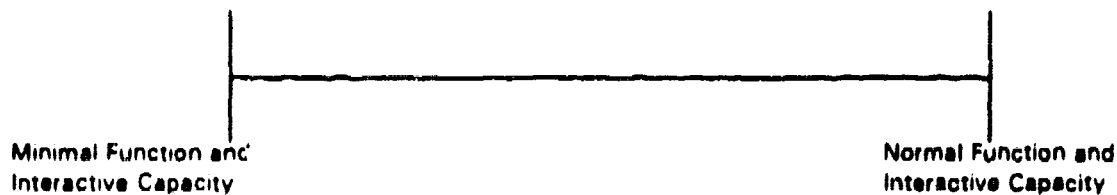
Since the medical reviewer, Dr. Rouzer-Kammeyer, does not believe the pendulum test should be accepted as a primary efficacy measure, this reviewer did not re-analyze this variable. The sponsor's results are convincingly in favor of tizanidine over placebo.

6. Results for the Global Score

6.1 Sponsor's Results

The global score was rated by the physical therapist on the scale shown below.

"Draw a vertical line on the scale to represent the patient's functional capacity at this time."



Unlike the global scores for the other studies, this score was measured at baseline and at the 2 plateau visits (only 19 patients had data at the first plateau visit so they are not included in the table below).

The sponsor's ANOVA results reveal no significant treatment differences (Table 26).

Table 26. Study 021-003
Global score

	Placebo Mean (N)	Tizanidine Mean (N)	P-value
Baseline	6.4 (58)	6.0 (58)	.64
Plateau 2	6.8 (36)	6.4 (37)	.90
LOCF	6.8 (50)	6.7 (45)	.57

6.2 Reviewer's Comments

The global score data shows no substantial improvement in overall functional capacity for either treatment group.

7.0 Reviewer's Overall Comments on Study 021-003

In the protocol for Study 021-003, 3 primary efficacy variables were named; the total Ashworth score, the pendulum test and spasm count. The total Ashworth score results for SCI patients were consistent with the results seen in DS-0502 for MS patients. The tizanidine-treated patients showed a significantly greater reduction in spasticity than the placebo patients. The pendulum test results showed a statistically significant treatment effect however this variable is not considered by the medical reviewer to be a primary measure of efficacy. The third primary efficacy measure, spasm count, failed to differentiate tizanidine from placebo (Tables 23 and 24).

Study S-1 (Investigator Lapierre)

Study S-1 was named as a supportive study by the sponsor and was not as thoroughly analyzed by the sponsor as the three main studies.

1. Design

Study S-1 was conducted in Montreal at a single center. It was a double-blind, randomized, placebo-controlled trial. The treatment period was 8 weeks; 3 weeks for dose titration and 5 weeks of maintenance treatment.

2. Patient Sample

Thirty-three patients diagnosed with multiple sclerosis were randomized to each treatment group; 28 (85%) tizanidine patients and 31 (94%) placebo patients completed the study.

About 1/2 the patients were female. The mean age of the patients was about 46 years.

Approximately 85% of the patients exhibited spasticity in the legs only with about 2/3's of the patients having moderately severe spasticity at baseline.

3. Sponsor's Results

No primary efficacy variables were named in the protocol. The protocol merely states that "clinical, neurological and functional evaluations will be performed by the investigator".

Listed in Table 27 on the following page is a summary of the results for functional disability and three total scores (tone, weakness and reflexes) presented in the study report.

Table 27. Study S-1
Sponsor's Efficacy Results

	Placebo	Tizanidine	p-value
Functional Disability ¹	No change	No change	NS
Total Limb Tone ²			
Baseline	29.9	23.9	.015
Change at Day 56	+1.5	+3.9	.21 ³
Total Limb Weakness			
Baseline	40.4	39.5	NS
Change at Day 56	+1.7	+0.9	NS
Total Deep Tendon Reflexes			
Baseline	13.7	12.1	.09
Change at Day 56	+0.2	-1.1	<.01
Antispastic Efficacy (% Responding Good or Excellent)			
Physician	10%	27%	.08
Patient	19%	22%	.58

Note that an increase in total score for limb tone and limb weakness indicates improvement. For total deep tendon reflexes, a decrease indicates improvement.

All 3 total scores were measured as the sum of scores for affected limbs only. Limb scores normal at baseline and endpoint were not included in the totals therefore, the baseline totals represent, for each patient, different numbers of limb sites. Also by excluding normal scores, patients with normal function at several sites can have total scores smaller than patients exhibiting spasticity at many sites (remember that improvement is defined by an increase in total score). This makes the total score difficult to interpret since large total values may not necessarily be associated with better overall function than small values. The baseline comparisons for the totals are impossible to interpret for this reason.

For all 3 totals, the treatment differences on Day 56 were due primarily to improvement in ankle function.

¹ Functional disability was defined by disability status, an ambulation index and an upper extremity index. All 3 measures showed no within group or between group differences.

² Limb tone was measured on a scale of 0 to 6 where 0=no movement, 4=normal and 6=marked hypotonic. Seven patients had scores of 5 or 6 for ankle plantarflex which were excluded from the analyses. Therefore the tone scores of the data analyzed were all 4 or less.

³ Table XI (Vol. 144, page 40) indicates that the total scores are statistically significantly different however Table 2.13.2 (Vol. 144, page 117) indicates that the p-value for the comparison is .21.

The mean dose used in this study was less than the dose used in the 3 main studies; the mean dose in the 3 main studies was 29 mg compared to 18 mg in this study.

4. Reviewer's Analyses and Comments

The presentation of this study by the sponsor provided insufficient information regarding the data and the analyses to provide statistical evidence of efficacy. In addition, the scores used in this study were different from those used in the other studies in this submission making it impossible to determine if the data is supportive of the findings in the other 3 main efficacy trials.

This reviewer requested the limb tone data from the sponsor. The sponsor was asked to transform the by-body site data to an Ashworth scale as shown in the table below and provide total scores for the original data and the recoded data.

Original Score	"Ashworth" Score
4, 5 and 6	0
3	1
2	2
1	3
0	4

Neither I nor the sponsor were able to replicate the results reported in the NDA study report (those analyses were performed by Sandoz) using the original scores with normal values excluded (compare the results in Table 28 below with the results in Table 27 on the previous page).

Note that the recoded scores show a significant difference between the groups at Day 56 while the originally coded scores with the normals excluded do not show a difference. Using the original scores without any exclusions, a p-value of .03 for the Day 56 comparison was found; the LOCF p-value was nonsignificant (p = .11). The recoded scores (Ashworth scale) reveal a significant difference between the groups at Day 56 and borderline significant results for the LOCF data (p = .08). Of the 5 tizanidine dropouts, 2 patients had only Day 10 data and 3 had Day 21 data; none of those patients, then, had any plateau data. The mean change for those tizanidine patients was 0. The 2 placebo dropouts both showed a decrease at Day 21 (-1 and -10). The results for the dropouts favor placebo which explains the difference between the endpoint and LOCF results.

Table 28. Study S-1
Reviewer's Results for Total Limb Tone Scores

	Placebo	Tizanidine	p-value ¹
Original Scores			
Baseline	31.5	26.2	.08
Change from Baseline			
Day 56	+ 1.3	+ 3.5	.10
Endpoint	+ 1.6	+ 3.0	.30
Recoded Scores			
Baseline	18.5	15.5	.23
Change from Baseline			
Day 56	-1.4 (n = 30)	-3.6 (n = 28)	.02
Endpoint	-1.6 (n = 32)	-3.1 (n = 33)	.08

The magnitude of the treatment effects are similar to what was observed in Study DS-0502 and Study 021-003 with changes of 3 to 4 seen in the Tizanidine group. These limb tone results offer supportive evidence of the efficacy of Tizanidine over placebo for the treatment of spasticity.

¹A Wilcoxon Rank Sum test was used to compare baselines and an ANCOVA adjusting for baseline was used for comparisons at Day 56 and at endpoint.

Study S-2 (Investigator Rinne)

Study S-2 was a crossover study with two 4-week periods. Dosing was initiated at 2 mg and increased to a maximum of 18 mg. Thirty-two patients were enrolled in the study; only one patient dropped out early. Twenty of the 32 patients were diagnosed with multiple sclerosis and 12 with chronic myelopathy. The efficacy measures were the Ashworth score and the Northwestern University Disability Scale.

The sponsor reported this study as supportive however most patients showed no changes on either efficacy measure. The sponsor concluded that the measures lacked sensitivity. (For additional details see Dr. Rouser-Kammeyer's medical review.)

In this crossover study there was no washout period between treatments. Also the sponsor performed no assessments of carryover so the effect of no washout was not quantified. It seems reasonable, then, to look at just the first period data. Using data listings provided in the study report, this reviewer analyzed the first period data. Only the data for the lower extremities was used since most of the upper extremity scores were normal. The results for the Ashworth Score (Table 29) show no significant difference between the treatment groups. Three of the 15 tizanidine-treated patients showed an improvement in their Ashworth total score while only 1 of the 15 placebo patients showed an improvement (20% vs 6%, $p = .26$).

Table 29. Study S-2
Period 1 Results for the Ashworth Total of Lower Extremities

	Placebo Mean (SD) (n = 16)	Tizanidine Mean (SD) (n = 15)	p-value
Baseline	5.3 (1.9)	5.1 (1.9)	.98 (Wilcoxon)
Change from Baseline	-0.1 (0.5)	-0.3 (0.7)	.33 (Blocked Wilcoxon)

This study does not offer any evidence to support the efficacy of tizanidine over placebo. The lack of response for tizanidine may be due to the short treatment period (4 weeks compared to 7 to 13 weeks in the other studies), the low dose (18 mg compared to about 29 mg for the 3 main studies) and the small sample size.

Dosing

Compliance as measured by percentage of tablets taken was high in both groups (>90%) in all the studies.

Placebo patients took more tablets on average than the tizanidine patients (Table 30) in all five studies. Also more placebo patients than tizanidine patients were titrated to and maintained at the maximum dose (36 mg/day) allowed in the 3 main studies. About one-fourth of the tizanidine patients were never titrated to the maximum dose.

The mean doses observed in Studies S-1 and S-2 were notably smaller than the mean doses in the 3 main studies. The maximum dose allowed in Study S-1 was 32 mg/day and in S-2 18 mg/day.

Table 30. Dosing Data¹

Study	Mean Daily Dose mg/day	% of Patients Maintained on Max Dose of 36 mg for the Whole Plateau Phase	% of Patients Maintained on Dose < 36 mg for the Whole Plateau Phase
DS-0502 Placebo Tizanidine	32.9 29.0	67% 30%	8% 27%
O21-001 Placebo Tizanidine	33.0 26.7	77% 39%	11% 21%
O21-003 Placebo Tizanidine	33.4 31.1	89% 69%	6% 17%
S-1 Placebo Tizanidine	22.5 18.4	NA	NA
S-2 Placebo Tizanidine	17.25 17.2	NA	NA

¹ The data in this table was extracted from the sponsor's study reports and from documents received June 10, 1994 in response to this reviewer's requests.

Summary and Conclusions

The sponsor presented the results from 3 large studies (Studies DS-0502, 021-001 and 021-003) and 2 smaller studies (Studies S-1 and S-2). The patients in Studies DS-0502, 021-001 and S-1 were all diagnosed with multiple sclerosis; 2/3's of the patients in S-2 were diagnosed with MS and 1/3 with chronic myelopathy and all the patients in 021-003 had spasticity secondary to spinal cord injury.

The Ashworth scale was a primary efficacy measure in 4 of the trials; in Study S-1, the Ashworth scale was not used but the tone data was recoded to an Ashworth scale (see page 34 for more details). Results for this variable are summarized in Tables 31 and 32 on the following page. In 2 studies (021-001 and 021-003), spasm count as recorded in patient diaries was named as an additional primary efficacy measure. The results for spasm count are summarized in Table 33.

The Ashworth change from baseline results for Studies DS-0502 and 021-003 show that tizanidine significantly decreases muscle tone compared to placebo; the results for Study S-1 are borderline significant. Note that the magnitude of the results in Study S-1 are consistent with the results seen in the 2 positive studies. This reviewer would consider the S-1 results as supportive evidence of efficacy. Notice also from Table 32 that more than 2/3's of the tizanidine-treated patients in these three studies showed a decrease on the Ashworth scale.

The results from S-2 (Table 31) are clearly not convincing; however there are several plausible reasons why this trial failed to differentiate tizanidine from placebo. S-2 was a very small ill-designed crossover trial with treatment periods of only 4 weeks duration where a low dose was administered (18 mg compared to 29 mg in the large trials) to patients with only mild spasticity (Table 29).

The negative Ashworth results from Study 021-001 are puzzling given that it is the largest study and that the other 2 studies (DS-0502 and S-1) of MS patients yielded favorable results. The sponsor reported protocol compliance problems with Center 4¹ (see page 11 for more details), however, the exclusion of Center 4 did not appreciably affect the results (see Tables 11 and 12 and Figure 4). To try to explain the lack of effect, the sponsor performed many exploratory analyses (effect vs dose; effect of each center on overall effect; worst muscle at baseline analysis; time of dosing vs time of measurement; concomitant use of amitriptyline/tricyclics). None of these analyses of the Ashworth score revealed any significant treatment effects. There appears to be no clear reason for the large placebo response seen in this trial and the lack of a significant treatment difference.

¹Investigations by the FDA Office of Compliance confirmed that problems existed at Center 4 regarding the conduct of the trial which were described earlier in this review.

Table 31. Ashworth Score Mean Change from Baseline at Endpoint

	PLACEBO Mean (SD) (n)	TIZANIDINE Mean (SD) (n)	P-VALUE ¹
DS-0502	-1.5 (5.4) (n = 93)	-3.9 (5.0) (n = 94)	.008
O21-001 Without Center 4	-2.8 (7.2) (n = 109)	-1.7 (7.2) (n = 112)	.46
With Center 4	-3.8 (9.5) (n = 120)	-3.2 (9.3) (n = 125)	.99
O21-003 ²	-0.4 (3.6) (n = 55)	-4.4 (4.0) (n = 49)	.0001
S-1	-1.6 (3.7) (n = 32)	-3.1 (4.5) (n = 33)	.08
S-2 Period 1 ²	-0.1 (0.5) (n = 16)	-0.3 (0.7) (n = 15)	.33

Table 32. % of Patients Showing a Decrease on the Total Ashworth Score at Endpoint

	PLACEBO	TIZANIDINE
DS-0502	49%	71%
O21-001	60%	60%
O21-003	46%	69%
S-1	66%	79%
S-2	6%	20%

¹P-values are results of reviewer's analyses.

² Scores are for the lower extremities only.

The treatment responses for the Ashworth score were consistent across demographic groups based on age and gender (Table 33). Note that only 14 patients were 65 years or older.

**Table 33. Percent Improved on Ashworth By Demographic Group
Trials DS-0502, 021-001 and 021-003 Combined**

	Placebo	Tizanidine
Age Groups		
< 40	46/92 (50%)	67/105 (64%)
40-64	97/176 (55%)	115/174 (66%)
≥ 65	5/9 (56%)	4/5 (80%)
Gender		
Male	76/111 (68%)	83/133 (62%)
Female	72/136 (53%)	103/151 (68%)

Summarized in Table 34 on the following page is the total spasm count. For Study 021-001, total count is the sum of the daytime spasms, nighttime spasms and clonus while for Study 021-003, total count equals just the daytime spasm count. Nighttime awakenings were recorded in Study 021-003 however the counts were very small and showed no change over the duration of the trial so they are not included in the totals here. Due to the large number of outliers and the nonnormality of the data, this data was transformed to a response ratio (see page 17) or to ranks for analysis. The endpoint results of analyses for both transformations consistently (Table 34) favored tizanidine over placebo. The completer results for Study 021-001 (see Table 15) were similar to the results shown below; for Study 021-003, the completer results were not significant (Table 24, $p = .32$).

Table 34. Results for Spasm Count at Endpoint

	PLACEBO Median	TIZANIDINE Median	P-value ¹
Study 021-001 (Including Center 4)² Total Spasm + Clonus Count			
Response Ratio	-0.26	-0.44	.03
Baseline Change at Endpoint	8.9 -1.8	8.6 -2.9	.66 .06
Study 021-003 Daytime Spasm Count			
Response Ratio	-0.06	-0.31	.04
Baseline Change at Endpoint	15.0 -1.5	19.1 -5.4	.79 .04

In conclusion, the results for the Total Ashworth scores in Studies DS-0502 and 021-003 offer statistical evidence of the efficacy of tizanidine compared to placebo for the treatment of spasticity; the results for Study S-1 offer supportive evidence of efficacy. For the largest study in the submission (Study 021-001), there are no significant decreases in the Ashworth Total score for the tizanidine group compared to the placebo group; in fact the treatment differences at several timepoints favor placebo over tizanidine. Study 021-001's results for the total daily spasm and clonus count (primary efficacy variable) and the physician's global score (secondary efficacy variable) both are favorable for tizanidine but do not offer sufficient statistical evidence of efficacy in the absence of positive results on the Ashworth Total score.

¹Reviewer's rank ANCOVA results.

²The results excluding Center 4 were nearly the same.

Joy D. Mele

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius *JDM 12-22-94*

Dr. Dubey *6*

12-22-94

cc:

Orig. NDA 20-397

HFD-120

HFD-120/Drs. Leber, Katz and Rouzer-Kammeyer

HFD-120/Mr. Grillay

HFD-713/Dr. Dubey [File: DRU 1.3.2]

HFD-713/Group 2 File

HFD-713/Ms. Mele

HFD-344/Dr. Lisook

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This review consists of 42 pages.

Statistical Review and Evaluation

JAN 29 1996

DETURN

JAN 31 1996

NDA #: 20-397 / 1-S

Name of Drug: Zanaflex (tizanidine HCL)

Applicant: Athena Neurosciences, Inc.

Indication: Treatment of spasticity of spinal cord origin

Documents Reviewed: Volumes 2 to 6 submitted September 11, 1995

Medical Input: Randy Levin, M.D. (HFD-120) was consulted during the review process.

Background

The sponsor, Athena Neurosciences, submitted the results of 3 double-blind, randomized, parallel studies (Studies DS-502, 021-001 and 021-003) which were reviewed by this statistician in a document dated 12/23/94. An overview of these studies is shown below.

Table 1. SUMMARY OF PLACEBO CONTROLLED TRIALS

Study Number	# of Centers	# of Placebo Patients	# of Tizanidine Patients	Patient Population	Duration of Treatment	Placebo Ashworth	Tizanidine Ashworth	P-value
DS-0502	16	93	94	MS	13 weeks	-1.5	-3.9	.008
021-001								
With Center 4	15	125	131	MS	13 weeks	-2.8	-1.7	.46
Without Center 4	14	109	112			-3.8	-3.2	.99
021-003	14	59	59	spinal cord injury	7 weeks	-0.4	-4.4	.0001

The Division of Neuropharmacology considered the data from these studies inadequate for establishing the efficacy of tizanidine for the treatment of spasticity. In a non-approval letter dated March 6, 1995, inconsistency of results and the lack of significant treatment effects on a compound measure of efficacy were cited as principal inadequacies. As part of the sponsor's reply to the non-approval letter, the sponsor has submitted the results of Study AN021-005. This study is the subject of this statistical review.

Study AN021-005

Study AN021-005 is a multicenter, double-blind, randomized, placebo-controlled trial with 3 treatment arms; placebo, 8 mg of tizanidine and 16 mg of tizanidine. Multiple sclerosis patients with established spasticity were randomized to treatment after a 2-week washout period and a 1-week placebo run-in. Dosing (at approximately 9 AM) occurred on a single day following the run-in.

To be eligible for this study, patients needed to have a minimum Ashworth score of 2 on a lower extremity muscle group and a total Ashworth ≥ 4 on the same limb.

The efficacy endpoints were Ashworth and pendulum test scores (best of 3 swings) for the limb with the most spastic muscle at trial entry and spasms plus clonus reported by the patient for the 6 hours post-dosing. The limb Ashworth score was based on 4 muscle groups; hip adductors, knee flexors, knee extensors and plantar flexors. Efficacy measurements were performed on the first day of the placebo run-in (Visit 2) and on the single day of drug administration (Visit 3) before dosing (Hour 0) and 1, 2, 3, and 6 hours after dosing. Ashworth and pendulum scores at Hour 1 were defined in the protocol as the primary efficacy parameters. A blinded physical therapist who was not involved with safety assessments evaluated the patient.

The sponsor's proposed labeling states that the maximum recommended dose of tizanidine is 36 mg/day. The labeling also recommends TID dosing henceforth the maximum single dose which would be recommended by the sponsor is 12 mg. A dose of 16 mg TID then is clearly well above the maximum dose recommended by the sponsor and more importantly there is scant safety data for doses above 30 mg/day. From consultations with Dr. Levin (the medical reviewer from HFD-120), this reviewer will focus primarily on the comparison of the 8 mg dose of tizanidine to placebo.

Sponsor's Results

A total of 142 patients (48 placebo, 45 tizanidine 8 mg and 49 tizanidine 16 mg) were randomized to treatment at 10 centers (7 to 20 patients in each center with equal numbers in each treatment group). Only 2 patients did not complete the study (one patient on 8 mg tizanidine due to patient decision and one patient on 16 mg due to adverse event). Nine patients completed the study but had incomplete data and were considered non-evaluable by the sponsor.

The patient population was predominantly white (>90%) and the average age was 45 years (range of 20 to 70). About $\frac{2}{3}$ of the patients in the placebo group and the tizanidine 16 mg group were female, while in the 8 mg group about half were female ($p = .15$ for 8 mg versus placebo). Severity of MS was rated as mild, moderate or severe at baseline; the percentages of patients in each category were 6%, 60% and 34%, respectively. The mean duration of MS was approximately 11 years.

The sponsor presented the results of 3 protocol-defined comparisons; baseline versus each hour on treatment for the tizanidine groups pooled (within treatment comparison), tizanidine groups pooled versus placebo and tizanidine 8 mg versus tizanidine 16 mg (between treatment comparisons). Results of these comparisons do not provide information about the treatment effect of tizanidine 8 mg compared to placebo therefore the sponsor's efficacy results are not presented here.

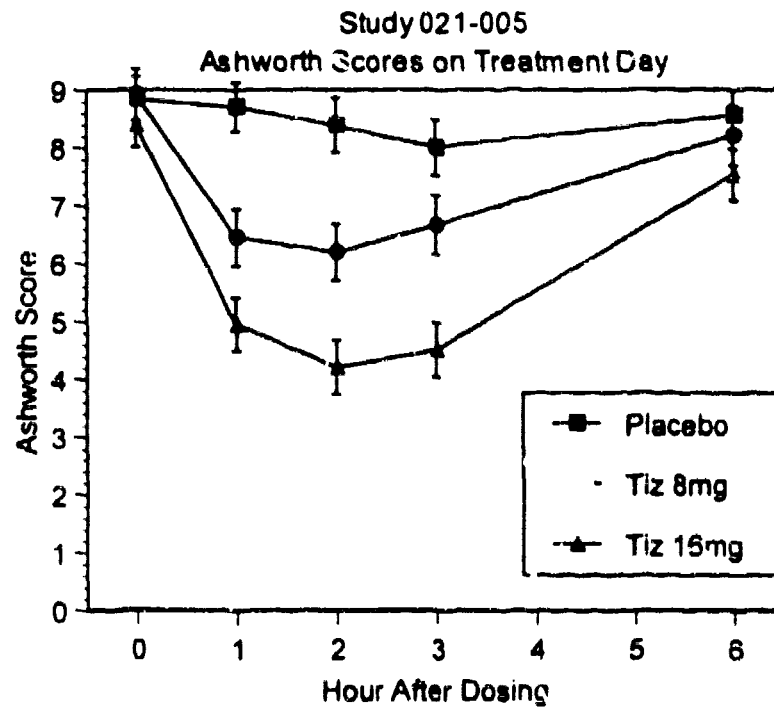
Reviewer's Results and Comments

Ashworth Total Results

The means and standard errors (SE) for the Ashworth score on the treatment day (Visit 3) are depicted in Figure 1 below followed by a table of the results (p-values) from Wilcoxon rank sum tests. Results from performing analyses of covariance (ANCOVA) with baseline as a covariate and with treatment and center as main effects were consistent with the results shown below. Also, the efficacy results were consistent across the centers.

Both the tizanidine 8 mg and 16 mg groups showed a significant decrease in the Ashworth score compared to placebo at Hours 1, 2 and 3 after dosing. By Hour 6, no treatment effects were apparent and values had returned to baseline for about 50% of the patients treated with 8 mg of tizanidine.

FIGURE 1



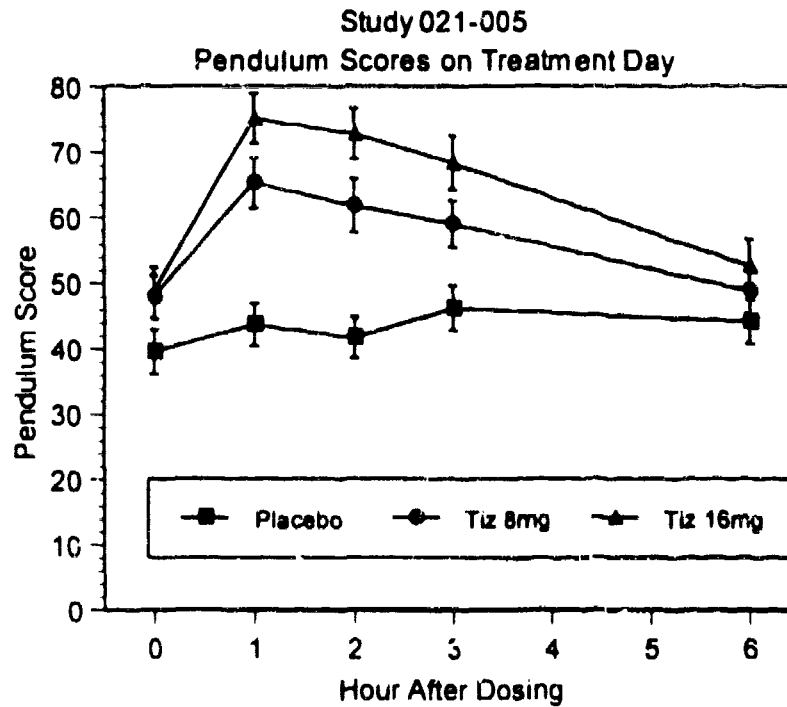
Study 021-005
Ashworth Score Results (p-values)

Hour	0	1	2	3	6
Tiz 8mg vs Placebo	.94	.0001	.0001	.0005	.13
Tiz 16mg vs Placebo	.41	.0001	.0001	.0001	.12

Pendulum Test Results

The means and standard errors (SE) for the pendulum test on the treatment day (Visit 3) are depicted in Figure 2 below. A Wilcoxon Rank Sum test at baseline revealed important treatment group differences ($p < .10$, see table below graph). To adjust for these baseline differences, this reviewer analyzed the by-hour data using ANCOVA with baseline as a covariate and with center and treatment as main effects (assumptions of the model were met). The results of the ANCOVA's are provided in the table below. The results from Hours 1 and 2 show that tizanidine 8 mg is significantly more effective than placebo; by Hour 3 the results are borderline significant and clearly by Hour 6, the groups are no longer different.

FIGURE 2



Study 021-005
Pendulum Test Results (p-values)

Hour	0	1	2	3	6
Tiz 8mg vs Placebo	.06	.0001	.0001	.06	.86
Tiz 16mg vs Placebo	.10	.0001	.0001	.0001	.56

Spasms and Clonus

Number of spasms and clonus were recorded by the patient on the first day of the placebo run-in visit (Visit 2) and at the dosing visit (Visit 3) for 6 hours. About 25% of the patients had no spasms or clonus for both 6-hour periods. Because of the high intrapatient and interpatient variabilities observed by hour, this reviewer looked at the counts summed over the 6 hours rather than by hour. The 6-hour sums ranged from 1 to 1920 (the coefficients of variation for all treatment groups were greater than 200%).

To compare the groups, this reviewer computed the % change as the difference of the 6-hour sums at Visit 2 and at Visit 3 divided by the sum at Visit 2 and performed pairwise comparisons using the Wilcoxon rank sum test. Those comparisons were statistically nonsignificant ($p > .6$). Analyses of the data transformed to stabilize the variance also revealed no significant differences between treatment groups.

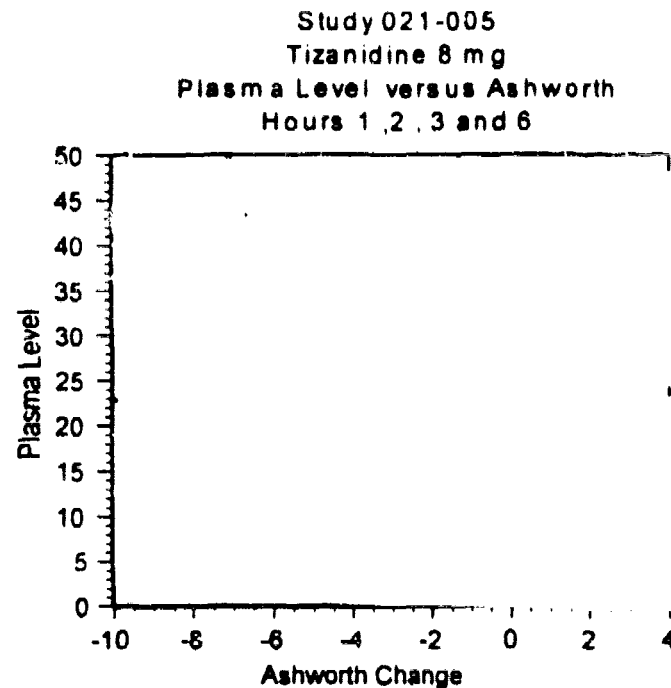
	Placebo	Tiz 8 mg	Tiz 16 mg	Tiz 8 mg vs Placebo	Tiz 16 mg vs Placebo
% Change					
Median	-12%	-21%	-33%	$n = .89$	$p = .68$
Mean	+52%	+469%	+106%		
SD	202	1524	429		

Plasma Concentrations and Response for 8 mg Tizanidine Group

Plasma concentrations were measured at Hours 0, 0.5, 1, 1.5, 2, 3, 4 and 6 at the treatment visit (Visit 3). The sponsor examined the correlation of plasma levels with the efficacy measures (Ashworth and pendulum) and with adverse events. This reviewer focused primarily on the relationship of plasma levels to change on the Ashworth scale and to changes in blood pressure as suggested by the medical reviewer, Dr. Levin (see Dr. Levin's review for more details). Only the data for the 8 mg Tizanidine group is explored here.

Figure 3 below graphically summarizes the relationship between plasma level and change in Ashworth score for the 8 mg Tizanidine group at Hours 1, 2, 3 and 6. About 30% of the variation in Ashworth score is explained by the plasma level. (A stepwise regression analysis showed that plasma level was a better predictor of Ashworth change than baseline Ashworth or blood pressure changes.) The correlation between plasma levels and Ashworth change was strongest at 2 and 3 hours after dosing ($r^2 > .4$). (The results for the 16 mg Tizanidine group were similar to the results reported here for the 8 mg group.)

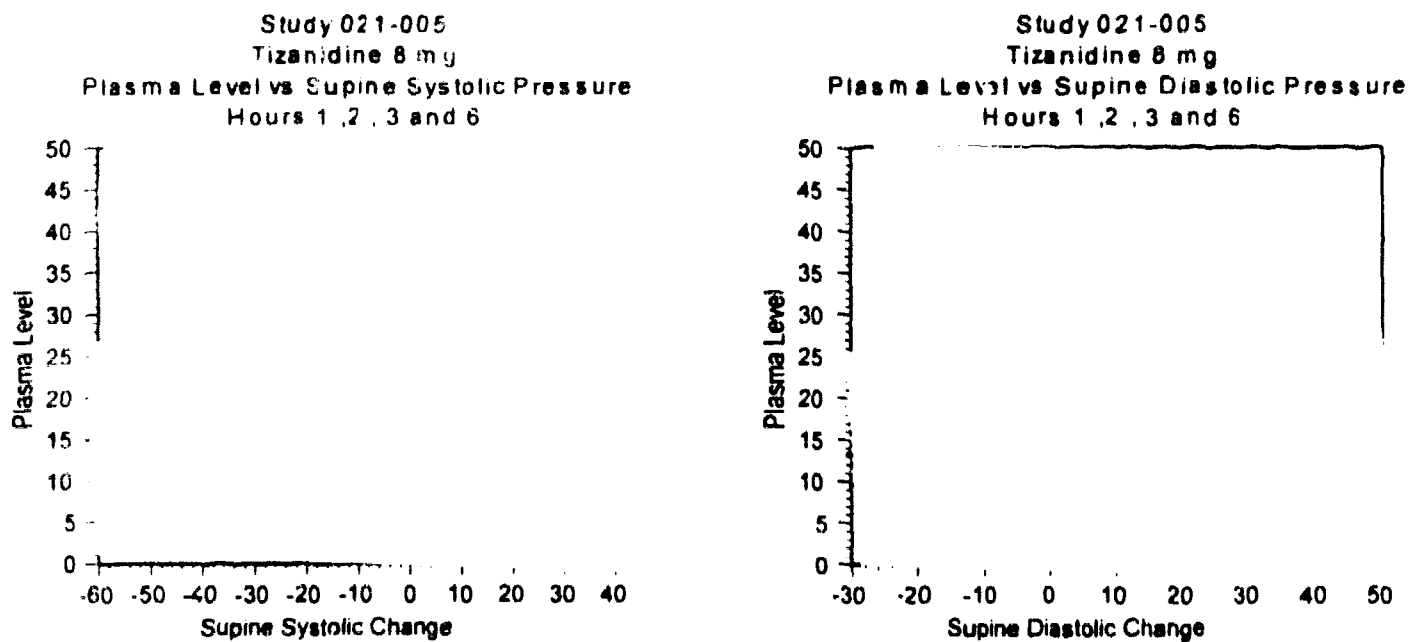
FIGURE 3



The relationship between change in blood pressure (BP) and plasma level of tizanidine was not examined by the sponsor but was considered to be important for this review due to the significant decreases in blood pressure observed for the tizanidine treatment groups¹ (additional details regarding this safety issue are presented in Dr. Levin's clinical review).

Decreases in supine diastolic and systolic blood pressure are positively correlated with plasma levels but it is clear from Figure 4 below that the relationship is a weak one ($r^2 = .02$, $p = .052$ and $r^2 = .21$, $p = .0001$, respectively).

FIGURE 4



¹ The decreases in BP seen in the tizanidine groups were statistically significant from changes observed in the placebo group at each time point. The mean changes in BP in the placebo group were less than 2 mmHg.

Changes from baseline of Ashworth scores are not strongly correlated with changes in supine systolic and diastolic pressure as can be seen in Figure 5 ($r^2 \leq .17$).

FIGURE 5

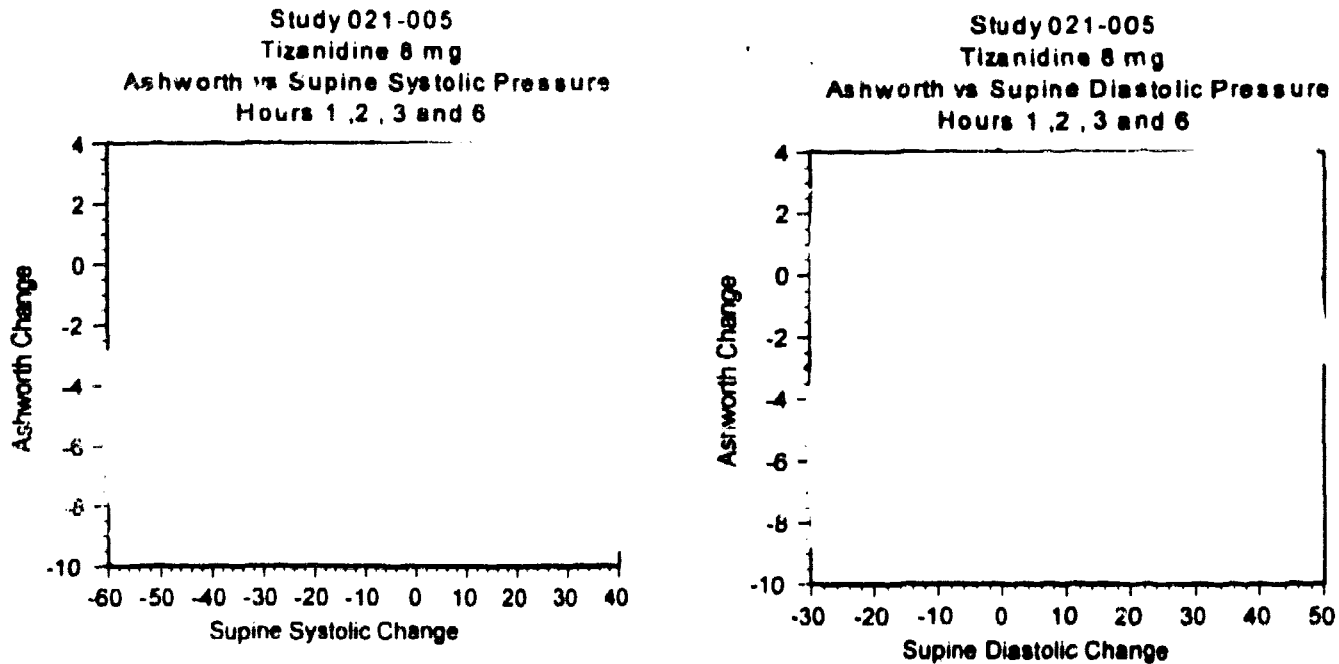


Table 2 below presents the mean changes observed for 5 increments of change of the Ashworth score at Hour 2 for tizanidine 8 mg. It appears that larger changes in the Ashworth are associated with larger changes in BP but as was illustrated above the two measures are not strongly correlated (this may be partly due to the small sample size and large variability).

**Table 2. Study 021-005
Results for Tizanidine 8 mg
Hour 2**

Decrease from Baseline of Ashworth	N	Diastolic BP Change Mean (SD)	Systolic BP Change Mean (SD)
≤0	8	-3.3 (10.6)	-3.5 (11.8)
>0, ≤2	13	-4.8 (18.0)	-14.3 (16.7)
>2, ≤4	12	-7.6 (10.7)	-23.9 (16.5)
>4, ≤6	9	-9.6 (10.3)	-22.0 (18.0)
>6	3	-10.0 (10.0)	-24.3 (9.3)

Within a subgroup of patients with clinically significant changes¹ in systolic or diastolic BP (about one-third of the 8 mg tizanidine patients), all patients showed a significant decrease in Ashworth score. So clinically significant changes in BP appear to be associated with significant changes in the Ashworth score but significant changes in the Ashworth score was not predictive of changes in blood pressure (Figure 5) for the majority of the patients.

¹ A clinically significant change was defined a priori as a 20% change from baseline for patients with a baseline systolic pressure greater than 80 mmHg and 10% change otherwise.

Overall Comments

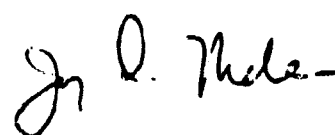
The Ashworth score and pendulum test results of Study 005 provide statistical evidence of the efficacy of tizanidine 8 mg for the treatment of spasticity compared to placebo. When given in a single dose, tizanidine was shown to be effective for 3 hours after dosing with the peak effect occurring at Hour 2 (51% of the tizanidine 8 mg patients reached their peak effect by Hour 2). By Hour 6, tizanidine scores had returned to baseline (Figures 1 and 2).

The results at Hour 2 for Study 005 appear to be consistent with the endpoint results from Study 003 (Table 3 below). For Study 003, efficacy measurements were made weekly for 7 weeks and were performed within 2.5 hours of dosing (for the other 2 studies in the submission, time of measurement was not stipulated). For the Ashworth score in Study 003 the lower extremities were assessed (3 sites on each lower extremity for a total of 6 sites) while in Study 005, 4 muscle sites in one lower extremity were used. This difference between studies in number of sites used to compute the Ashworth score total may explain the difference in magnitude of response for tizanidine shown below (Table 3).

Table 3. Efficacy Results for Studies 003 and 005
Mean Change from Baseline¹

	Placebo	Tizanidine	P-value
Ashworth			
Study 003 Endpoint (6 sites)	-0.4 (n = 55)	-4.4 (n = 49)	< .0001
Study 005 Hour 2 (4 sites)	-0.5 (n = 47)	-2.7 (n = 45)	< .0001
Pendulum Test			
Study 003 Endpoint	+ 2.0 (n = 53)	+ 13.5 (n = 45)	.004
Study 005 Hour 2	+ 2.0 (n = 47)	+ 14.1 (n = 42)	.0001

Study 005 provides convincing efficacy data for single dose administration of tizanidine 8 mg. The major shortcoming of this study is that it fails to provide safety or efficacy data for chronic use of tizanidine.



Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Sahlroot *JTS* 1-22-96

Dr. Chi *Chi* 1/24/96

¹ Mean baseline Ashworth score in Study 003 was about 11 and in Study 005 about 9. Baseline pendulum scores were between 40 and 48 in both studies.

BIO Review

NDA-020397

FIRM: ATHENA NEUROSCIENCES

4 OF 7

TRADE NAME: ZANAFLEX ORAL TABS. 4MG

GENERIC NAME: TIZANIDINE HCL

Zanaflex[®]
(Tizanidine) Tablets

NDA 20-397

Biopharmaceutics

Volume 7 of 7

JAN 31 1995

**Tizanidine HCl (ZANAFLEX[®])
4 mg Tablet (Scored)**

**Athena Neurosciences, Inc.,
South San Francisco, CA
Submission Dates:**

Reviewer: Vijay K. Tammara, Ph.D.

**December 3, 1993
July 8, 1994
July 26, 1994
July 27, 1994
July 31, 1994
August 1, 1994
August 15, 1994
August 16, 1994
August 18, 1994
August 29, 1994
September 9, 1994
September 23, 1994
October 3, 1994**

**DETTION
JAN 31 1995**

Type of Submission: NDA 20-397 (NME)

Review of an NDA

SYNOPSIS

Tizanidine, a centrally acting α_2 -adrenergic agonist, is a muscle relaxant and antispasmodic agent which does not produce muscle weakness. A maximum dose of 36 mg is recommended daily in three equally spaced doses with 12-24 mg as the daily optimum therapeutic dose. Tizanidine is rapidly and well absorbed reaching peak plasma concentrations in 1.5 hours. The absolute oral bioavailability of Tizanidine from Zanaflex 4 mg oral Tablets was only 38% (CV = 24%). Tizanidine is widely distributed throughout the body; mean steady state volume of distribution is 2.4 L/Kg (CV = 21%) following intravenous administration in healthy adult volunteers. Tizanidine undergoes extensive metabolism in the liver and forms about 15 metabolites, of which 3, 4, and 10 are the major metabolites in humans. Metabolites 3 and 4 were reported to be inactive, while the activity of 10 is unknown. Following a single 5 mg or 20 mg oral dose of ¹⁴C-tizanidine, an average of 53% and 23% of total radioactivity was recovered in the urine and feces, respectively, over 120 hours, for combined recovery of about 76% of the administered dose. Upon administration of multiple oral doses of 4 mg ¹⁴C-tizanidine (as q 8 h for 13 doses), an average of 66% and 17% of total radioactivity was recovered in the urine and feces, respectively, over 120 hours, for a combined recovery of about 83% of the administered dose. The parent drug represented less than 6% of the radioactivity in human plasma and 2% of the dose in human urine. The terminal half-lives of tizanidine and total radioactivity were 2.2 hrs and 43-90 hrs, respectively. Little or no accumulation of parent drug occurred during the

multiple dosing regimen, while total radioactivity accumulated in blood by a factor of 3.1 times compared to single dose levels. Tizanidine displayed linear pharmacokinetics over a dose range of 1-20 mg. Tizanidine is approximately 30% bound to plasma proteins. Food increases Cmax by 32% and decreases Tmax by 44%; the extent of tizanidine absorption was not affected.

Gender has no effect on the pharmacokinetic parameters of tizanidine. A moderate intrasubject variability in tizanidine pharmacokinetic parameters (AUC and Cmax) was observed. It was observed that the intrasubject variability (AUC: 17%; Cmax: 20%) is lower than the intersubject variability (AUC: 41%; Cmax: 26%). Retrospective analysis of age on the pharmacokinetic differences indicated that clearance is 4 times faster in younger subjects compared to elderly subjects. Pharmacokinetic features related to race have not been studied.

Tizanidine clearance decreased 7-fold in subjects with renal insufficiency (creatinine clearance < 25 ml/min) compared to healthy young subjects. However, it was observed that the average age of renally impaired subjects was 61 years (range 42-82 years), which was comparable to the age seen in the study performed on elderly subjects. Elderly subjects had a four-fold decrease in clearance as compared to healthy young subjects. It would therefore appear that the contribution of renal impairment to the diminishing of clearance in this renal population is about 2-fold. No other groups with mild or moderate renal impairment were included in this study.

Pharmacokinetic differences due to hepatic impairment have not been studied.

Tizanidine delayed acetaminophen Tmax by 16 minutes, while acetaminophen had no effect on the pharmacokinetics of tizanidine. Coadministration of ethanol resulted in a 20% increase in AUC and a 15% increase in Cmax of tizanidine.

Retrospective analysis of a multiple dose study indicated that females taking oral contraceptives concurrently with tizanidine had a 2-fold decrease in their clearance of tizanidine as compared to females not taking oral contraceptives.

RECOMMENDATION:

This submission (NDA 20-397) has been reviewed by the Division of Biopharmaceutics and has been found to be acceptable for meeting the Division of Biopharmaceutics' requirements. However, it is strongly recommended that the sponsor fulfill items as outlined in Comments 2-5 as part of Phase IV commitments. Please forward Comments 2-8 to the sponsor.

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I. ADME STUDY

- S-74: The absorption, blood levels, and excretion of ¹⁴C DS 103-282 in human plasma and urine after oral administration of the radiolabelled drug.**
- S-75: Biotransformation Study in Man: To characterize and to quantitate the metabolites of DS 103-282 in human plasma and urine after oral administration of the radiolabelled drug.**
- S-76: Pharmacokinetic characteristics of DS 103-282 during multiple oral administration of ¹⁴C DS 103-282 in healthy volunteers.**
- S-77: To determine the pharmacokinetics of DS 103-282 in human plasma and urine after oral administration of the radiolabelled drug.**
- S-79: To determine the pharmacokinetic parameters and the metabolic pattern of DS 103-282 using ³H-labelled substance.**

II. ABSOLUTE BIOAVAILABILITY STUDY

S-80: A Two-Way Crossover Bioavailability Study Evaluating Zanaflex absolute bioavailability using 4.0 mg Tablets Orally Versus Zanaflex 0.4 mg I.V administration.

III. DOSE PROPORTIONALITY STUDY

S-74: The absorption, blood levels, and excretion of ¹⁴C DS 103-282 in human plasma and urine after oral administration of the radiolabelled drug.

S-84: The dose-bioavailability relationship of DS 103-282: Relative bioavailability of four dose levels (1, 2, 4, and 8 mg) of DS 103-282 capsules.

S-87: A double-blind, placebo controlled, randomized, cross-over clinical-experimental study to assess the correlation between pharmacodynamic action and blood levels of oral Sirdalud.

IV. BIOEQUIVALENCE STUDY

S-83: The biological availability of DS 103-282 in man. A comparison of three sets of DS 103-282 4.0 mg tablets showing differing dissolution rates.

V. MULTIPLE DOSE STUDY

S-72: Sirdalud MR Bioavailability study with DS 103-282 in man under steady-state conditions (Beckett-Temmler-retard-pellets vs normal tablets).

S-76: Pharmacokinetic characteristics of DS 103-282 during multiple oral administration of ¹⁴C DS 103-282 in healthy volunteers.

VI. FOOD EFFECT STUDY

S-70: Study of the influence of food on bioavailability of Tizanidine in normal volunteers.

VII. SPECIAL POPULATION STUDIES

Renal Insufficiency

S-73: Pharmacokinetic study with DS 103-282 in patients with renal insufficiency.

Age

S-78: A two-way crossover bioavailability study evaluating Zanaflex 6.0 mg tablets versus Zanaflex 6.0 mg capsules given orally (Younger).

S-84: The dose-bioavailability relationship of DS 103-282: Relative bioavailability of four dose levels (1, 2, 4, and 6 mg) of DS 103-282 capsules (Elderly).

Gender

S-72: Sirdalud MR Bioavailability study with DS 103-282 in man under steady-state conditions (Beckett-Temmler-retard-pellets vs normal tablets).

S-88: A study on the Intra- and Intersubject variability of DS 103-282 in Healthy Volunteers.

VIII. DRUG INTERACTION STUDIES

S-67: Investigation in healthy volunteers of single dose effects of tizanidine, ethanol, and the two in combination, as compared to placebo.

S-72: Sirdalud MR Bioavailability study with DS 103-282 in man under steady-state conditions (Beckett-Temmler-retard-pellets vs normal tablets); (Tizanidine-OC interaction)

S-82: Evaluation of the safety and pharmacokinetic interaction of the (1) one DS 103-282 4 mg tablet, and (2) two Tylenol (Acetaminophen) 325 mg tablets taken separately and in combination.

IX. PHARMACODYNAMIC-THERAPEUTIC EFFECT STUDIES

S-87: A double-blind, placebo controlled, randomized, cross-over clinical-experimental study to assess the correlation between pharmacodynamic action and blood levels of oral Sirdalud.

X. PROTEIN BINDING STUDIES

B-16: Binding studies with blood cells and plasma proteins.

APPENDIX II- Analytical Methodology

APPENDIX III- Drug Formulation

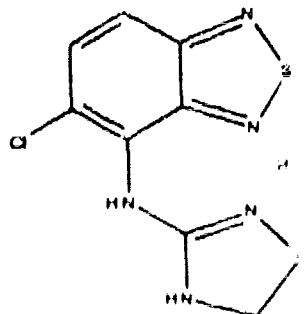
APPENDIX IV- In Vitro Dissolution

INTRODUCTION:

Zanaflex (Tizanidine Hydrochloride), a centrally acting $\alpha 2$ -adrenergic agonist, is a muscle relaxant and antispastic agent which does not produce muscle weakness. It is marketed as Sirdalud in European market. Tizanidine is extensively metabolized with metabolites 3 (inactive), 4 (inactive), and 10 (activity unknown) being the major ones in humans. The focus of the NDA is the parent drug. Plasma concentrations are expressed in ng of tizanidine (DS 103-282) free base, which was the specie measured.

The chemical name is 5-Chloro-4-(2-imidazolylamino)-2,1,3-benzothiazole hydrochloride (1:1). The empirical formula is $C_9H_8ClN_5S.HCl$ and the gram molecular weight is 290.2.

Tizanidine is a white to off-white, fine crystalline powder that melts at 288-290°C. It is approximately 5% soluble in water and methanol. Solubility in water decreases as the pH increases from 5 to 9. The structural formula is presented below:



The imidazoline chemical structure of tizanidine is related to that of the antihypertensive drug clonidine. Pharmacological studies in animals have shown similarities between the two compounds, with tizanidine found to be 10-50 times less potent than clonidine in blood pressure-lowering ability.

INDICATIONS AND USAGE:

The sponsor is proposing Zanaflex for the treatment of spasticity of spinal cord origin. Further, the sponsor claims that the drug is effective in reducing spasticity in patients with multiple sclerosis and spinal cord trauma.

DOSAGE AND ADMINISTRATION:

The initial daily dose is 6 mg, given in three divided doses, using a 4 mg scored tablet. The dose should be increased slowly at weekly or half-weekly intervals. Optimum therapeutic response is generally achieved with a daily dose of between 12 and 24 mg administered in three equally spaced doses. The maximum recommended daily dose is 36 mg, as three equally spaced doses.

MANUFACTURER:

Manufactured by Sandoz Pharma Ltd., Basel, Switzerland for Athena Neurosciences, Inc., South San Francisco, California.

SUMMARY OF HUMAN BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS

I. BIOAVAILABILITY:

A. Absolute Bioavailability:

The mean (%CV) absolute bioavailability of tizanidine was about 38% (24%) from Zanaflex 4 mg tablets (S-80).

II. PHARMACOKINETICS:

A. Absorption:

Following multiple oral doses of 4 mg Zanaflex (S-72), mean (%CV) C_{max} was 13.3 ng/mL (60%) with T_{max} of about 1.6 hours (40%).

B. Distribution:

Following single IV administration 0.4 mg tizanidine to 6 healthy adult volunteers (S-70), the mean (%CV) steady state volume of distribution was 2.4 L/Kg (21%).

C. Metabolism:

Tizanidine was found to be rapidly and extensively metabolized by man as demonstrated by a radiolabelled study (S-76). Parent drug was detected in traces only (plasma 6%; urine 2%). Metabolite pattern revealed the presence of about 15 metabolites, of which 3 (17%), 4 (20%), and 10 (9%) were the major metabolites in plasma; and 3 (6%) and 4 (12%) were the major metabolites in urine. The identified metabolites demonstrate that tizanidine is metabolized by two different main routes: (1) oxidative degradation of the imidazoline ring to yield 2, 3, and 4; and by (2) oxidation of the aromatic ring system to yield 1a (epoxide) which is subsequently transformed to the metabolites 6 and 9, and the conjugates 7 and 8 (Appendix A).

The proportion of metabolites is different and the major metabolites found in humans were not present in certain animal species (Appendix A1).

In a preliminary pharmacokinetic and metabolism study (S-78) with ³H-tizanidine (2 mg oral solution) in 6 subjects, it was observed that plasma radioactivity reached mean maximal level of 39 ± 4 ng-equiv./mL at 1.5 hours, indicating rapid absorption. Elimination occurred with two disposition half-lives; a short one of 2.3 hours and longer one of 19 hours. Cumulative urinary excretion of radioactivity after 96 hours was found to be $51\% \pm 11\%$ of the administered dose. No feces were collected; no analysis was performed to measure unchanged drug.

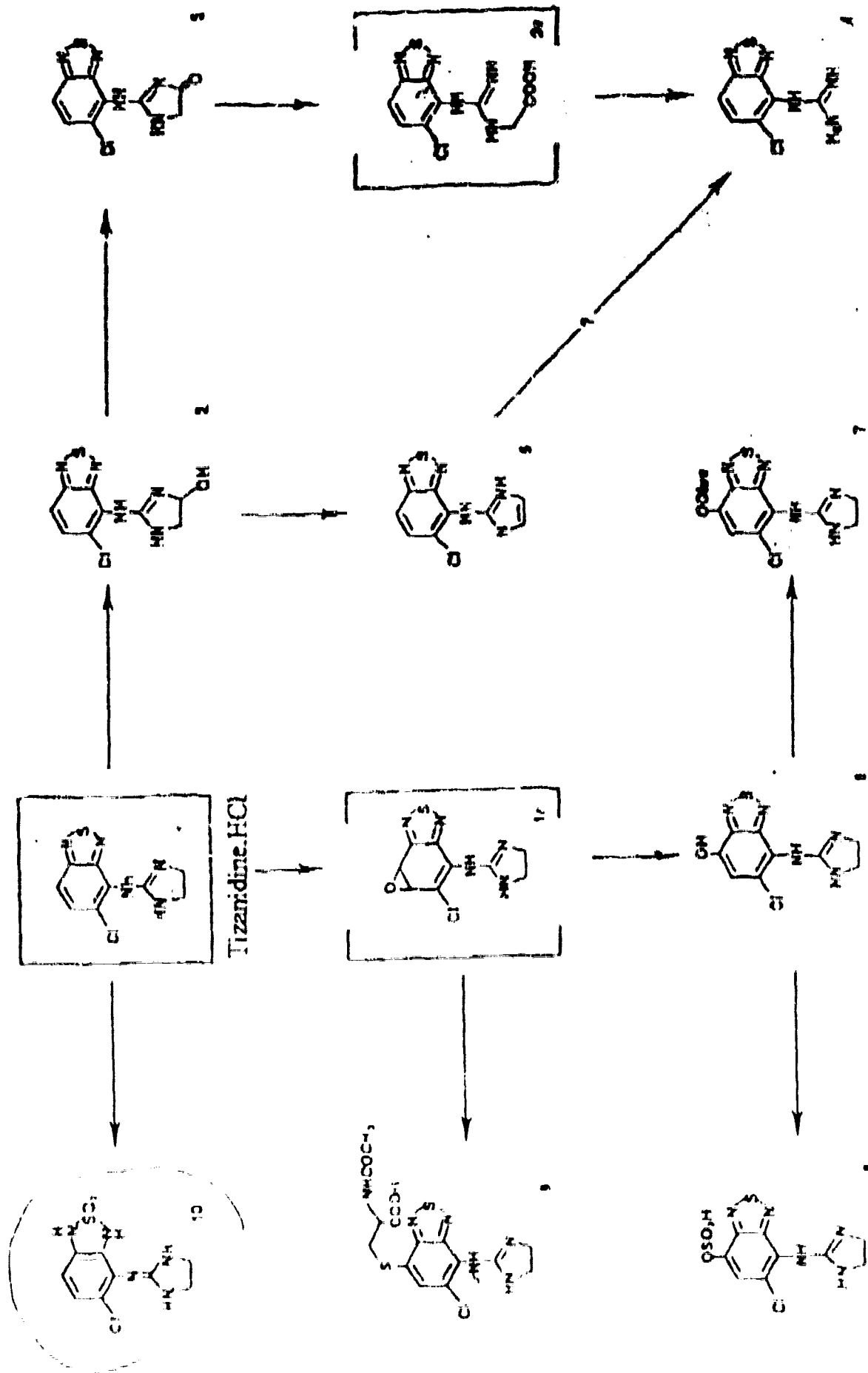
In a further disposition study (S-79) with 12 male volunteers, groups of 6 subjects received single oral doses of either 5 mg or 20 mg ¹⁴C-tizanidine in the form of 5 mg tablets. It was observed that the total recovery of radioactivity in urine (53%) and feces (23%) within 120 hours was about $76 \pm 15\%$ of the administered dose, irrespective of whether 5 mg or 20 mg were administered. Recovery of unchanged drug in urine and feces was less than 1.5% of the administered dose. Further, it was observed that the total radioactivity as well as the unchanged tizanidine displayed linear kinetics between 5 mg and 20 mg doses.

In another study (S-77; elderly) when ¹⁴C-tizanidine (4 mg oral solution) was evaluated in 4 healthy volunteers, the C_{max} of radioactivity was found to be 63 ± 0.1 ng equiv./mL and was found to occur at 1.0 hour. Further, mean

APPENDIX A

FIGURE 1

Metabolic Pathways of Tizanidine in Animals and Man



Figures in parentheses indicate theoretically possible intermediates

8a

APPENDIX A1

The parent drug represented less than 1% of the dose in human urine and only 6% of the radioactivity in human plasma (pool 0-24 h), consequence of a high first pass effect (50-80%). Accordingly an absolute bioavailability of about 34% was determined.

Table 1. The following table compares the percentage of the different metabolites in the plasma at Cp(max) and in 0-24 h pooled urine, in order to facilitate the inter-species comparison of metabolism.

Metabolites	man	rat	dog	mouse	rabbit
(Sirdalud) 1 plasma urine bile	Little interspecies differences; either not detectable (N.D.) or at trace levels.				
2 plasma urine bile	0-2.7 N.D. *	N.D. 6.8 N.D.	N.D. 2.7 *	N.D. * *	N.D. * *
3 plasma urine bile	16.7 5.5 *	N.D. 2.9 7.4	11 5.4 *	N.D. * *	3.5 N.D. *
4 plasma urine bile	14.7 11.4 *	N.D. 23.2 5.4	23.3 31.7 *	4.8 * *	1.0 N.D. *
5 plasma urine bile	N.D. N.D.	This metabolite was found in rat and dog urine but not in plasma, and is thought to be a degradation product of 2 rather than a true metabolite.			
6 plasma urine bile	has not been found in any species but is certainly formed as shown by the presence of its glucuronide 7				
7 plasma urine bile	1.3 6.6 *	N.D. 1.4 10.9	4.0 3.7 *	0-6.1 * *	37 37.2 *
8 plasma urine bile	2.7 N.D.	N.D. N.D.	33.2 *	2.4 *	2.1 N.D.
bile was never isolated (assignment by HPLC with the synthetic reference compound)					
9 plasma urine bile	6.4 4.5 *	N.D. 10.5 6.9	4.2 5.1 *	64.3 * *	26.1 19.8 *
10 plasma urine bile	12.5 11.6 *	>98 37.4 6.9	3 N.D. *	N.D. * *	10.7 N.D. *

N.D. = Not Detectable,

* = sample not analysed

cumulative urinary excretion of radioactivity after 96 hours was observed to be $65 \pm 6\%$ (% of dose). The terminal half-life of radioactivity in plasma was found to be about 22 hours. No feces were collected; no analysis was performed to measure unchanged drug.

In a multiple dose study with q 8 hour dosing for 13 doses (S-76), pharmacokinetic characteristics of ^{14}C -tizanidine (4 mg tablets) was evaluated in 6 healthy volunteers. The mean peak plasma concentrations of unchanged tizanidine and radioactivity were observed to be 5.7 ± 5.50 ng/mL and 75 ± 18 ng. equiv./mL, respectively at 1 hour after the final (13th) dose. Within 120 hours of the final dose, the total radio-activity recovered in urine was found to be $66 \pm 8\%$ of the dose, and in feces it was found to be $17 \pm 12\%$. Therefore, mean total recovery was 83% of the administered dose. The terminal half-lives of tizanidine and total radioactivity were 2.2 and 43-90 hours, respectively. Little or no accumulation of the parent drug occurred during multiple dosing regimen, while total radioactivity accumulated in blood by a factor of 3.1 compared to single dose levels.

D. Elimination:

The mean apparent half-life of tizanidine following administration of 4 mg tablets was found to be 2.5 hours (CV 33%).

III. DOSE PROPORTIONALITY:

Dose proportionality of tizanidine pharmacokinetics was assessed from three studies by this reviewer. In one study (S-84) the dose-bioavailability relationship of tizanidine at four dose levels (1, 2, 4, and 6 mg) was evaluated in 20 normal healthy volunteers, following single oral dose capsule administration. AUC and C_{max} of tizanidine increased proportionally with dose, while half-lives stayed constant at about 1.3 hours across doses. Thus, it can be concluded that tizanidine displays linear kinetics in the 0-6 mg dose range.

From the disposition study (S-74), dose proportionality was seen between 5 and 20 mg dose levels. In this study, two groups of 6 male subjects received single oral doses of either 5 mg or 20 mg ^{14}C -tizanidine in the form of 5 mg tablets. Mean AUC and C_{max} of tizanidine were observed to increase proportionally with dose for both total radioactivity and unchanged tizanidine.

Further, dose proportionality at three dose levels (2, 4, and 8 mg tablets) was evaluated in 16 patients (4M, 12F) (S-87), following single oral dose administration. The mean AUC and C_{max} values for 2, 4, and 8 mg doses were found to be proportional.

Since the maximum daily dose is 36 mg given in three equally spaced divided doses (viz. 12 mg as a single dose), dose proportionality should cover 0 - 12 mg in a single dose as there is no drug accumulation. In the three different dose proportionality studies mentioned above the dose range covered was 1-6 mg (S-74), 5-20 mg (S-74), and 2-8 mg (S-77). It was observed that at these dose levels, the drug displayed linear kinetics. Further, to achieve optimum therapeutic response, 12-24 mg daily dose is recommended in three equally spaced and divided doses (i.e., 4-8 mg as a single dose). This single dose range has been covered in the dose proportionality studies. Thus, as the drug does not accumulate, dose proportionality covering the single dose range of 1-20 mg is acceptable.

IV. BIOEQUIVALENCE STUDY

The sponsor reported that since the clinical/pharmacokinetic programs had used the same tizanidine 4 mg tablets as the proposed marketed formulation, no pivotal bioequivalence study was performed to compare the two formulations. However, the bioavailability of tizanidine 4 mg tablets differing in age and storage conditions - (Condition 1. old, 44 months/25°C vs new, 3 months/25°C; Condition 2. old, 39 months/30°C vs new, 3 months/25°C), was evaluated in 24 normal male volunteers (S-83) to investigate relevance of such changes in the bioavailability of tizanidine. Older stored batches of tablets showed equivalency to newest batch of tablets. Thus, it can be concluded that the long term storage of tablets does not affect the bio-performance of tablets as indicated by the comparison of older lots to newer lots.

V. MULTIPLE DOSE STUDY

Pharmacokinetic investigations were carried out on a group of 17 healthy volunteers in order to evaluate the relative bioavailability of tizanidine Beckett-Temmler-Retard (MR) 12 mg formulation both under "single dose" and "steady state" conditions in comparison to the tizanidine 4 mg Immediate Release (IR) tablets (S-72) given t.i.d; both regimens were dosed for 14 days. The trough plasma concentrations or C_{min} values of tizanidine measured on days 12, 13, and 14 are not different indicating that steady state had been attained. It appeared that mean AUC_{0-24} had increased by about 30% at steady state (132 ng*hr/mL) compared to single dose (100 ng*hr/mL) while C_{max} was unaffected (about 13 ng/mL). This increase in AUC is explained due to higher values observed in 3 out of 4 females on concomitant contraceptive therapy. However, the AUC values calculated excluding these 4 female values were observed to be same under both single dose and steady state conditions. Overall, it appears that there is no drug accumulation.

Amongst females (n=6), four were on oral contraceptives (OC). It was observed that 3 out of 4 females who were taking oral contraceptives had the highest AUC and C_{max} for tizanidine. Mean steady state AUC (215//94 ng*hr/mL) and C_{max} (24//14 ng/mL) values were computed in females with//without oral contraceptives. A two-fold difference in the mean values of both AUC and C_{max} was observed in females taking oral contraceptives (n=4) as compared to those not taking oral contraceptives (n=2). Thus, it appears that clearance in females on oral contraceptives was 50% lower; however the number of subjects is small.

In another study (S-70), pharmacokinetic characteristics of ¹⁴C-tizanidine and unchanged tizanidine (4 mg tablets) were studied during multiple dose oral administration in 6 healthy male volunteers. Each subject received 13 consecutive doses of tizanidine (4 mg q 8 hours). C_{min} values for total radioactivity progressively increased from 9 ng. equiv./mL after the first dose to 28 ng. equiv./mL following the 13th dose. In contrast, C_{min} values for the parent drug were constant throughout the dosing period (about 0.3 ng/mL). Thus, little or no accumulation of the parent drug occurred during multiple dosing regimen, while total radioactivity accumulated in blood by a factor of 3.1 compared to single dose levels. The terminal half-lives of tizanidine and radioactivity were observed to be 2.2 and 43-90 hrs, respectively.

VI. FOOD EFFECT STUDY

The influence food on the bioavailability of tizanidine 4 mg tablets was studied in 12 (6M and 6F) healthy volunteers in a single dose, two treatment (fasting and fed) randomized crossover study (S-70). Each treatment was separated by an 8-day washout period. Subjects received one 4 mg tablet after an overnight fast or one 4 mg tablet along with a standardized calorie-rich breakfast (tea or coffee, bread, 2 boiled eggs, cheese, and ham). It was observed that in the presence of a calorie-rich meal, C_{max} increased (32%), t_{max} decreased (44%), with no change in AUC. Thus, oral administration of tizanidine during a meal resulted in a more rapid rate of absorption compared to its administration in a fasted state. This should be noted in the labelling of this drug.

Further, it was observed that C_{max} was 33% and 16% higher in both fasted and fed states respectively, in females than in males. However, no such difference was observed in AUC values (See Also Effect of Gender).

VII. SPECIAL POPULATION STUDIES

Effect of Age:

The sponsor did not investigate age differences in the pharmacokinetics of tizanidine. However, retrospective analysis and cross comparison of data from two studies (~~3-84~~ young and ~~3-78~~ elderly) indicated that clearance of tizanidine in younger subjects (mean age 25 yrs; mean AUC = 35 ng*hr/ml) was 4 times greater than in elderly subjects (mean age 71 yrs; mean AUC = 135 ng*hr/mL). Precaution should be exercised in elderly subjects due to their decreased clearance of tizanidine (See Labelling).

Effect of Renal Insufficiency:

A cross-study comparison of severely renally impaired subjects ($Cl_{cr} < 25$ ml/min) to healthy young subjects indicated that renally impaired subjects had a seven-fold decrease in their clearance (~~3-73~~ and ~~3-80~~). Thus, accumulation of tizanidine is expected to occur upon chronic administration of tizanidine (as q 8 hours) in subjects with Cl_{cr} values of less than 25 ml/min. However, it was observed that the average age of renally impaired subjects was 61 years (range 42-82 years), which was comparable to the age seen in the elderly subjects' study (~~3-78~~). As noted above, elderly subjects had a four-fold decrease in clearance as compared to healthy young subjects. It would therefore appear that the contribution of renal impairment to the diminishing of total clearance in this renal population is about 2-fold. Therefore, Precaution should be exercised in subjects with renal insufficiency ($Cl_{cr} < 25$ ml/min) (See Labelling).

No other groups with mild or moderate renal impairment (eg., Cl_{cr} 25-70 mL/min) were included in this study.

Effect of Gender:

The effect of gender differences on the pharmacokinetics of tizanidine was compiled from three studies. In one study (~~3-72~~) the differences in the pharmacokinetics of tizanidine following single and multiple dose administration of 4 mg tizanidine was evaluated in 12 (6M, 6F) healthy volunteers. From the given data, a 2-fold increase in mean AUC and C_{max} values was observed in females than in males. However, retrospective analysis of the given data, excluding data of 4 females who were on concomitant contraceptive therapy and had shown highest AUC and C_{max} values, appears to indicate that there may be no gender difference in the pharmacokinetics of tizanidine under both single and multiple dose conditions (n = 6 males; n = 2 females); however the study lacks power.

Following single dose oral administration of 4 mg tizanidine (S-68) in 18 (9M, 9F) healthy volunteers, no gender effect is seen.

Retrospective analysis of pharmacokinetic data from the food study (S-70), indicated that mean C_{max} value was 33% and 16% higher in females than in males in fasted and fed conditions, respectively. However, no significant difference in mean AUC was observed.

VIII. DRUG INTERACTION STUDIES

Alcohol: The interaction of tizanidine with alcohol (S-67) was investigated in 12 healthy male volunteers. Each subject received, at one week intervals, single doses of (i) placebo, (ii) 4 mg tizanidine, (iii) 8 mg of tizanidine, (iv) 0.5 g/kg of ethanol, (v) 4 mg tizanidine + 0.5 g/kg of ethanol, and (vi) 8 mg of tizanidine + 0.5 g/kg of ethanol. The median C_{max}, T_{max} and AUC values were reported but not the mean data. The results indicated that there was a 20% increase in AUC and a 15% increase in C_{max}, indicating that ethanol affects the pharmacokinetics of tizanidine.

Oral Contraceptives: Retrospective analysis of pharmacokinetic data of study S-72 indicated a possible drug interaction between tizanidine and oral contraceptives. From the data given, it was observed that mean AUC and C_{max} were 2-fold greater in females than in males at steady state. Inspection of demographic and individual data, indicated that females on concomitant contraceptive therapy showed high plasma concentrations of tizanidine (n = 4). Further, it was observed that 3 out of these 4 females taking oral contraceptives have the highest AUC and C_{max} for tizanidine. The AUC and C_{max} values calculated excluding the 4 females on OC were observed to be same in both males and females under both single dose and steady state conditions (n = 6M; n = 2F). It is very clearly evident that even a small number of subpopulation (n = 4) could show a significant interaction between oral contraceptives and tizanidine.

Even though oral contraceptives used in this study were European, they appear to have corresponding counterparts in the US market.

Acetaminophen: The pharmacokinetic interaction of one tizanidine 4 mg tablet, two Tylenol (Acetaminophen) 325 mg tablets, and one tizanidine 4 mg plus two acetaminophen 325 mg tablets taken in combination was evaluated in 20 healthy male volunteers (S-82). Each subject received in an open label, 3 x 3 replicated Latin square crossover design, single doses of the three dosing sequences. Each dosing sequence was separated by a 5-day washout period. It was observed that coadministration of acetaminophen did not influence the pharmacokinetics of tizanidine. In turn, tizanidine caused a 16 minute increase

in the t_{max} of acetaminophen. Thus, it can be concluded that coadministration of acetaminophen did not affect tizanidine bioavailability, while administration of tizanidine affected the T_{max} of acetaminophen but not its extent.

IX. PHARMACODYNAMIC-THERAPEUTIC EFFECT STUDIES

The dose-effect relationship of tizanidine tablets was assessed in a clinical efficacy study (9-97). The study was a double-blind, placebo controlled, randomized, cross-over design and was performed in 16 patients suffering from spasticity due to multiple sclerosis. Each patient received 3 single doses of tizanidine (2, 4, and 8 mg) and 1 dose of placebo in a random order using a Latin square design with a washout period of 3 days between treatments.

Efficacy was assessed at intervals during 8 hours on each treatment day by measuring: 1. Tone -- Flexors and Extensors (Ashworth Scale for muscle tone) and 2. Strength -- Flexors and Extensors (BMRC Scale (British Medical Research Council Scale for muscle strength)). Nominally, in the Ashworth scale -- 0 indicates normal and 4 indicates rigidity of limb; in the BMRC scale -- 0 indicates poor muscle strength and 5 indicates normal muscle strength.

The results regarding flexion revealed that increasing doses lead to a decrease in muscle tone with no change in muscle strength. In case of extension, tone decreased with increasing doses of 2 and 4 mg, while with 8 mg decreased tone was observed for up to 4 hours, subsequent to which the tone returned. Across doses there was no significant difference in strength extension.

X. PROTEIN BINDING STUDIES

Equilibrium dialysis study (9-10) showed the degree of plasma protein binding of tizanidine to be 30% and concentration independent over the range 3 - 11000 ng/mL. It was also demonstrated that tizanidine binds to plasma proteins other than albumin.

APPENDIX II- Analytical Methodology

APPENDIX III- Drug Formulation

Tizanidine tablet formulation used in the clinical trials and the proposed to be marketed formulation are identical. The proposed market presentation for the 4 mg dosage strength is in the form of scored tablet. The composition of the tizanidine 4 mg tablet is as follows:

Ingredient	Composition (per tablet)

* equivalent to 4 mg of base.

APPENDIX IV- In Vitro Dissolution

Medium:
Apparatus:
Specification:

COMMENTS TO THE MEDICAL OFFICER:

- 1a) It appears that elderly subjects show a four-fold decrease in the clearance of tizanidine in comparison to young healthy subjects. Since, the initial daily dose recommended is 6 mg in three divided doses, it would appear that the initial daily dose for the elderly be 2 mg. Further, the maintenance dose in elderly be 2 mg bid or tid, as the normal recommended daily maintenance dose is 12-24 mg in three divided doses.

- 1b) In elderly patients with renal insufficiency (creatinine clearance < 25 mL/min), clearance is found to be further decreased by 50% as compared to elderly alone. Therefore, the initial dose in elderly, renally impaired subjects be 2 mg every other day. Further, the maintenance dose in this population be 2 mg qd or 4 mg qd.
- 1c) Pharmacokinetics of tizanidine in young subjects with renal impairment was not investigated. However, retrospective analysis of data appear to indicate that clearance in young renally impaired subjects will be 50% lower than that in young healthy subjects. Since, the initial daily dose recommended is 6 mg in three divided doses, the initial dose for young renally impaired subjects be 4 mg qd. Further, the maintenance dose in this population be 2 mg tid to 4 mg tid, as the normal recommended daily maintenance dose is 12-24 mg in three divided doses.

COMMENTS TO BE SENT TO THE FIRM:

- 7) The sponsor is requested to adopt the following dissolution methodology and specification for Tizanidine 4 mg tablet:

Medium:

Apparatus:

Specification:

- 8) Initially the NDA contained several illegible and unreadable figures. Upon request the sponsor provided legible figures. In future submissions, the sponsor is requested to provide legible and readable figures at the outset of the submission.
-

2 Pages

Purged

Vijay K. Tammara
01/31/95

Vijay K. Tammara, Ph. D.
Pharmacokinetics Evaluation Branch I

First Draft prepared on August 10, 1994

Second Draft prepared on October 25, 1994

Second Draft Reviewed by Raman Baweja, Ph. D. on January 17, 1994

FT Initialed by R. Baweja, Ph. D.

R. Baweja
1/31/95

CC: NDA 20,397 (orig.), HFD-120, HFD-426 (Tammara, Baweja, Fleischer),
HFD-340, Drug, Chron, Division, and Reviewer Files.

FEB 26 1996

OB

NDA 20-397
Tizanidine HCl (ZANAFLEX®)
4 mg Tablet (Scored)

Athena Neurosciences, Inc.,
South San Francisco, CA

Submission Dates:

September 08, 1995

September 11, 1995

October 04, 1995

Type of Submission: Review of Responses

In this submission, the sponsor provided responses to the Agency's "Not Approvable Letter" dated March 6, 1995 (Attachment 1).

Upon review of the responses, the reviewer concurs that the sponsor has responded satisfactorily to Biopharm's Comments except for the Comment 3 (Attachment 1).

In response to Comment 3, the sponsor submitted the results of the in-vitro inhibitory spectrum of Tizanidine and its metabolites 3 and 4, using substrates metabolized by major CYP450 isoforms viz., CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These studies demonstrate a lack of inhibition by Tizanidine and metabolites 3 and 4 of the major CYP450 isoforms and therefore lead to the conclusion that these compounds will not inhibit oxidative metabolism of other drugs when coadministered (Attachment 2). Thus, it is unlikely that Tizanidine, and the metabolites 3 and 4 will affect the plasma levels of other drugs metabolized by CYP450.

However, the sponsor did not investigate for the isozymes responsible for the oxidative metabolic processes of Tizanidine as Tizanidine itself is metabolized by CYP450. In a telephonic conversation with the sponsor on January 17, 1996, this reviewer was informed that the sponsor is still in the process of investigating and fully characterizing the oxidative metabolic processes of Tizanidine.

Ashworth scores (Figures 1 & 2; Tables 1 & 2) and mean arc of the first swing of the pendulum test (Figure 3; Table 3). Mean total Ashworth scores significantly decreased during hours 1, 2, and 3 with both Tizanidine treatment groups and between Tizanidine and placebo (Tables 1 & 2). Similarly, the mean arc of the first swing of the pendulum test significantly increased at hours 1, 2, 3, and 6 with in the Tizanidine group and at 1, 2, and 3 hours between Tizanidine and placebo (Table 3). There were statistically significant correlations observed between the Ashworth scores (Figure 4; Table 4) and pendulum test (Figure 5; Table 5) results with Tizanidine plasma levels at 1, 2, and 3 hours in both Tizanidine treatment groups. But the correlation was not significant for Tizanidine 8 mg, Tizanidine 16 mg and pooled Tizanidine groups at 6 hours for both total Ashworth scores and pendulum test (Tables 4 & 5). However, dose and plasma concentrations did not fully predict the effect of Tizanidine on muscle tone. Further, it was observed that plasma Tizanidine concentrations are variable and are not predicted by individual patient dose. The variability in plasma concentration and efficacy confirms the need for individual patient titration.

The incidence of the "marker" adverse events (viz., dizziness, drowsiness, dry mouth, and tiredness) increased post drug administration, in the Tizanidine 8 mg and 16 mg groups compared to placebo, with a gradual return to baseline (Tables 6 & 7). A dose-response relationship was observed for the proportion of patients reporting elicited adverse events. Increased incidence of adverse events corresponded to the increased mean plasma concentrations of Tizanidine, suggesting a potential correlation (Tables 8 & 9). Further, a correlation was observed between decreases in blood pressure and pulse and increases in plasma levels of Tizanidine (Tables 10 & 11). The significant correlation noted at 6 hours between cardiovascular parameters and Tizanidine plasma concentrations, suggests that the cardiovascular effects of Tizanidine persist after the measured therapeutic effects have returned to baseline.

COMMENTS TO BE SENT TO THE FIRM:

1) The sponsor has investigated the potential for inhibition of the major CYP450 isoforms following Tizanidine administration, which will aid in predicting potential *in vivo* drug interactions. However, isozymes involved in the metabolic oxidative processes of Tizanidine have not yet been determined. The sponsor is requested to investigate and fully characterize the isozymes involved in the metabolic processes of Tizanidine, *in vitro*.

2) The sponsor is encouraged to provide information regarding ethnic differences on the pharmacokinetics and pharmacodynamics of Tizanidine.

3) The sponsor has agreed to adopt the following dissolution methodology and specification for Tizanidine 4 mg tablets:

Medium:

Apparatus:

Specification:

1

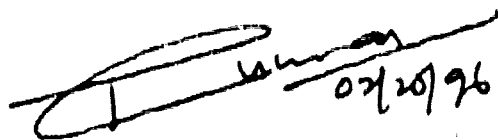
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RECOMMENDATION:

This submission (NDA 20-397) has been reviewed by the Division of Biopharmaceutics and has been found to be acceptable for meeting the Division of Biopharmaceutics' requirements. However, it is recommended that the sponsor fulfill items as outlined in Comments 1 and 2 as part of Phase IV commitments. Please forward Comments 1-3 to the sponsor.



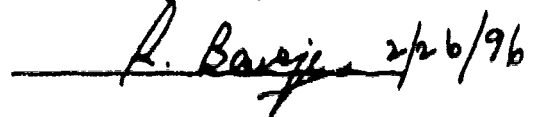
02/20/96

Vijay K. Tammara, Ph. D.
Pharmacokinetics Evaluation Branch I

First Draft prepared on February 15, 1996

RD Initialed by R. Baweja, Ph. D. February 20, 1996

FT Initialed by R. Baweja



2/26/96

CC: NDA 20,397 (orig.), HFD-120, HFD-860 (Tammara, Baweja, Hossain, Malinowski), HFD-340, Drug, Chron, Division, and Reviewer Files.

ATTACHMENT 1

**Response to Not Approvable Letter
NDA 20-397**

CHEMISTRY AND MANUFACTURING CONTROLS

1. Environmental assessment deficiencies described in our letter of September 13, 1994 and discussed in a meeting held between representatives of your firm and the Agency on October 25, 1994 need to be addressed.

The response to the environmental assessment deficiencies is included in Attachment M and the revised Environmental Assessment is included in Volumes 9 and 10.

BIOPHARMACEUTICS

1. Tizanidine undergoes extensive metabolism with multiple metabolites. Only four metabolites have been identified. Identified metabolites account for about 50% of the dose administered. The total radioactivity has a long half-life (43-90 hours) leading to concerns about accumulation of unidentified species. We strongly recommend that you identify these unidentified species.

This issue was addressed in the August 1, 1994 response to Biopharmaceutics questions (a copy of the relevant question and answer are included in Attachment N for ease of review). As discussed in the August 1 response, a re-evaluation of the data being referenced suggested that the reference to a terminal half-life of 43-90 hours for total radioactivity is misleading, if not erroneous. Athena presented the position that the disappearance of total radioactivity following the last dose of tizanidine is at least biphasic and that the prolonged terminal phase is a complex period of both redistribution and elimination. It is probable that the early disappearance phase (0-24 hours) represents the true elimination phase. The slower phases operating between 120 and 216 hours represents distribution from tissues which accounts for a very small amount of radioactivity in relation to the radioactivity accumulated during multiple dosing. These redistribution terminal phases are observed with many lipophilic drugs when sensitive analytical methods are available. Athena believes the August 1, 1994 response resolves this issue.

2. which is a major metabolite in humans, has not been characterized for its activity. Therefore, you should ascertain the activity of major

Please refer to the response to the *Safety Reports: Preclinical* question, the August 1, 1995 response to Biopharmaceutics questions, and the July 27, 1995 meeting minutes (Attachment A). Since Sandoz/Athena are unable to synthesize we cannot characterize its activity.

3. The specific enzymes involved in the metabolic oxidative processes have not yet been determined. The specific enzymes involved can predict drug-drug interactions and, in some cases, inter-individual differences in pharmacokinetics. Please investigate

**Response to Not Approvable Letter
NDA 20-397**

and fully characterize the enzymes involved in the metabolic processes of tizanidine. It may be possible to use in vitro methods for some of this characterization.

As previously discussed with the Biopharmaceutics reviewer, Athena had .
at the conduct a study of the potential for tizanidine and
metabolites 3 and 4 to inhibit cytochrome (CY)P450 isoenzymes from human liver.
Based on these findings 't is unlikely that tizanidine or the two metabolites tested would
interfere with oxidative metabolism of any drugs via known (CY)P450 isoenzymes. A
copy of the final report is included in Attachment O.

4. Since the drug undergoes extensive metabolism, the effect of liver disease on its pharmacokinetics should be investigated.

Athena feels it would be unethical to conduct a study in patients with impaired hepatic function using a drug known to cause even modest toxic effects on the liver. Athena proposes working with the Agency to develop appropriate wording for the Package Insert to reflect the difference in treatment for hepatically impaired patients.

5. Please adopt the following dissolution methodology and specification for Tizanidine 4 mg tablet:

Medium:

Apparatus:

Specification:

The media, apparatus and specification noted above are the specified conditions for dissolution testing of tizanidine 4 mg tablets. This was clarified in the September 9, 1994 response to Biopharmaceutics questions and also in the January 20, 1995 response to CMC questions; the latter response is incorporated herein by reference.

6. Initially, the NDA contained several illegible and unreadable figures which upon request were corrected. In your resubmission and all future submissions, please provide legible and readable figures.

Athena apologizes for the illegible and unreadable figures originally submitted in the NDA and agrees to provide legible and readable figures in all future submissions.

CLINICAL

1. We request that you supply additional, detailed information on the number of patients receiving specific doses as well as the duration for which these patients have been exposed.

Additional, detailed information on the number of patients receiving specific doses as well as the duration for which these patients have been exposed is included in Attachment O.

**EXCERPT FROM RESPONSE TO FDA REQUEST FOR INFORMATION
AUGUST 1, 1994**

- 2) **Study S-75 (Volume 1.25):** The $t_{1/2}$ is 2.2 hours for the parent drug (tizanidine) and 43-90 hours for the metabolites with accumulations of 3.6 fold. Are there more data on accumulation following multiple doses to explain these findings? Are the metabolites doing anything?

The observations referred to in this question are actually contained in Sandoz Report S-76.¹ The figures/tables referenced in this section are those in the actual report S-76 (the NDA location is indicated). Reevaluation of these data confirm most of the authors' conclusions. However, we propose that the reference to a terminal half-life of 43-90 hours for total radioactivity is misleading, if not in error. In the following response we present the position that the disappearance of total radioactivity following the last dose of tizanidine is at least biphasic and that the prolonged terminal phase is a complex period of both redistribution and elimination.

Figure 1 (NDA volume 1.25, page 18) shows measured and predicted blood levels of radioactivity for the duration of multiple dosing (TID for 4 days) as well as 5 days following the last dose. Eight C_{min} values were obtained during the 4 days of multiple dosing. Fourteen values obtained during the following 5 days define a full kinetic profile following the last dose as well as a terminal decay phase lasting an additional 112 hours.

Accumulation during multiple dosing can be assessed by the two C_{min} values in the Summary Table (NDA volume 1.25, page 3): C_{min} after the first dose=9 ng Eq/mL and after the 13th dose=28 ng Eq/mL. These values indicate an Accumulation Ratio of 3.1 as opposed to 3.6 in the report where C_{min} was used.

The recalculation assumes that radioactivity levels reached steady state in 96 hours and inspection of the data suggests that this is the case. Using 3.1 as the Accumulation Ratio the kinetic profile of radioactivity levels following the last dose can be reevaluated.

Figure 4 (NDA volume 1.25, page 24), in which the time from last dose at 96 hours (Figure 1) is expressed as 0-120 hours, indicates that the kinetic behavior of radioactivity following the last dose is multiphasic. It would be erroneous to conclude from examination of this curve that radioactive metabolites have an elimination half-life of 90 hours. It is probable that the early disappearance phase (0-24 hours) represents the true elimination phase. This is supported by the Accumulation Ratio calculated above and the following calculation:

$$\text{Accumulation Ratio} = 1/(1 - e^{-kt})$$

**Excerpt From Response to FDA Request for Information
August 1, 1994 (continued)**

where k represents the effective elimination constant for a multicompartment system and t is the dosing interval. This relationship assumes that each dose is administered in the postdistributive phase of the preceding dose.

Equating the Accumulation Ratio to 3.1 and substituting the value of the dosing interval $t=8$ hours, the value of k is 0.0481 / hour, which corresponds to an effective half-life of 14.4 hours. This is consistent with the effective half-life of 17 hours calculated in the report using 3.6 as the Accumulation Ratio. Inspection of the curve indicates that the 14.4 hours value is also consistent with the behavior of radioactivity levels from 96-120 hours in Figure 1 as well as from 0-24 hours in Figure 4. In this regard it should be noted that seven metabolites were assayed from the plasma of a single male in one pharmacokinetic study. While there were only two time points available, these were used to determine a rough estimate of the half-life of each metabolite (Table 2, Section 2 above and Figure A2-3). The estimated half-life of each is longer (with the exception of metabolite 4) than that of the parent drug. These half-lives are all consistent with an effective half-life of 14.4-17 hours for total radioactivity with the exception of metabolite 7 (glucuronide conjugate) which as a probable secondary or tertiary metabolite is increasing as the others decline.

The slower phases operating between 120 and 216 hours (Figure 1) represent distributional phenomena from tissues which account for a very small amount of radioactivity in relation to the radioactivity accumulated during multiple dosing. These redistribution terminal phases are observed with many lipophilic drugs when sensitive analytical methods are available. Indeed, the last three points between 168 and 216 hours in Figure 1 (72-120 hours in Figure 4) yield a slope which is slightly positive or at best equal to zero; neither of which can be interpreted in terms of true elimination phenomena. Therefore, the reference in the report to metabolites with an elimination half-life of 43-90 hours is probably misleading.

ATTACHMENT 2

3. RESULTS

Experiments measuring the activity of the P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 using specific probes did not reveal significant concentration-dependent inhibition by tizanidine or either of its metabolites (M3 or M4). These findings were consistent in microsomes from all livers tested. The results of the experiments are presented in Tables 1-8.

Measurement of CYP1A2 activity.

Table 1. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP1A2 as Measured by 6-Hydroxylation of (R)-warfarin

	Liver 125	Liver 127	Liver 135
Control Activity pmol/nmol P450/min	106.7	39.7	54.7
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
1 μ M	91.9	97.7	101.8
2 μ M	84.3	93.7	94.9
10 μ M	94.8	83.4	94.3
Metabolite 3			
1 μ M	92.7	95.7	100.2
2 μ M	86.8	95.7	89.2
10 μ M	86.3	89.9	97.6
Metabolite 4			
1 μ M	89.8	85.1	86.3
2 μ M	84.1	92.2	96.7
10 μ M	85.6	92.7	105.9

Measurement of CYP2A6 activity.

Table 2. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP2A6 as Measured by 7-Hydroxylation of Coumarin

	Liver 123	Liver 127	Liver 135
Control Activity pmol/nmol P450/min	155	114	325
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
0.1 μ M	101.8	117	102.3
0.2 μ M	101.3	94	105
1.0 μ M	100.5	101.3	76
Metabolite 3			
0.1 μ M	99.1	93.6	102.8
0.2 μ M	132	101.2	105.6
1.0 μ M	97.9	101.9	100.1
Metabolite 4			
0.1 μ M	102.0	98.0	103.5
0.2 μ M	96.5	97.0	99.8
1.0 μ M	108.9	100.4	100.0

Measurement of CYP2C9 activity.**Table 3. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP2C9 as Measured by 7-Hydroxylation of (S)-warfarin**

	Liver 125	Liver 127	Liver 135
Control Activity pmol/nmol P450/min	9.0	9.8	4.9
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
1 μ M	105.5	100.3	99.5
2 μ M	103.9	93.8	102.1
10 μ M	108.2	105.5	100.3
Metabolite 3			
1 μ M	102.7	99.8	101.6
2 μ M	98.1	100.3	102.6
10 μ M	105.1	106.5	105.7
Metabolite 4			
1 μ M	102.7	99.1	103.2
2 μ M	103.7	98.1	96.1
10 μ M	112.5	95.4	101.6

Measurement of CYP2C19 activity.**Table 4. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP2C19 as Measured by 4'-Hydroxylation of (S)-mephenytoin**

	Liver 125	Liver 131*	Liver 135
Control Activity pmol/nmol P450/min	16.8	16.3	87.7
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
0.1 μ M	91.7	92.2	117.8
0.2 μ M	154.8	75.9	109.5
1.0 μ M	69.7	113.6	108.5
Metabolite 3			
0.1 μ M	85.1	95.6	102.0
0.2 μ M	65.1	97.2	95.6
1.0 μ M	102.5	94.8	95.0
Metabolite 4			
0.1 μ M	107.3	98.7	109.8
0.2 μ M	124.1	112.9	110.2
1.0 μ M	151.7	99.3	106.4

*Liver #127 was found to be a poor metabolizer of (S)-mephenytoin and was consequently replaced in this experiment by Liver #131

Measurement of CYP2D6 activity.**Table 5. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP2D6 as Measured by α -Hydroxylation of (S)-Metoprolol**

	Liver 125	Liver 127	Liver 135
Control Activity pmol/nmol P450/min	149	97.6	46.1
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
0.1 μ M	111.3	88.0	98.5
0.2 μ M	117.6	76.4	98.5
1.0 μ M	104.0	78.6	99.1
Metabolite 3			
0.1 μ M	105.1	98.2	95.9
0.2 μ M	108.3	106.0	98.6
1.0 μ M	104.6	77.4	94.4
Metabolite 4			
0.1 μ M	95.4	104.1	87.4
0.2 μ M	92.0	85.3	92.4
1.0 μ M	89.1	103.3	88.7

Measurement of CYP2E1 activity.**Table 6. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP2E1 as Measured by Hydroxylation of p-Nitrophenol**

	Liver 125	Liver 127	Liver 135
Control Activity nmol/nmol P450/min	1.90	1.45	0.392
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
0.1 μ M	97.6	97.5	103.4
0.2 μ M	95.5	100.9	127.1
1.0 μ M	97.8	101.0	104.4
Metabolite 3			
0.1 μ M	90.3	103.3	102.1
0.2 μ M	99.7	120.7	102.1
1.0 μ M	97.2	107.1	101.6
Metabolite 4			
0.1 μ M	95.4	104.9	102.8
0.2 μ M	98.6	107.6	98.2
1.0 μ M	82.4	112.0	102.3

Table 7. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP3A4 as Measured by Epoxidation of Carbamazepine

	Liver 123	Liver 127	Liver 135
Control Activity nmol/minol P450/min	3.86	1.17	7.15
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
0.1 μ M	91.7	87.4	91.6
0.2 μ M	95.1	97.9	82.6
1.0 μ M	86.8	100.9	89.7
Metabolite 3			
0.1 μ M	91.6	89.0	86.5
0.2 μ M	96.9	85.3	82.9
1.0 μ M	99.1	85.6	88.6
Metabolite 4			
0.1 μ M	94.7	84.0	87.9
0.2 μ M	95.9	81.8	89.6
1.0 μ M	100.4	82.9	84.7

Table 8. Effect of Tizanidine and Metabolites 3 and 4 on the Activity of CYP3A4 as Measured by 10-Hydroxylation of (R)-warfarin

	Liver 125	Liver 127	Liver 135
Control Activity pmol/minol P450/min	284	55.6	765
	% Remaining Activity	% Remaining Activity	% Remaining Activity
Tizanidine			
1 μ M	93.5	111.8	114.4
2 μ M	84.1	101.8	94.5
10 μ M	104.6	101.1	115.2
Metabolite 4			
1 μ M	99.3	113.1	92.3
2 μ M	87.2	104.1	105.3
10 μ M	93.7	118.1	98.3
Metabolite 3			
1 μ M	95.2	103.6	98.8
2 μ M	92.4	106.5	107.3
10 μ M	70.1	100.7	97.3

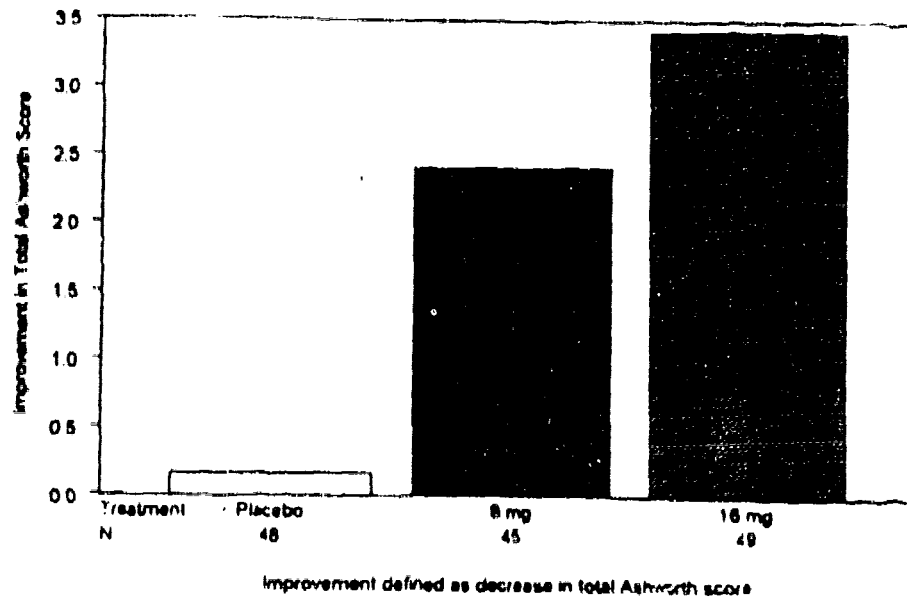
4. DISCUSSION AND CONCLUSION

These studies demonstrate a lack of inhibition by tizanidine and metabolites M3 and M4 of the major CYP450 isoforms and therefore lead to the prediction that these compounds will not inhibit the oxidative metabolism of other drugs when coadministered. Since tizanidine is itself metabolized by CYP450, competitive inhibition would be expected if concentrations of tizanidine were sufficiently high. However, these experiments were planned to elucidate the potential for inhibition following tizanidine administration and therapeutically relevant concentrations of parent compound (84.2 nM) and circulating metabolites (M3, 219 nM, M4, 177 nM). In fact, concentrations considerably higher than expected C_{max} were used in order to prevent "false negatives". Additionally, incubations for each isoform were conducted in microsomes made from livers of one male donor, one female donor and one donor known to have been treated with enzyme-inducing drugs thus insuring that the lack of inhibition is not a phenomenon that exists in a single liver. Finally, the rates of control activity for each isoform represent a range of activity and indicate that none of the livers were deficient in the isoform required to metabolize each specific probe. Practically, it is highly unlikely that tizanidine, M3 or M4 will affect the plasma levels of other drugs metabolized by CYP450.

ATTACHMENT 3

Figure 1

Mean Improvement in Ashworth at Hour 1 on Visit 3



Hour	Placebo				Tizanidine 8 mg			Tizanidine 16 mg			P-Values		
	N	Mean	SEM	P-Value	N	Mean	SEM	N	Mean	SEM	Within Pooled Tizanidine ^a	Between Pooled Tizanidine and Placebo ^b	Between Tizanidine 8 mg and 16 mg ^b
Hour 0.0													
Actual	48	8.8	0.38		45	8.9	0.44	49	8.4	0.39			
Difference	48	0.0	0.26	0.874	45	-0.1	0.26	49	0.3	0.26	0.525	0.857	0.327
Hour 1.0													
Actual	48	8.7	0.41		44	6.3	0.50	48	4.9	0.45			
Difference	47	-0.1	0.24	0.534	42	-2.0	0.48	48	-2.9	0.45	<0.001	<0.001	0.150
Hour 2.0													
Actual	46	8.4	0.48		44	6.3	0.49	45	4.2	0.48			
Difference	46	0.1	0.28	0.814	43	-2.7	0.37	45	-3.6	0.52	<0.001	<0.001	0.062
Hour 3.0													
Actual	48	8.0	0.49		44	6.7	0.51	47	4.5	0.46			
Difference	47	-0.5	0.27	0.080	44	-1.6	0.36	46	-2.9	0.42	<0.001	<0.001	0.010
Hour 6.0													
Actual	47	8.6	0.44		44	8.2	0.52	48	7.5	0.44			
Difference	47	-0.1	0.29	0.658	44	-0.6	0.29	48	-0.2	0.35	0.090	0.496	0.438

Pooled=tizanidine 8 mg and 16 mg combined. Actual=Mean total Ashworth score at the visit and hour specified. Difference=Mean difference between the total Ashworth score on Visit 3 and Visit 2 at the hour specified

^a P-values for within treatment comparisons of changes in scores from Visit 2 to Visit 3 are from paired t-tests.

^b P-values for between treatment comparisons of changes in scores from Visit 2 to Visit 3 are from two-way ANOVA models with center and treatment group (pooled tizanidine and placebo or tizanidine 8 mg and tizanidine 16 mg) main effects.

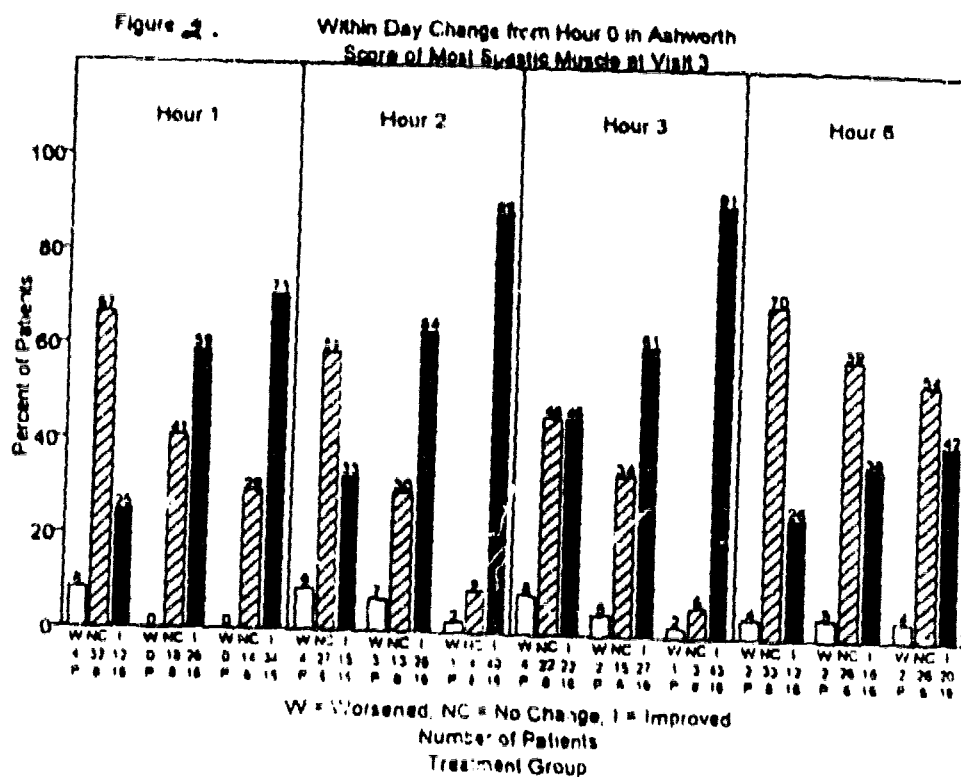


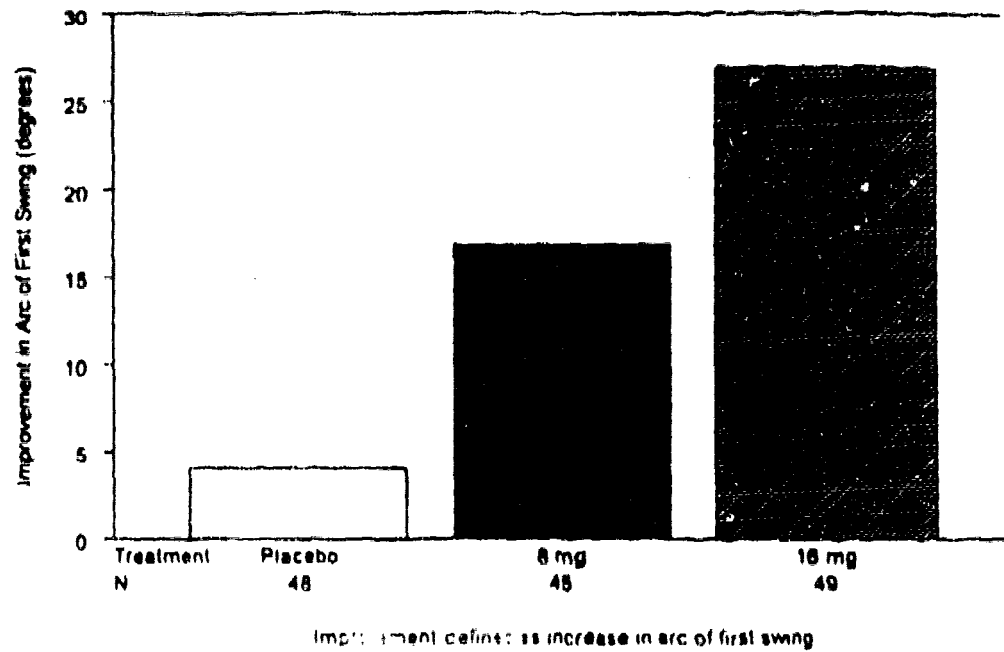
TABLE 2. Summary of Muscle Tone: Within Day Change From Hour 0.0 in Ashworth Score of Most Spastic Muscle - At Visit 3 Intent-To-Treat Patients

Hour	Placebo			Tizanidine 8 mg			Tizanidine 16 mg			P-Value			
	N	Improve N (%)	No Change N (%)	Worsen N (%)	N	Improve N (%)	No Change N (%)	Worsen N (%)	N		Improve N (%)	No Change N (%)	Worsen N (%)
1.0	48	12 (25)	32 (67)	4 (8)	44	26 (59)	18 (41)	0	48	34 (71)	14 (29)	0	<0.001
2.0	46	15 (33)	27 (59)	4 (9)	44	28 (64)	13 (30)	3 (7)	45	40 (89)	4 (9)	1 (2)	<0.001
3.0	48	22 (46)	22 (46)	4 (8)	44	27 (61)	15 (34)	2 (5)	47	43 (91)	3 (6)	1 (2)	<0.001
6.0	47	12 (26)	33 (70)	2 (4)	44	16 (36)	26 (59)	2 (5)	48	20 (42)	26 (54)	2 (4)	0.137

P-values are from Cochran-Mantel-Haenszel tests of nonzero correlation using modified ridit scores. The analysis compares the distribution of changes in Ashworth scores from hour 0 to each hour post dosing between the three treatment groups.

results on Visit 3 and Visit 2 at the hour specified. Figure F shows the change in the

Figure 3. Mean Improvement in Arc of First Swing of Pendulum Test at Hour 1 on Visit 3



arc of the first swing of the pendulum test at the primary outcome period, hour 1, at Visit 3

TABLE 3. Summary of Pendulum Test Results At Visit 3 and Comparison to Visit 2 Pendulum Test Results - Intent-To-Treat Patients

Hour	Placebo				Tizanidine 8 mg			Tizanidine 16 mg		P-Values		
	N	Mean	SEM	P-Value	N	Mean	SEM	Mean	SEM	Within Pooled Tizanidine ^a	Between Pooled Tizanidine and Placebo ^b	Between Tizanidine 8 mg and 16 mg
Hour 0.0												
Actual	48	39.5	3.40		45	47.8	3.29	45	48.5	3.51		
Difference	48	0.9	2.74	0.748	45	0.2	2.13	45	2.0	2.22	0.448	0.911
Hour 1.0												
Actual	48	41.5	3.13		43	65.5	3.78	45	75.1	3.84		
Difference	48	2.9	2.51	0.259	40	17.6	3.25	45	26.8	3.51	<0.001	<0.001
Hour 2.0												
Actual	46	41.6	3.21		41	61.4	4.13	45	72.7	4.05		
Difference	45	0.8	2.17	0.719	41	13.4	3.04	45	21.2	3.69	<0.001	<0.001
Hour 3.0												
Actual	48	46.1	3.43		43	59.0	3.59	45	68.4	3.96		
Difference	48	2.5	2.64	0.354	43	9.9	2.45	46	18.0	3.06	<0.001	<0.001
Hour 6.0												
Actual	47	44.0	3.35		44	48.7	3.54	47	52.5	4.13		
Difference	47	4.7	2.71	0.088	44	5.3	2.49	47	5.0	3.74	0.027	0.901

Pooled=tizanidine 8 mg and 16 mg combined. Actual=Mean pendulum test score at the visit and hour specified. Difference=Mean difference between the pendulum test score on Visit 3 and Visit 2 at the hour specified

^a P-values for within treatment comparisons of changes in scores from Visit 2 to Visit 3 are from paired t-tests.

^b P-values for between treatment comparisons of changes in scores from Visit 2 to Visit 3 are from two-way ANOVA models with center and treatment group (pooled tizanidine and placebo or tizanidine 8 mg and tizanidine 16 mg) main effects.

Extracted from Appendix B.7.1.

Figure 4. Mean Improvement in Ashworth (Change from Hour 0) (bars) and Mean Plasma Tizanidine Concentration (lines)

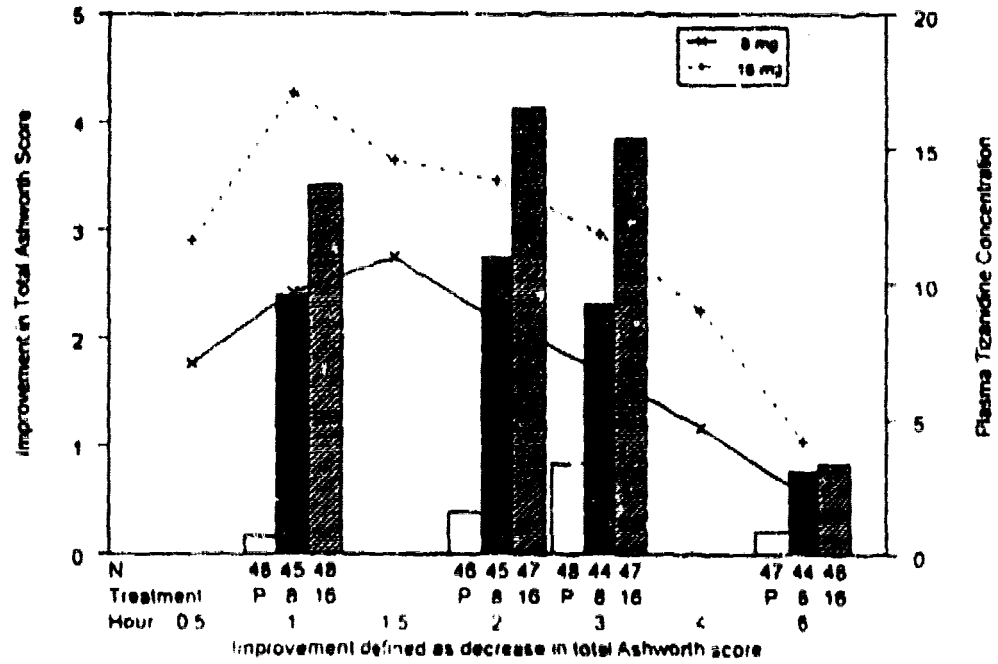


TABLE 4. Summary of Plasma Concentrations and Changes in Ashworth Scores: Within Day Change From Hour 0.0 on Visit 3 - Intent-To-Treat Patients

Hour	Tizanidine 8 mg						Tizanidine 16 mg						Pooled Correlation	P-Values
	Ashworth		Conc.				Ashworth		Conc.					
N	Mean Change	N	Median	Correlation	P-Value	N	Mean Change	N	Median	Correlation	P-Value			
1.0	44													
2.0	44													
3.0	44													
6.0	44													
O.C.	176													

Conc.=plasma tizanidine concentration
Pooled=tizanidine 8 mg and 16 mg combined
O.C.=Overall correlation for all hours combined
The correlation refers to Pearson's correlation. The p-value is from Student's t-test comparing the observed correlation to zero.
Extracted from Appendix B.8.1.

Figure 5. Mean Improvement in Arc of First Swing (Change from Hour 0) [bars] and Mean Plasma Tizanidine Concentration [lines]

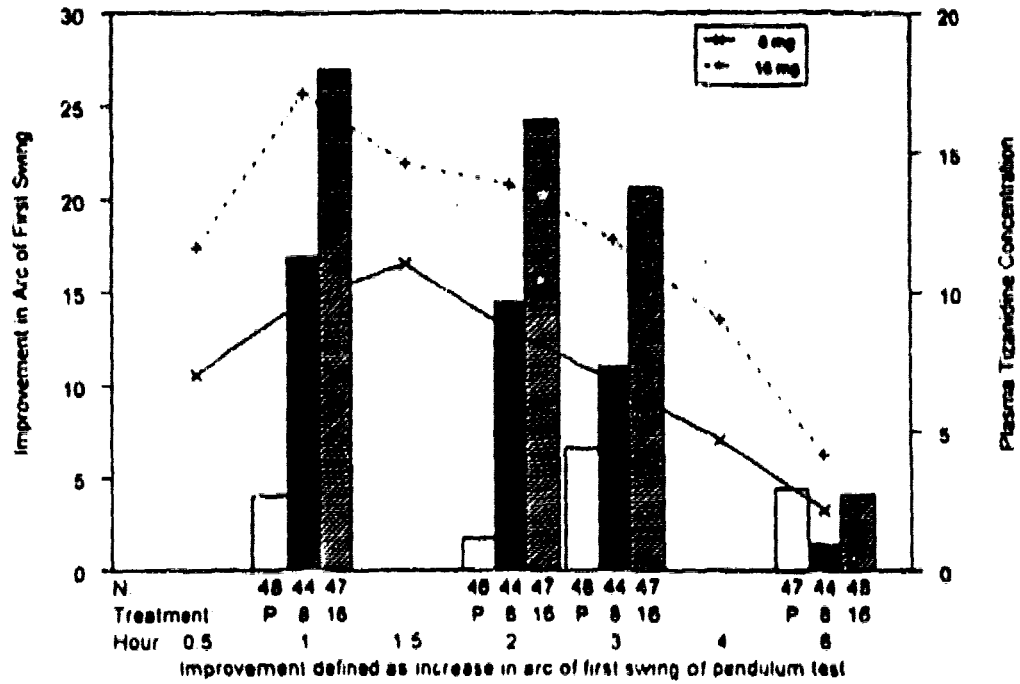


TABLE 5. Summary of Plasma Concentrations and Changes in Pendulum Test Results: Within Day Change From Hour 0.0 on Visit 3 - Intent-To-Treat Patients

Hour	Tizanidine 8 mg						Tizanidine 16 mg						Pooled Correlation		P-Value	
	Ashworth		Conc		Correlation	P-Value	Ashworth		Conc		Correlation	P-Value				
N	Mean Change	N	Median	N			Mean Change	N	Median	N			Median			
10																
20																
30																
60																
OC																

Conc = plasma tizanidine concentration

Pooled = tizanidine 8 mg and 16 mg combined

OC = Overall correlation for all hours combined

The correlation refers to Pearson's correlation. The p-value is from Student's t-test comparing the observed correlation to zero.

Extracted from Appendix B.9.1.

TABLE 6. Summary of Percent of Patients with Elicited Adverse Events, Time of Peak Effect and Duration of Effect at Visit 3 - Intent-To-Treat Patients

Event	Placebo N=48	Tizanidine 8 mg N=45	Tizanidine 16 mg N=49
Patients with an Elicited Adverse Event at Any Timepoint	63%	87%	100%
Dizziness At Any Timepoint Range Time of Peak Effect Duration of Effect	4% 0-4% Hour 0.5 N/A	22% 0-20% Hour 1 Hours 1-3	45% 4-39% Hour 1 Hours 0.5-6
Drowsiness At Any Timepoint Range Time of Peak Effect Duration of Effect	31% 2-19% Hour 3 N/A	78% 9-71% Hour 1.5 Hours 0.5-4	92% 4-80% Hours 1.5-2 Hours 0.5-6
Dry Mouth At Any Timepoint Range Time of Peak Effect Duration of Effect	35% 15-27% Hour 0.5 N/A	76% 11-67% Hour 2.0 Hour 1-4	88% 14-78% Hours 1.5-2 Hours 0.5-6
Tiredness At Any Timepoint Range Time of Peak Effect Duration of Effect	40% 10-19% Hour 6 N/A	67% 9-51% Hour 3 Hours 0.5-4	78% 16-63% Hour 1.5 Hours 0.5-6

Range=Percentage of patients reporting adverse events across 6 hours post-dosing
Time of Peak Effect=Post-dosing time at which highest percentage of patients reported elicited adverse event
Duration of Effect=Hours during which a percentage of patients in tizanidine 8 mg or 16 mg groups reporting event is greater than 10 percentage points above placebo. Events were elicited through hour 6 post-dosing
N/A=not applicable
Extracted from Appendix B.15.5

TABLE 7. Summary of Percent of Patients With Elicited Adverse Events Over All Timepoints at Visit 2 - Intent-To-Treat Patients

Event	Placebo N=48 Range (%)	Tizanidine 8 mg N=45 Range (%)	Tizanidine 16 mg N=49 Range (%)
Dizziness	2-6	2-7	0-12
Drowsiness*	4-13	7-20	10-29
Dry Mouth	13-21	13-29	12-24
Tiredness	17-23	22-29	14-31

* Drowsiness increased over 6 hours in all treatment groups.
Extracted from Appendix B.15.1.

TABLE 8. Summary of Relationship of Elicited Adverse Events and Plasma Concentration At Visit 3 - Intent-To-Treat Patients

Event	Hour	Placebo		Tizanidine 8 mg		Tizanidine 16 mg			
		N	(%)	N	(%)	Median Plasma Concentration	N	(%)	Median Plasma Concentration
Dizziness	0.0	1	(2)	0		0.00	2	(4)	0.00
	0.5	2	(4)	2	(3)	13.14	7	(13)	12.90
	1.0	1	(2)	8	(21)	11.25	17	(40)	16.00
	1.5	1	(2)	8	(19)	12.09	12	(29)	24.85
	2.0	0		7	(16)	13.40	14	(31)	17.90
	3.0	0		5	(12)	7.86	12	(27)	13.10
	4.0	1	(2)	2	(5)	14.98	8	(18)	12.81
Drowsiness	0.0	1	(2)	4	(9)	0.00	2	(4)	0.00
	0.5	2	(4)	13	(30)	8.34	15	(33)	14.10
	1.0	6	(13)	20	(51)	11.25	32	(74)	16.23
	1.5	7	(15)	29	(69)	12.00	34	(81)	12.20
	2.0	8	(17)	29	(67)	8.79	36	(80)	12.20
	3.0	9	(19)	23	(53)	6.66	33	(73)	10.00
	4.0	6	(13)	14	(33)	4.14	28	(62)	9.26
6.0	6	(13)	5	(11)	1.82	23	(51)	4.27	

TABLE 8. (Continued)

Event	Hour	Placebo		Tizanidine 8 mg		Tizanidine 16 mg			
		N	(%)	N	(%)	Median Plasma Concentration	N	(%)	Median Plasma Concentration
Dry Mouth	0.0	7	(15)	5	(12)	0.00	7	(14)	0.00
	0.5	13	(27)	14	(33)	9.14	20	(43)	12.40
	1.0	10	(21)	21	(54)	10.70	30	(70)	16.75
	1.5	9	(19)	27	(64)	11.70	32	(76)	14.30
	2.0	9	(19)	29	(67)	8.09	35	(78)	13.30
	3.0	9	(19)	25	(58)	6.66	32	(73)	10.95
	4.0	7	(15)	13	(31)	4.42	24	(53)	12.05
Tiredness	0.0	6	(13)	4	(9)	0.00	8	(16)	0.00
	0.5	7	(15)	12	(30)	8.34	17	(36)	12.30
	1.0	7	(15)	17	(44)	11.30	23	(53)	14.40
	1.5	8	(17)	22	(52)	10.37	27	(64)	13.20
	2.0	7	(15)	22	(51)	9.17	26	(58)	12.75
	3.0	8	(17)	22	(51)	6.97	25	(57)	10.60
	4.0	5	(10)	11	(28)	4.52	21	(47)	12.10
6.0	9	(19)	8	(20)	1.62	20	(46)	2.93	

TABLE 9. Summary of Relationship of Elicited Adverse Event of Drowsiness and Ashworth Score Change From Baseline at Visit 3 - Intent-To-Treat Patients

Hour	Placebo		Tizanidine 8 mg		Tizanidine 16 mg	
	Drowsiness N (%)	Mean Change from Baseline	Drowsiness N (%)	Mean Change from Baseline	Drowsiness N (%)	Mean Change from Baseline
0.0	Reported	1 (2)	4 (9)	2 (4)		
	Not Reported	47 (98)	41 (91)	47 (96)		
1.0	Reported	6 (13)	23 (52)	36 (75)	-4.1	
	Not Reported	42 (88)	21 (48)	12 (23)	-1.5	
2.0	Reported	8 (17)	30 (68)	37 (83)	-4.6	
	Not Reported	30 (63)	14 (32)	8 (16)	-1.9	
3.0	Reported	9 (19)	23 (52)	36 (77)	-4.2	
	Not Reported	39 (81)	21 (48)	11 (23)	-2.8	
6.0	Reported	6 (13)	7 (16)	24 (50)	-6.9	
	Not Reported	41 (87)	37 (84)	24 (50)	-6.8	

Summary of Cardiovascular Parameters At Visit 3 - Baseline and Maximum Change for Visit 2 to Visit 3 - Intent-to-Treat												
Hour	Placebo				Tizanidine 8 mg			Tizanidine 16 mg			P-Values	
	N	Mean	SEM	P-Value	N	Mean	SEM	N	Mean	SEM	Within Pooled Tizanidine ^a	Between Pooled Tizanidine and Placebo ^b
Supine Systolic Blood Pressure (mm Hg)												
Hour 0.0 Actual	48	119.8	2.29		45	120.3	2.32	49	122.1	2.17		
Difference	48	0.4	1.90	0.844	45	-2.2	1.36	49	-3.2	1.69	0.020	0.145
Hour 1.0 Actual	48	119.2	2.42		45	103.2	2.52	48	95.9	1.58		
Difference	48	-0.6	1.49	0.698	45	-19.3	2.80	48	-23.3	2.29	<0.001	<0.001
Supine Diastolic Blood Pressure (mm Hg)												
Hour 0.0 Actual	48	74.0	1.54		45	75.1	1.47	49	73.3	1.40		
Difference	48	0.2	1.44	0.874	45	-2.1	1.31	49	-0.9	1.25	0.107	<0.001
Hour 1.0 Actual	48	73.1	1.52		45	68.8	1.80	49	63.6	1.47		
Difference	48	-0.2	0.98	0.865	45	-7.6	1.72	49	-10.9	1.68	<0.001	<0.001
Hour 2.0 Actual	48	74.3	1.33		45	68.5	1.99	48	61.3	1.24		
Difference	48	-0.2	0.99	0.850	45	-7.3	1.79	48	-14.1	1.69	<0.001	<0.001

TABLE 10. (Continued)												
Hour	Placebo				Tizanidine 8 mg			Tizanidine 16 mg			P-Values	
	N	Mean	SEM	P-Value	N	Mean	SEM	N	Mean	SEM	Within Pooled Tizanidine ^a	Between Pooled Tizanidine and Placebo ^b
Supine Pulse Rate												
Hour 0.0 Actual	48	76.0	1.54		45	74.2	1.71	49	72.5	1.54		
Difference	48	1.1	1.63	0.486	45	0.2	1.47	49	-0.8	1.20	0.743	0.381
Hour 1.0 Actual	48	70.4	1.29		45	68.4	1.40	48	65.8	1.78		
Difference	48	-1.4	1.03	0.184	45	-4.1	1.32	48	-5.0	1.34	<0.001	0.035
Hour 1.0 Actual	48	71.0	1.22		45	66.4	1.58	48	61.4	1.21		
Difference	48	-1.1	1.19	0.378	45	-3.9	1.51	48	-9.0	1.48	<0.001	0.002
Sitting Systolic Blood Pressure (mm Hg)												
Hour 0.0 Actual	43	118.5	2.31		40	120.3	2.64	45	120.7	2.33		
Difference	43	2.0	1.97	0.316	37	-2.3	2.02	40	-1.4	2.33	0.314	0.106
Hour 2.0 Actual	43	120.0	2.59		39	100.4	2.48	45	92.0	1.97		
Difference	41	0.6	1.45	0.664	36	-21.3	3.41	40	-28.6	3.22	<0.001	<0.001

TABLE 10. (Continued)												
Hour	Placebo				Tizanidine 8 mg			Tizanidine 16 mg			P-Values	
	N	Mean	SEM	P-Value	N	Mean	SEM	N	Mean	SEM	Within Pooled Tizanidine ^a	Between Pooled Tizanidine and Placebo ^b
Sitting Diastolic Blood Pressure (mm Hg)												
Hour 0.0 Actual	43	74.3	1.30		40	76.7	1.64	45	75.8	1.45		
Difference	41	0.9	1.12	0.411	37	-1.1	1.49	40	0.3	1.50	0.713	0.358
Hour 2.0 Actual	43	74.6	1.31		39	65.1	1.82	45	58.9	1.39		
Difference	41	-0.8	1.24	0.545	36	-14.1	1.89	40	-18.8	1.88	<0.001	<0.001
Sitting Pulse Rate												
Hour 0.0 Actual	43	78.3	1.42		40	76.8	1.93	45	74.4	1.46		
Difference	41	0.2	1.42	0.891	37	-0.4	1.79	40	-1.7	1.40	0.347	0.481
Hour 2.0 Actual	43	73.7	1.44		39	70.0	1.75	45	67.9	1.36		
Difference	41	-0.3	1.44	0.853	36	-4.2	1.76	40	-4.5	1.54	<0.001	0.028

^a Pooled=tizanidine 8 mg and 16 mg combined.

Actual=Mean blood pressure/pulse at the visit and hour specified.

Difference=Mean difference between the blood pressure/pulse on Visit 3 and Visit 2 at the hour specified.

^b P-values for within treatment comparisons of changes in scores from Visit 2 to Visit 3 are from paired t-tests.

^c P-values for between treatment comparisons of changes in scores from Visit 2 to Visit 3 are from two-way ANOVA models with center and treatment gr.-p (pooled tizanidine and placebo or tizanidine 8 mg and tizanidine 16 mg) main effects.

Extracted from Appendix B 10.3.

TABLE I. Summary of Plasma Concentrations and Changes in Pulse and Blood Pressure: Within Day Change from Hour 0.0 on Visit 3 - Intent-to-Treat

Hour	Tizanidine 8 mg						Tizanidine 16 mg						Pooled Correlation P-Values	
	N	Mean Change	N	Median	Correlation	P-Value	N	Mean Change	N	Median	Correlation	P-Value		
Supine Systolic Blood Pressure														
1.0	45	-14.4	39	6.29	-0.332	0.039	49	-20.2	43	14.90	-0.248	0.109	-0.340	0.002
2.0	45	-17.2	43	5.94	-0.389	0.010	48	-26.6	45	11.80	-0.448	0.002	-0.461	<0.001
3.0	44	-12.3	43	3.90	-0.558	<0.001	48	-21.9	44	9.93	-0.410	0.006	-0.516	<0.001
6.0	44	-4.9	40	1.27	-0.449	0.004	48	-7.7	45	2.92	-0.411	0.005	-0.431	<0.001
O.C.	178	-12.2	165	3.90	-0.453	<0.001	193	-19.1	177	9.59	-0.452	<0.001	-0.481	<0.001
Supine Diastolic Blood Pressure														
1.0	45	-6.3	39	6.29	-0.081	0.622	49	-9.7	43	14.90	-0.107	0.494	-0.155	0.165
2.0	45	-6.6	43	5.94	-0.045	0.775	48	-14.1	45	11.80	-0.483	0.001	-0.321	0.002
3.0	44	-6.5	43	3.90	-0.310	0.043	48	-9.9	44	9.93	-0.392	0.009	-0.383	<0.001
6.0	44	-4.7	40	1.27	-0.353	0.025	48	-5.2	45	2.92	-0.258	0.087	-0.280	0.009
O.C.	178	-6.0	165	3.90	-0.150	0.054	193	-9.7	177	9.59	-0.362	<0.001	-0.303	<0.001

TABLE II. (Continued)

Hour	Tizanidine 8 mg						Tizanidine 16 mg						Pooled Correlation P-Values	
	N	Mean Change	N	Median	Correlation	P-Value	N	Mean Change	N	Median	Correlation	P-Value		
Supine Pulse Rate														
1.0	45	-5.9	39	6.29	-0.470	0.003	48	-6.8	43	14.90	-0.362	0.018	-0.399	<0.001
2.0	45	-7.8	43	5.94	-0.303	0.048	48	-11.1	45	11.80	-0.465	0.001	-0.408	<0.001
3.0	44	-6.2	43	3.90	-0.153	0.327	48	-9.7	44	9.93	-0.167	0.279	-0.202	0.061
6.0	44	-3.6	40	1.27	-0.382	0.015	48	-3.4	45	2.92	-0.141	0.355	-0.224	0.039
O.C.	178	-5.9	165	3.90	-0.323	<0.001	192	-7.8	177	9.59	-0.337	<0.001	-0.340	<0.001
Sitting Systolic Blood Pressure														
1.0	38	-19.1	39	6.29	-0.340	0.053	40	-24.3	43	14.90	-0.315	0.065	-0.352	0.003
2.0	38	-19.9	43	5.94	-0.490	0.002	43	-28.7	45	11.80	-0.556	<0.001	-0.549	<0.001
3.0	37	-14.9	43	3.90	-0.716	<0.001	44	-24.1	44	9.93	-0.426	0.006	-0.565	<0.001
6.0	39	-4.7	40	1.27	-0.624	<0.001	44	-8.0	45	2.92	-0.518	0.001	-0.550	<0.001
O.C.	152	-14.6	165	3.90	-0.555	<0.001	171	-21.2	177	9.59	-0.527	<0.001	-0.552	<0.001

TABLE III. (Continued)

Hour	Tizanidine 8 mg						Tizanidine 16 mg						Pooled Correlation P-Values	
	N	Mean Change	N	Median	Correlation	P-Value	N	Mean Change	N	Median	Correlation	P-Value		
Sitting Diastolic Blood Pressure														
1.0	38	-10.8	39	6.29	-0.234	0.190	40	-12.6	43	14.90	-0.368	0.030	-0.334	0.005
2.0	38	-11.3	43	5.94	-0.482	0.003	43	-16.5	45	11.80	-0.450	0.004	-0.487	<0.001
3.0	37	-8.3	43	3.90	-0.502	0.002	44	-12.2	44	9.93	-0.373	0.018	-0.446	<0.001
6.0	39	-5.3	40	1.27	-0.427	0.011	44	-5.2	45	2.92	-0.284	0.072	-0.325	0.004
O.C.	152	-8.9	165	3.90	-0.436	<0.001	171	-11.6	177	9.59	-0.455	<0.001	-0.460	<0.001
Sitting Pulse Rate														
1.0	38	-2.0	39	6.29	-0.418	0.016	40	-6.6	43	14.90	-0.147	0.398	-0.313	0.009
2.0	38	-6.6	43	5.94	-0.364	0.029	43	-6.3	45	11.80	-0.173	0.284	0.255	0.026
3.0	37	-4.7	43	3.90	-0.035	0.841	44	-6.3	44	9.93	0.198	0.221	0.068	0.562
6.0	39	-3.1	40	1.27	-0.222	0.199	44	-4.7	45	2.92	-0.109	0.493	-0.185	0.110
O.C.	132	-4.1	165	3.90	-0.270	0.001	171	-5.9	177	9.59	-0.066	0.416	-0.179	0.002

Conc.=plasma tizanidine concentration--

Pooled=tizanidine 8 mg and 16mg combined

O.C.=Overall correlation for all hours combined

The correlation refers to Pearson's correlation. The p-value is from Student's t-test comparing the observed correlation to zero.

Extracted from Appendix B.10.9 correlation

OCT/IRN

OCT 9 1996

OCT 10 1996

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-397

Tizanidine HCl (ZANAFLEX®)
4 mg Tablet (Scored)

Athena Neurosciences, Inc.,
South San Francisco, CA

Submission Date:

August 09, 1996

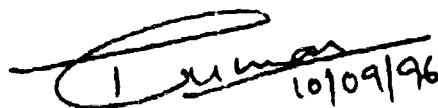
Type of Submission: Review of Responses to AE Letter

=====
In this submission, the sponsor provided responses to the Agency's "Approvable Letter" dated March 11, 1996 (Attachment 1).

Upon review of the responses (Attachment 2), the reviewer concurs that the sponsor has responded satisfactorily to OCPB's Comments (Attachment 1). However, in response to OCPB Comment 2 provided in the Approvable Letter, the sponsor submitted the Integrated Summary of Efficacy containing an analysis of the effects of race on the change from baseline in lower body Ashworth score, which showed no race differences (P=0.301). No information regarding the effect of race on the pharmacokinetics of tizanidine was provided. A statement to reflect this fact has already been placed in the labeling.

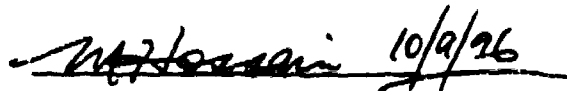
RECOMMENDATION:

This submission (NDA 20-397) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and the responses provided by the sponsor have been found to be acceptable.


10/09/96

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by M. Hossain, Ph. D.


10/9/96

CC: NDA 20,397 (orig.), HFD-120, HFD-850 (Tammara, Hossain, Malinowski), HFD-340, Drug, Chron, Division, and Reviewer Files.

Pharmacologist Review

Zanaflex[®]
(Tizanidine) Tablets

NDA 20-397

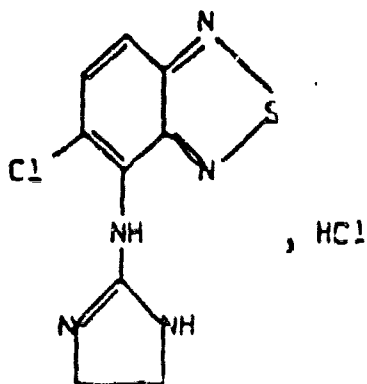
Pharmacology

Pharmacology and Toxicology Review of NDA# 20-397

Reviewer: Aisar H. Atrakchi, Ph.D. AA
Supervisor: Glenna Fitzgerald, Ph.D.
Rev Date: July 28 1994

Drug: Zanaflex (tizanidine HCl)
Sponsor: Athena Neurosciences, Inc.
800F Gateway Blvd.
S. San Francisco, CA 94080

Category: Adrenergic α_2 Agonist.
Indication: Treatment of Spasticity due to Spinal Cord Injury.
Code Name: DS 103-282
Chemical Name: 5-chloro-4-(2-imidazolin-2-yl-amino)-benzothiadiazole hydrochloride.
Molecular Weight: 253.7 as free base.
Chemical Structure:



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

Clinical Dose and Form: 36 mg/day tablets
Related IND(s):

cc: Orig NDA
HFD-120/Div File
/Fitzgerald 393 1/24/95
/Atrakchi AA
/Grilley

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Tizanidine labelling:
Reviewer: Aisar Atrakchi, Ph.D.
Date: Nov 28 1995

Clinical Pharmacology:
Mechanism of Action

Delete "at supra spinal" 2nd line 1st paragraph/page1.
3rd line add "fibers" after skeletal muscle,....

Delete the sentence before last in the 1st paragraph: "Further, the effects of tizanidine are greatest on polysynaptic pathways".

Last sentence replace with: "The overall effect of tizanidine is to reduce facilitation of spinal motor neurons".

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Two dietary carcinogenicity studies were conducted in rodents. Tizanidine was administered to mice for 78 weeks at doses up to 16mg/kg which is equivalent to 3.2x the maximum recommended human dose on a mg/m² basis. Tizanidine was also administered to rats for 104 weeks at doses up to 9mg/kg which is equivalent to 3.6x the maximum recommended human dose on a mg/m² basis. There was an increased incidence of periacinar eosinophilic hepatocytic hypertrophy, but there was no significant increase in incidence of pretumerous hepatic hyperplastic foci comparing treatment and control groups. There was no statistically significant increase in tumors in either species at these doses. The carcinogenic potential of tizanidine in humans is unknown.

Last sentence in the 1st paragraph replace with the following text and introduce a new paragraph:

Tizanidine was not mutagenic or clastogenic in the following assays: the in vitro bacterial Ames test, mammalian gene mutation in Chinese hamster/V79-HGPRT test, and mammalian chromosomal aberration in Chinese hamster/V79 cells; the in vivo bone marrow micronucleus in mice, bone marrow micronucleus and cytogenetics in Chinese hamsters, dominant lethal in mice, and Unscheduled DNA Synthesis (UDS) in mice.

2nd paragraph replace with the following text:

Tizanidine did not affect fertility in male rats at doses approximately 4 times the maximum recommended human dose on a mg/m² basis and in females at doses equal to the maximum recommended human dose on a mg/m² basis. However, fertility was reduced in males receiving 12 times the maximum recommended human dose on a mg/m² basis and in females receiving 4 times the maximum recommended human dose on a mg/m² basis. At these doses, maternal behavioral effects and clinical signs were observed including marked sedation, weight loss, and ataxia.

Usage in Pregnancy:

Replace this section with the following text:

Pregnancy Category C; Reproduction studies performed in rats at doses equal to the maximum recommended human dose on a mg/m² and in rabbits at 16x the maximum recommended human dose on a mg/m² basis, did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 12x the maximum recommended human dose on a mg/m² increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Postimplantation loss was increased in rabbits at doses at doses $\geq 0.8x$ the maximum recommended human dose on a mg/m² basis. Tizanidine has not been studied in pregnant women.

Page 7

Drug Abuse and Dependence:

2nd paragraph/2nd line add the following:

but abrupt cessation of tizanidine produced transient signs of withdrawal in monkeys at doses >100 times the maximum recommended human dose on a mg/kg basis.

Executive Summary:

Tizanidine, a benzothiadizole, is a centrally acting skeletal muscle relaxant. It is without a direct effect on muscle fibers or on the neuromuscular junction. It binds selectively and with high affinity to α_2 receptors. Tizanidine acts at the spinal and supraspinal level (locus coeruleus). It may act pre-synaptically on modulating release or, post-synaptically on modulating responses of excitatory amino acids (EAA) in spinal motoneurons, or both. It inhibited in animal models α -rigidity (Thalamonal-induced), γ -rigidity (decerebrate rigidity), and polysynaptic brainstem lingumandibular reflex (supraspinal) with ED₅₀ values of 0.48 mg/kg orally, 0.48 mg/kg i.v., and approximately 0.01 mg/kg i.v. respectively. Tizanidine at 0.055 mg/kg i.v. completely abolished thalamonal-induced muscle rigidity in rats a dose that is 40x more effective than diazepam, 80x as potent as baclofen, and 130x as potent as dantrolene on a mg/kg basis (table below).

Effect of Tizanidine and Reference Compounds on Droperidol/Fentanyl-Induced Rigidity in the Rat

Test Compound	Oral Efficacy (mg/kg)		Intravenous Efficacy (mg/kg)		
	N	ED ₅₀	N	ED _{min}	ED _{block}
Tizanidine	35	0.48	22	0.013	0.055
Diazepam	24	4	8	0.011	2.2
Baclofen	18	5.2	8	0.78	4.5
Dantrolene	24	>80	10	0.34	7.1

ED_{min}: dose inhibiting rigidity by 10%; ED₅₀: dose inhibiting by 50%; ED_{min}=dose caused 10% reduction in tone.
 ED_{block}: dose completely abolishing rigidity.

Tizanidine inhibited tonic stretch reflexes in rabbits with an ED₅₀ of 0.02 mg/kg (i.v.) compared with 0.23 mg/kg for diazepam, 0.3 for baclofen and 20 mg/kg for dantrolene. However, the effect of tizanidine on mono- and polysynaptic spinal reflexes in C1-spinalized cats was inconsistent. The monosynaptic patellar reflex was unchanged or weakly, but not dose-dependently, reduced and the polysynaptic flexor reflex was reduced in some animals at 0.1 mg/kg i.v., but facilitated in others, specially at high doses (0.3-1 mg/kg i.v.). In other studies, these reflexes were suppressed in a dose-dependent manner by tizanidine with cumulative doses of 0.025-1.2 mg/kg i.v. and complete suppression of reflex activity seen at >0.05 mg/kg. These conflicting findings were contributed

to differences in the amount and type of stimulation as well as to high doses. With respect to the latter, it was speculated that high doses of tizanidine may interact with α_1 receptors which are excitatory. This was supported by a study where prazosin but not clonidine blocked the polysynaptic facilitating effects of tizanidine noted in spinalized rats. From these and other studies in monkeys, the site of action of tizanidine was proposed to be either one or more of the following:

1. inhibition of spontaneous excitatory activity of the locus coeruleus imposed on the spinal reflex or,
2. decrease the excitability within the neurons of the flexor reflex arc or,
3. direct effect on Renshaw neurons, group II interneurons or other interneurons mediated by EAA in the spinal cord.

All or any of the above will lead to muscle relaxation.

Radioligand binding assays demonstrated high binding affinity of tizanidine to α_2 receptors (EC_{50} 2 nM vs. 1.1 nM for clonidine), and moderate affinity to dopamine receptors (EC_{50} 35 μ M vs. 0.001 μ M for haloperidol). Binding to other sites was weak (EC_{50} >100 μ M). Tizanidine similar to clonidine, is not a subtype-selective receptor antagonist (since the difference between receptor subtype affinities was 2.5 fold or less) (table below). Tizanidine was shown at least in amphibian hemisected spinal cord model, to have no direct effect on EAA receptors e.g. NMDA and quisqualate. The drug also had no effect on D-aspartate uptake into spinal cord slices and failed to antagonize NMDA- or AMPA-induced depolarization in the long-duration ventral root reflex preparation. In rat kidney membranes, tizanidine bound to imidazoline receptors with 20x the affinity to α_2 (K_i 4.17 nM; clonidine K_i was 9 nM). The physiological significance of central and peripheral imidazoline receptors is unknown at this time.

Receptor binding profile for tizanidine

alpha2	2.1nM IC_{50}
2A	65nM K_i
2B	167nM K_i
2C	107nM K_i
alpha1	4,687 nM IC_{50}
Beta ¹	>100 μ M EC_{50}
DA ²	35 μ M EC_{50}
Cholinergic ³	>100 μ M EC_{50}
imidazoline	4.2 nM K_i

¹ displacement of dihydroalprenolol
² displacement of haloperidol
³ displacement of QNB

Other pharmacological effects of tizanidine include antinociceptive activity investigated using standard animal pain models (chemical, thermal, electrical and experimental-induced arthritis) in mice, rats and monkeys (summary table 1). The mechanism responsible for this effect is believed to be through α_2 (table 1). Tizanidine was ineffective in protecting against electroshock-induced seizures and NMDA-induced seizures (table attached). However, tizanidine was effective anticonvulsant (tonic and clonic seizures) in audiogenic seizures induced in mice at ED_{50} of 0.45-0.76 mg/kg i.p. and in phototically induced seizures in baboons at 16-32 mg/kg p.o. and 2-4 mg/kg i.v. (protection for upto 1 hr postdose).

Tizanidine similar to other α_2 agonists, decreased gastric movements and intestinal motility, and gastric acid secretion; these effects were less potent than those of clonidine. Other effects of tizanidine are presented in the table below.

Screening Studies Performed To Evaluate for Other Pharmacological Activities

Species/ Strain (Weight)	No. Animals	Dose (mg/kg) & Route of Admin.	Effects of Tizanidine	Effects of Reference Compounds	Ref. No./ Laboratory
Mouse/ CD1/ Charles River (18-22 g)	10 (both sexes)	20-100 po	No ability to inhibit oxotremorine-induced tremors	Diazepam ED_{50} = 71 mg/kg Baclofen ED_{50} = 37 mg/kg Dantrolene not effective	1 /Sandoz AG Bern
Rat/ Sprague Dawley (90-160 g)	4-10 (both sexes)	2.5-10 sc	No ability to inhibit apomorphine-induced gnawing up to 20 min post-dose	No effect of diazepam, dantrolene or phenoxybenzamine Baclofen at 10 mg/kg = 42% decrease	1 /Sandoz AG Bern
Rat/ Sprague Dawley (90-160 g)	5-26 (both sexes)	2.5-10 sc	No ability to inhibit stereotypies induced by d-amphetamine up to 60 min post-dose	No effect of diazepam, baclofen, or dantrolene	1 /Sandoz AG Bern
Rat/ Sprague Dawley (120-150 g)	5F	0.1-5.0 sc	No ability to antagonize catalepsy induced by reserpine	Not done	1 /Sandoz AG Bern
Mice/ ddY Shizuoka (18-22 g)	8M	2.5-10 po	Decreased rectal temperature, antagonism by yohimbine and not naloxone	Clonidine also decreased temperature	26/Univ. Meijo/ Japan
Rat/ Sprague Dawley (115-134 g)	6 (both sexes)	1, 5 po	Slight decrease in rectal temperature	Not done	1 /Sandoz AG Bern
Rabbit/ Swiss (3-3.5 kg)	3 (both sexes)	5 po	Increased rectal temperature	Not done	1 / Sandoz AG Bern

Admin. = administration; min = minutes; NS = not specified; po = oral; sc = subcutaneous

Response of the cardiovascular system to the effects of tizanidine was bimodal. Initially there was a transient hypertension mediated by α_1 receptors, followed by a more prolonged hypotension particularly after i.v. administration, mediated through central mechanisms. The CVS effects are similar to those of clonidine but clonidine was 10-50x more potent than tizanidine (table 3). The effects of tizanidine were greater after i.v. than after oral dosing and the transient hypertension was observed only after the i.v. administration. The CVS effects of tizanidine occurred at oral doses higher than those required for muscle relaxation (no CVS changes at doses <1 mg/kg p.o.).

Tizanidine at 0.1 or 1 mg/kg did not interact with diazepam, haloperidol, or acetaminophen. However, at 1 mg/kg it significantly enhanced the effect of 10 and 30 mg/kg imipramine (reduced mouse locomotor activity).

Tizanidine had a reinforced self-administration without physical dependence, at 10 ug/kg i.v. injected into monkeys for 5 wks; no withdrawal symptoms were observed. Monkeys orally dosed with 10 mg/kg twice daily for 5 wks, showed transient signs of withdrawal such as autoaggression and fear, and increased aversive behavior, locomotion, and motility. After 32 mg/kg oral doses for 5 wks, 4/4 monkeys developed withdrawal signs. There were no physical dependence of tizanidine tested at 0.32 mg/kg i.p. in rats (table 4).

The pharmacokinetics of tizanidine were investigated in the mouse, rat, rabbit, dog, and monkey (table 5). The PKs were studied with unlabelled and ^{14}C - and ^3H -labelled drug. Analytical methods used to identify and quantify metabolites included HPLC, NMR, and MS. Doses tested ranged between 0.03-8 mg/kg for the oral and parenteral (i.v., i.p.) routes of administration (up to 330 mg/kg in one rat metabolism study). Tizanidine was rapidly absorbed following single or repeated oral dosing. In mice and rats, the drug appeared in blood within 0.25-0.5 hr after single oral dose and within 3 min in the dog. Peak plasma levels in mice ranged between 8-26 ug equiv./g whole blood reached within 0.5-0.75 hr, in rats peak was 1 ug equiv/g reached within 0.75 hr, in the dog peak plasma level was 52 ng/g plasma reached within 2.25-5 hr. Absorption in the dog was slow and concentration increased gradually with time. In monkeys, mean peak plasma levels were 14-28 ng/ml reached by 4.5 hr. One monkey out of 3 showed an unusual concentration rebound at 8 hr postdose that was perhaps due to metabolite formation but this was not confirmed. Plasma protein binding of tizanidine is small and similar between humans and rats at therapeutic concentration of <20 ng/ml (30%; except its higher in bovine blood, 40-50%). Free fraction of tizanidine in whole blood accounted for 30% in plasma water, 60% in blood cells, and only 10% in plasma proteins. There was no difference in plasma protein binding in vitro and in vivo indicating similar binding affinities of the parent and its metabolites. At higher drug

levels (>13 ug/ml) in animals, protein binding was reduced indicating saturation of binding sites. Tizanidine is widely distributed into tissues and organs with highest levels of radioactivity detected in excretory organs: liver and kidneys. Pattern of tissue distribution of total radioactivity was similar across animal species. Tizanidine entered the BBB efficiently, it also crossed into the fetus through the placenta and appeared in milk of lactating animals. Multiple dosing did not affect PK parameters in animals but decreased placental transfer and/or increased the efficiency of fetal elimination of the drug. Tizanidine is eliminated mainly in the urine (60-80%) with some in feces and about 29% in bile as determined in bile fistula rats. Most of radioactivity was eliminated by 24-48 hr of dosing (almost complete elimination, 90%, by 96 hr). Elimination half life in mice was 5 hr for both oral and i.v. dosing with absolute oral bioavailability of 70%. Elimination half life in rats was 1.5 hr for both oral and i.v. routes with absolute bioavailability of 89%. Dogs had a very long elimination half life of 90-110 hr for the oral and i.v. routes, absolute bioavailability was 97%. In monkeys, elimination half life ranged between 2-4 hr compared with 2 hr in humans; mean volume of distribution was 7 and 2 l/kg in monkey and humans respectively, and mean plasma clearance in monkey ranged between 1.4-2.5 l/hr/kg vs 0.35-1.4 l/hr/kg in humans. There appear to be no drug accumulation with repeated dosing. Tizanidine is extensively biotransformed to a number of metabolites in all species. Except in the mouse (13%) and dog (11.5%), the parent drug could not be detected in plasma. Attached table 6 summarizes the major metabolites in all animal species and humans. Figure 1 shows that the metabolic profile is similar in all species and humans but there are quantitative differences specially in plasma levels of the 3 major human metabolites (3, 4, and 10) (table 7). Differences in the amount of metabolites formed between species are important in evaluating toxicity studies (including carcinogenicity and reproductive) and their relevance in assessing human risk. The dog and rabbit are more closely similar to humans in their metabolic profile of tizanidine than are the rat and the mouse. The pharmacological activity of metabolites 3 and 4 were investigated in mice and rats. In mice, metabolite 3 did not modify motility or body temperature at oral doses up to 100 mg/kg and only weak and dose-independent inhibition occurred with metabolite 4 at oral doses 3-320 mg/kg. Neither metabolite blocked Thalamonal-induced alpha rigor in rats at i.v. doses up to 10 mg/kg. Metabolite 10 was not tested for biological activity.

The oral LD₅₀ values for the acute toxicity of tizanidine in mice and rats were 200-860 mg/kg, and >100 mg/kg in rabbits. The i.v. LD₅₀ in mice and rats was 40 mg/kg and 20 mg/kg in rabbits. Most deaths occurred within 24 hr of dosing. Signs of toxicity included sedation, salivation, drowsiness, piloerection, and ataxia. In rats, a marked dose-dependent lagophthalmos with decreased blinknig occurred immediately after dosing, and corneal opacity was noted at

the end of the observation period. Following a single i.v. injection of 0.1 mg/kg to dogs, pulse frequency was reduced to 60% of baseline values within 30 min of dosing and QT interval was prolonged after 30 and 120 min of injection. At 0.3 and 1 mg/kg similar change in pulse occurred and twin-peaked precordial T-waves or PQ interval prolongation were found. All changes were normal by 24 hr.

The following table summarizes the subchronic/chronic and carcinogenicity studies conducted:

Multidose Study Designs

Species/Strain/ Source	Route of Admin.	No. Animals	Dose (mg/kg/day)	Treatment (wks)	Recovery (wks)	Reference/ Laboratory
Rat/KFM-WIST/ Fullinsdorf	ip	14M/14F	0, 0.3, 1, 3	6	4	5/Sandoz AG, Basel
Dog/Beagle/ Marshall	iv	3M/3F	0, 0.3, 0.1, 1.0	6	4	8/Sandoz AG, Basel
Rat/OFA/ Sandoz	po (diet)	10M/10F; 15M/15F (high dose)	0, 1.7, 8, 40	13	4	4/Sandoz AG, Basel
Dog/Beagle/ Marshall	po (capsule)	2M/2F	0, 0.3, 1, 3-4	13	None	6/Sandoz AG, Basel
Dog/Beagle/ Marshall	po (capsule)	4M/4F	0, 0.15, 0.45, 1.5	52	6	7/Sandoz AG, Basel
Mouse/ OF-1/Sandoz	po (diet)	50M/50F	0, 1, 4, 16	78	None	9/Sandoz AG, Basel
Rat/CD/ Sprague Dawley	po (capsule)	60M/60F	0, 1, 3, 9	104	None	11/LSR, England

In the 6-week i.p. study in rats, there was one death of unknown cause in HDm (3 mg/kg) on wk 4. A statistically significant increase was found in relative mean testes weight of HDm compared with the control. High dose males and females showed a marked accumulation of hemosiderin in pulmonary macrophage with vascular congestion and bronchial exudation. These results may indicate pulmonary hypertension which may be an extension of the pharmacological effect of tizanidine on the CVS as reported by the sponsor. In the 6-week i.v. in dogs, SGPT level was elevated 187% in dogs dosed 0.3 mg/kg (HD), on weeks 3 and 6 and in 1 HDf there was dystrophic calcification of the myocardium perhaps due to muscle fiber degeneration as indicated by the sponsor. All these effects in rats and dogs disappeared during the 4-wk recovery period. Rats orally dosed 1.7, 8, or 40 mg/kg for 13 wks showed miosis and piloerection mainly in MD and HD. Corneal clouding, sensitivity to touch, and convulsions (females only) occurred in HD rats. Mean body weight and food intake were significantly reduced in MD and HD on weeks 6 and 13 (40-70% B.wt and 18-30% food). SGPT blood level was significantly increased (20-33%) in HD rats on week 13 and/or 6. The relative wt of the liver was significantly reduced (20%) in HDm and in both sexes of the HD the mean relative weights of the heart and adrenals were significantly increased 42 and 11% respectively, as well as the relative wt of the testes (14%) over the corresponding control weights. Histopathology included slightly increased incidence of single and focal cell necrosis of the heart and liver in HD rats, proliferative corneal keratitis and ulceration (1/20) of HD, high incidence of prostatitis in MD (5/10) and HDm (4/10). The sponsor indicated that all of the above effects reversed during the 4-week recovery period. The NOEL in this study was 1.7 mg/kg. Dogs orally administered tizanidine at 0.3, 1, and 3 mg/kg for 13 weeks showed some dose-related sedation, slight reduction in body temperature, ataxia (HD), and slowing of heart rate and prolongation of QRS and QT intervals; all signs were normal by 24 hr or study end. Alkaline phosphatase and SGPT levels were increased in HD. The only histopathology was a slight to moderate polymorphonuclear infiltration of livers in 3/4 HD and 2/4 MD dogs. The NOEL in this study was 0.3 mg/kg. In a 1-year dog study, tizanidine at 0.15, 0.45, and 1.5 mg/kg caused no deaths and only in HD signs included sedation, salivation, sporadic emesis, and equilibrium disturbances. Bradycardia (40% reduction) and QT prolongation occurred 2 hr postdose in HD dogs. SGPT levels were elevated in HD dogs throughout the study but returned to normal levels after end of treatment. No microscopic findings. The NOEL in this study was 0.45 mg/kg.

Two lifetime bioassays were conducted to assess the carcinogenic potential of tizanidine, one in rats for 104 weeks and the 2nd in mice for 78 weeks. Tizanidine was mixed with the diet to provide in mice doses of 1, 4, and 16 mg/kg and in rats 1, 3, and 9 mg/kg. The basis for dose selection in mice was not provided; the rat doses were based on the 3 month study mentioned above. As mentioned earlier under the metabolism discussion, one or more of

the 3 major metabolites found in humans could not be detected or was found at trace amount in the rat and mouse. Therefore, although qualitatively the metabolic pathway of tizanidine in humans is similar to that in mice and rats, differences were found in the amount of these metabolites. Quantitative differences in metabolites are important in predicting and extrapolating toxicity data from animals to humans. It is noted however, that different metabolic pathways (qualitative difference) between animals and human play more important role than quantitative differences in predicting risk.

In the mouse carcinogenicity study, there was no significant drug related effects in LD and MD. Clinical signs in HD included piloerection and self-inflicted wounds. There was a dose-dependent increase in frequency of ear necrosis and corneal opacities. In one each HDm&f mice the number of lymphocytes increased with marked leukocytosis and increased number of smudge cells (Gumprecht's shadows) and in one mouse agranulocytosis was found. Statistical analysis of tumor data by the sponsor, showed a positive trend in bone hyperplasia of females and a significant difference in incidence between the control and HDf. Other tumor incidences were slightly higher than the background value (historical data not provided) but did not reach statistical significance. These tumors included lymphoreticular, pulmonary, and liver.

In the rat carcinogenicity study, clinical signs were observed in all groups including the controls. Body weight was significantly reduced in treated rats from week 13 till study end. Food intake was also decreased but not significantly. A significant increase was found in the relative weight of the brain and heart of HD rats the toxicological significance of which is unknown. Also a significant decrease was noted in the weight of the liver, kidney, spleen, prostate, and testes. A significant finding was the statistically significant increased incidence of hind-limb granuloma, ocular opacities, swollen eye lids/keratits, and hair loss on the abdomen and limbs. All treated females had centriacinar fatty vaculation of the liver, and HD rats had hepatocyte hypertrophy and hyperplastic nodule. Statistical analysis of tumors by the sponsor showed a significant increase in pancreatic islet cell adenoma or hyperplasia in female rats and skin fibroma in males relative to the incidence in the control animals.

None of the above lesions in mice or rats occurred in both sexes, both species, or showed dose-relationship. Statistical analysis have not been conducted by the Agency at this time due to lack of raw data on disk from the sponsor. Based on the sponsor's analysis, tizanidine is not a carcinogenic agent in animals at doses that are in mice 200x and in rats 113x the maximum clinical dose on a mg/kg basis. Based on these data, it appears that tizanidine is not carcinogenic in rat and mouse under the experimental conditions.

The reproductive/developmental and teratogenic potential of tizanidine was studied in rats and rabbits. Segments I, II, and III were conducted in rats and one Segment II in rabbits. Doses used ranged between 0.3-100 mg/kg which are 0.5-167x the clinical dose on a mg/kg basis. Plasma drug levels were not measured in any of these studies. In rabbits at 1, 3, and 30 mg/kg and at 30 mg/kg in rats, there was a significant increase in postimplantation loss and smaller litter size (in rats only). A significant but not dose-dependent postnatal loss in rat pups was found at 3, 10, and 30 mg/kg and pre- and peri-natal loss was significantly increased in the 10 and 30 mg/kg (dose-dependently). Maternal and fetal toxicity was clearly evident at 100 mg/kg in rats and rabbits. At this dose litter size was significantly reduced, significant postimplantation loss, 100% dam mortality in rabbits, and significantly increased fetal anomalies type A and C in rats (encephalocoele and microphthalmia). However, fetal anomalies were not observed in a Segment II rabbit study at doses up to 100 mg/kg. The sponsor indicated (referring to a published article), that the 100 mg/kg dose (which is 167x the human dose), is an irrelevant dose because it was highly toxic and caused 100% mortality in rabbit dams. In a separate rat study, doses of 0.3 and 1 mg/kg did not cause any mortality or maternal toxicity or teratogenicity.

In a Segment III study, rats dosed 30 mg/kg had 100% loss of pups (pp days 0-21) but at 3 and 10 mg/kg there were no teratogenic findings or effects on fertility parameters of F1 generation. In a separate Segment II study in rats, pups physical, behavioral, and functional development was evaluated for up to pp day 21. Tizanidine had no effect on any of these parameters. However, pre-natal findings included significantly reduced fetal weights at 10 and 30 mg/kg, retarded skeletal ossifications, and significantly smaller placentas in the 30 mg/kg dosed dams. There were no embryoletality or teratogenicity in this study for up to 30 mg/kg, the reproductive NOEL was 1 mg/kg. When tizanidine was administered to pregnant rats at 10 and 30 mg/kg doses 2-6 days prior to delivery, the mean number of pups was significantly reduced in both doses and a significant increase in postnatal mortality occurred in 30 mg/kg within 4 days after delivery with 100% mortality after day 4. The sponsor indicated that pup mortality was perhaps secondary to maternal toxicity since the dams were heavily sedated for several hours at the high dose therefore, unable to care for the pups.

It is concluded that tizanidine is teratogenic at >30 mg/kg and at very high doses (100 mg/kg), fetotoxicity is secondary to maternal toxicity. Tizanidine did not affect physical, behavioral, or functional development of F1 generation at doses $\leq$ 30 mg/kg. However, at this and lower doses tizanidine caused a significant post-implantation loss. Since the human reproductive/developmental and teratogenic potential of tizanidine are unknown, administration of this drug to pregnant women should be based on risk/benefit

assessment. Based on the animal findings, tizanidine is labelled Category C.

Tizanidine was tested in in vitro bacterial and mammalian gene mutation assays and in vivo chromosomal aberration and gene mutation tests. There was no indication that tizanidine is mutagenic or genotoxic agent in any of these assays.

TABLE I
(Continued)

Antinociceptive Screening Models (Continued)

Ref. No	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
19	Rat	Thermal: timed movement of tail from radiant heat source	Range not stated po	ED ₅₀ of response inhibition = 19.0 μmol/kg (3.3 mg/kg)	Morphine: ED ₅₀ = 12.9 μmol/kg
21	Rat	Thermal: timed movement of tail from radiant heat source	0-25 μg/rat (0-75 μg/kg) i.c.v.; 5x daily doses of 25 μg/rat i.c.v.	Significant antinociception at 25 μg/rat; reduced effect of low tizanidine at 25 μg/rat after 3 days.	Clonidine: Significant antinociception at 25 μg i.c.v./rat Morphine: Significant antinociception at 25 μg i.c.v./rat
1,2	Monkey (rhesus)	Electrical: shock titration (self selected electrical shock avoidance)	3.2-10.0 mg/kg po	No effect on pain at 3.2 mg/kg; higher doses caused sedation and ataxia	Not done
6	Rat	Arthritis: mycobacterium butyricum injection into paw	Range not stated po	ED ₅₀ of inhibition vocalization after foot laceration = 3.7 mg/kg po	Baclofen: ED ₅₀ = 12 mg/kg Dantrolene: ED ₅₀ = 21 mg/kg Morphine: ED ₅₀ = 46 mg/kg Acetylsalicylic acid: ED ₅₀ = 140 mg/kg

Mechanism of Action

Ref. No	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
19	Mouse	Timed movement of tail from radiant heat source	0.5, 1.0 mg/kg sc	Prolonged latency of response at both doses	Dopaminergic, serotonergic, GABA system antagonists had no effect on tizanidine effect; Y inhibition, not generally effective at blocking tizanidine effect
24	Mouse	Timed movement of tail from radiant heat source	0.86 - 6.89 μmol/kg (0.250-2.0 mg/kg) sc	ED ₅₀ of response inhibition = 1.79 μmol/kg (0.5 mg/kg)	Clonidine: ED ₅₀ = 0.98 μmol/kg (0.25 mg/kg) Serotonergic system: No effect at 5, 6 μg/kg Dopaminergic system: No effect at 5, 6 μg/kg GABA system: No effect at 5, 6 μg/kg Morphine: No effect at 5, 6 μg/kg Acetylsalicylic acid: No effect at 5, 6 μg/kg Phenazone, reduced antinociceptive effect of tizanidine and clonidine

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Ref. #s here don't match those in table 2 p. 222 VR 1.1

TABLE I
(Continued)

Mechanism of Action (Continued)

Ref No	Species	Test Model/T-est System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
24	Rat, halothane anesthesia	A and C fiber response measured in dorsal horn convergent neurons, evoked after transcutaneous supramaximal (50x) stimulation, or innocuous cutaneous stimulation	0.125 - 1.0 mg/kg iv Intrathecal application	Dose-dependent, long-lasting depression of evoked response. At 0.25 - 1.0 mg/kg iv, max effects after 5-10 min, recovery in less than 1 hr. Greater effects on C fiber than A fiber response; No effect on innocuous stimuli	Intrathecal baclofen depressed responses to nociceptive and innocuous stimuli Intrathecal morphine effect similar to tizanidine
23	Cat, L ₁ spinalized	Dorsal horn neuron response to peripheral innocuous or nociceptive stimuli	0.07-0.14 mg/kg iv Intrathecal application	Dose-dependent, long-lasting inhibition of dorsal horn response induced by nociceptive, but not innocuous stimuli. Effect on nociceptive stimulus response not affected by substance P	Epileptics affected both nociceptive and innocuous responses Allylgabapentin as intrathecal analgesic
23	Cat, L ₁ spinalized	Dorsal horn neuron response to peripheral innocuous or nociceptive stimuli	0.25-1.0 mg/kg iv Intrathecal application	Systemic or intrathecal tizanidine selectively depresses response to nociceptive, but not innocuous stimuli. Small diameter primary afferents (nociceptive?) evoked responses depressed by iv tizanidine	Diclofenac not selective for nociceptive versus innocuous stimuli Effect of tizanidine not antagonized by naloxone

Ref No. = Reference number; po = oral; ip = intraperitoneal; iv = intravenous; sc = subcutaneous; lv = intrathecal; TBQ = p-aminop-benzoquinone

TABLE 2
Anticonvulsant Activity

Species/Strain (Weight)	No Animals	Tizanidine Dose, Route of Administration	Test Model/System	Effects of Tizanidine	Effects of Reference Compounds	Ref. No./Reference Laboratory
Mouse/OF-1 (18-22 g)	10 (both)	ip	Inhibition of electrically-induced tonic extensor seizures	No protection up to 10 mg/kg po	Diazepam: ED ₅₀ ~ 6 mg/kg po Bucklain: No protection up to 20 mg/kg po	
Mouse/DBA-2 strain (6-12 g)	7-16 (either)	0.33-3.33 mg/kg ip	Inhibition of audiogenic seizures	Protective against tonic and clonic seizures at 0.66-3.33 mg/kg	Not done	
Mouse/DBA-2 strain (8-12 g)	10 (either)	0.5-4.0 mg/kg ip	Inhibition of audiogenic seizures	ED ₅₀ clonic seizures = 0.76 mg/kg. ED ₅₀ tonic seizures = 0.45 mg/kg	Protective effects reduced by pretreatment with aminophyllin (adenosine antagonist), yohimbine, and phytolacca no effect of methylsergide (serotonergic antagonist)	
Mouse/Albino Swiss (20-25 g)	10M	3.3 mg/kg, 10 mg/kg ip	Inhibition of NMDA-induced seizures	No effect on NMDA-induced seizures at 1D ₅₀	Not done	
Mouse/OF-1 (18 g)	6-10M	0.5-20 mg/kg ip	Inhibition of chemically-induced (strychnine, bicuculline, 3-mercaptopropionic acid) seizures	Minimum effective anticonvulsant ip dose: Strychnine = 0.5 mg/kg Bicuculline = 20 mg/kg Mercaptopropionic acid = 1 mg/kg	Same endpoints - Diazepam: Strychnine-2 mg/kg Bicuculline-0.5 mg/kg Mercaptopropionic acid-0.5 mg/kg Same endpoints - Bucklain: Strychnine-10 mg/kg Bicuculline-20 mg/kg Mercaptopropionic acid-5 mg/kg	
Rabbits/Papio papio (4-6 kg)	3 (NS)	8, 16, 32 mg/kg po average 1, 2, 4 mg/kg iv	Inhibition of physically-induced seizures	Effective at 16-32 mg/kg po, not 8 mg/kg po. Effective for 1 hour after 2-4 mg/kg, iv	Not done	

Ref. No. = Reference number; NS = not stated; Univ. = university; po = oral; ip = intraperitoneal; iv = intravenous; ns = subcutaneous

TABLE 1
Cardiovascular/ Respiratory Effects of Tizanidine

Ref No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compound
1,2	Rat, conscious	Normotensive, aortic cannulation	0.1, 0.3, 1.0 mg/kg po	0.1-1.0 mg/kg po, transient and slight ↓ in blood pressure followed by ↑, and weak bradycardia (12% maximum change for all 3 measures)	Chlorthalidone caused a greater ↓ in blood pressure, no bradycardia at 0.1-10x lower doses (0.01 - 0 mg/kg po)
37	Rat, conscious	Normotensive, femoral artery cannulation	0.3, 1.0, 3.0 mg/kg po	No blood pressure change at 0.3 or 1 mg/kg, slight ↓ at 3 mg/kg. No heart rate change at 0.3 mg/kg, slight effect at 1 mg/kg, appreciable effect for 2 h at 3 mg/kg	Chlorthalidone caused a slight blood pressure ↓ at 0.03 mg/kg, more pronounced at 0.1 mg/kg, and slight bradycardia at 0.03 mg/kg, more pronounced at 0.1 mg/kg
1,6	Rat	EOCA, nephrectomized hypertensive, aortic cannulation	1.0, 4.5, 5.0 mg/kg orally and for 3 days	Activity, 5 mg/kg = ↑, then ↓ in blood pressure + bradycardia. At 3 days, 1 mg/kg = no appreciable blood pressure change, 5 mg/kg ↓ blood pressure < 0.1 mg/kg chlorthalidone	0.3 mg/kg chlorthalidone caused similar, but delayed blood pressure changes = 5 mg/kg tizanidine. Aorta bradycardia = 0.3 mg/kg at 5 mg/kg tizanidine. Three day effects at 0.1 mg/kg > than 3 mg/kg chlorthalidone
1,6	Rat	Griffiths hypertension, carotid artery cannulation	0.035% in food for 7 days	No effect on blood pressure or heart rate at 24 h or 7 d	Chlorthalidone ↓ blood pressure and bradycardia at the same dose
37	Rat, urethane anesthetized	Interaction with p[araldehyde]doxamine, NE, ACh, A:upregulation II; carotid occlusion	0.0008, 0.004, 0.020 mg/kg iv	Dose-dependent bradycardic increase, then ↓ in blood pressure. No effect on phenylephrine, norepinephrine II or carotid occlusion response	Chlorthalidone more potent in bradycardia and blood pressure response. Potentiation of carotid occlusion response
37	Rat	Formoterol, urethane anesthetized, femoral artery catheter	0.010, 0.030, 0.10 mg/kg iv	Dose-dependent pressure, then depressor response, with bradycardia	Chlorthalidone - similar effects at 0.001-0.01 mg/kg iv. Atropine ↑, and phenylephrine ↓ pressure, and depressor effect
37	Rat	Pitdrol, carotid artery cannulation	0.0001 - 0.030 mg/kg iv	Pressor, not depressor or bradycardia effect. Yohimbine and prazosin inhibited pressor response	Chlorthalidone 2x more pressor response
24	Rat	Anticoagulative effects on constrictor dorsal horn neurons	0.125-1.0 mg/kg iv	Immobilization ↑, followed by dose-dependent ↓ in blood pressure or paralytic values	Not done
1,2	Rat	Pitdrol, carotid artery cannulation	0.01-1.0 mg/kg iv	Dose to cause 100 mm Hg ↑ in blood pressure = 0.3 mg/kg iv	Same effect for chlorthalidone at 0.02 mg/kg iv
37	Rat, urethane anesthetized	Intracranial cannula	0.020 mg/kg iv	↓ blood pressure, bradycardia. Yohimbine reduced pressor response	Chlorthalidone response ↓ by yohimbine

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TABLE XI
 (Continued)

Ref. No.	Species	Test Method/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
21	Rat	Autoneurotomy study	0.010-0.250 mg/kg, $\pm$ 0.05-0.23 mg/kg intrathecal	No significant change in blood pressure at highest dose	Not done
1,2	Dog, chloralose anesthesia	Open chested, aortic cannulation, ECG	0.004, 0.016, 0.08 mg/kg iv	Individual differences in blood pressure response; tachycardia, eliminated by vagotomy; $\downarrow$ total peripheral resistance	Clonidine had similar, but more pronounced effects
1	Dog, pentobarbital anesthesia	Mesenteric blood flow measurement	0.001 - 1.000 mg/kg, ix; 1.005 mg/kg iv	Transient $\uparrow$ in blood pressure and $\downarrow$ mesenteric blood flow	Clonidine response blocked by phenoxybenzamine (α 1 adrenergic antagonist)
37	Dog, pentobarbital anesthesia	Femoral/brachial artery cannula, ECG	0.003, 0.010, 0.030, 0.100 mg/kg iv	Dose-dependent bradycardia ($\approx$ 0.1 mg/kg); increase, then $\downarrow$ in blood pressure ($\approx$ 0.01 mg/kg). No effect on respiratory rate or ECG; Dose-dependent $\downarrow$ in cardiac output and peripheral bed blood flow, $\uparrow$ vascular resistance in periphery ($\approx$ 0.03 mg/kg)	Not done
1,2	Dog, lucin anesthesia	Bladder catheterization (Rumal study)	0.1, 1.0 mg/kg iv	No effect at 0.1 mg/kg, transient $\uparrow$, then fall at 1.0 mg/kg	Not done
1,2	Cat, urethane/chloralose anesthesia	Effects with NE, isoproterenol; carotid occlusion; ECG	0.005-18.7 mg/kg cumulative dose iv	Dose-dependent $\downarrow$ in blood pressure and heart rate, maximum of 40% and 65%, respectively. Isoproterenol bradycardia potentiated, no clear effect on NE or carotid occlusion response. No effect on ECG	Clonidine blood pressure $\downarrow$ less than with tizanidine. Bradycardia and isoproterenol bradycardia more pronounced T-t-wave potentiated
16	Rabbit tissue	Aortic strips	10^{-7} - 10^{-5} M in bath	pD_{50} = 5.64 to induce contractility; effect protracted, not yetalotidine inhibitable	Clonidine pD_{50} = 5.24 to induce contractility; effect protracted, not yetalotidine inhibitable

iv = intravenous, iv = intracerebroventricular, ECG = electrocardiogram, NE = norepinephrine, ACB = acetylcholinesterase, po = oral, d = days

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TABLE 16

Studies Assessing Tizanidine's Potential to Induce Physical Dependence

Species/Strain/ Source (Weight)	No. Animals	Tizanidine Dose, Route of Admin	Test Model/System	Effects of Tizanidine	Effects of Reference Compounds	Study No./ Laboratory
Rat OFA/ Sandoz (300- 400 g)	3-8M	0.02-8.32 mg/kg, ip	Discrimination training: generalization and antagonism	Tizanidine training acquired Tizanidine-trained rats did not generalize phenobarbital, diazepam, morphine or cocaine Tizanidine-trained rats did generalize clonidine	Phenyl- cocaine, or diazepam- trained rats did not generalize to tizanidine Yohimbine antagonized discrimination of tizanidine and clonidine, but not caffeine	
Rhesus monkeys/NS (2.6-4.2 kg)	3M/1F	20, 36, 64 mg/kg/day, ig for 5 weeks	Potential for physical dependence	No signs of withdrawal at 20 and 36 mg/kg; mild withdrawal symptoms lasting 2 days after 5 weeks at 64 mg/kg	Not done	
Rhesus monkeys/NS (2.6-4.2 kg)	3M/1F	Sequential doses of 3.2, 7, and 18.0 µg/kg daily injections, iv for 5 weeks	Measurement of self- selected dosing and withdrawal Tizanidine administered for 5 weeks, then saline, then morphine	Self-selected dosing, especially at highest dose (18µg/kg) not socially palatable at this dose) before withdrawal decreased self- administered doses, no withdrawal signs	Typical signs of opiate withdrawal after end of morphine segment	

NS-not stated in report, ip-intraperitoneal, ip-intraperitoneal, iv-intravenous, M-male, F-female

TABLE I

Summary of nonclinical absorption, distribution, metabolism and excretion studies with tizimidine

References	Species/Strain	Sex/WT	No. Animals	Tizimidine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Dose(s) [Radioisotope] / Analyte measured	Study Results
1	Male/ OF-1	Male/ 22-31 g	72 (3/admin. route/sampling interval)	4 mg/kg, intubation or iv (5% glucose soln)	Absorption and blood level time course of radioactivity following single dose of ¹⁴ C-tizimidine	Single dose; [¹⁴ C] Total radioactivity in blood	Absorption rapid (t _{max} = 0.83 h) and extensive (>71%); elimination half-life t _{1/2} = 5.2 h (oral) and 3.4 h (iv) for mean 6-24 h post dose
2	Rat/ Sprague Dawley OFA	Male/ 250-300 g	12 (6/admin. route)	1.5 mg/kg, intubation or iv (5% glucose soln)	Absorption and blood level time course of radioactivity following single dose of ¹⁴ C-tizimidine	Single dose; [¹⁴ C] Total radioactivity in blood	Absorption rapid (t _{max} = 0.75 h) and extensive (>67%); elimination half-life t _{1/2} = 1.5 h (oral) and 1.4 h (iv) between 3-7 h post dose
2	Rat/ Sprague Dawley OFA	Male, bil- duct caused/ 250-300 g	10 (5/admin. route)	1.5 mg/kg, intubation or iv (5% glucose soln)	Absorption and bile level time course of radioactivity in bile duct-caused rats following single dose of ¹⁴ C-tizimidine	Single dose; [¹⁴ C] Total radioactivity in bile, urine and feces	Absorption rapid and extensive; 91% dose excreted within 72 h in urine and bile
3	Rat/ Wistar OFA	Male/ 200 g	10 (5/dose)	1.5 mg/kg, intubation or 0.3 mg/kg iv (5% glucose soln)	Absorption and blood level time course of radioactivity following single dose of ³ H-tizimidine	Single dose; [³ H] Non-voidable tissue in blood	Absorption rapid (t _{max} = 1 h) and extensive (>67%); elimination half- life t _{1/2} = 7 h (between 2-24 h post dose)
21	Rat/ EFM- Wistar SPF	Male/ 172-234 g Female/ 137-183 g	4-5/dosing group/sex	0, 0.3, 1, or 3 mg/kg/day/ dosing group for 6 weeks, ip (acetic acid, sodium acetate, sodium chloride, water, carbon dioxide, pH 4.6)	6-week intraperitoneal toxicity study; plasma levels of metabolized tizimidine after the last dose	Multiple doses, once a day for 6 weeks (individual drug) Tizimidine in plasma after last dose	Plasma levels proportional to the dose; plasma half-life t _{1/2} = 0.3 h between 0.25-3 h post dose; no net difference
23	Rat/ Wistar	Male/ 300 g	3/absorption situation point	0.65 mg/kg, in situ (potassium phosphate buffer, pH 6.5 (jejunum), pH 7.0 (ileum), pH 7.5 (colon); 0.1 N HCl (stomach))	In situ gastro-intestinal site of absorption of ¹⁴ C-tizimidine	Single dose in situ; [¹⁴ C] Total radioactivity not absorbed	Jejunum and ileum are the main sites of absorption; absorption over the entire intended tract but not from the stomach

Absorption/Pharmacokinetics

5
TABLE I
(Continued)

Absorption/Pharmacokinetics (Continued)

Reference	Species/ Strain	Sex/Wt	No. Animals	Toxication Dose, Route of Admin. (Vehicle)	Study Description	Treatment Dose/ [Radioisotope] Entry measured	Study Results
4	Rabbit/ New Zealand	Female/ 3.5 kg	6 (3/dose/trous)	3 mg/kg, intrabdominal (2% gelatin susp.) or 1 mg/kg, iv (saline)	Absorption and blood level time course of radioactivity following single dose of ¹⁴ C-tizanidine	Single dose; [¹⁴ C] Total radioactivity in blood	Absorption rapid (t _{max} = 1 h) and extensive (97.9%); elimination half-life t _{1/2} = 2.5 h (oral) and 2.3 h (iv) between 1-12 h post dose
5	Dog/ Beagle	Female (n=1); male (n=2) 3.2-9.9 kg	3	0.1 mg/kg, intrabdominal or iv (5% glucose saline)	Absorption and blood level time course of radioactivity following single dose of ¹⁴ C-tizanidine	Single dose; [¹⁴ C] Total radioactivity in blood	Absorption slower than in other species (t _{max} = 2.5 h), but complete (97.9%); elimination half-life t _{1/2} = 10.4 h (oral) between 6-24 h post dose; no sex differences
3	Dog/ Beagle	Female (n=2); male (n=1) 10.0 kg	3 ¹	0.3 mg/kg, intrabdominal; 0.05 mg/kg, iv (5% glucose saline)	Absorption and blood level time course of radioactivity following single dose of ³ H-tizanidine	Single dose; [³ H] Non-reticulated in blood	Absorption slower than in other species (t _{max} = 1-7 h)
6	Dog/ Beagle	Male/ 8.5-12.3 kg	6 ²	4 mg/kg, po (tablet, oral or oral)	Relative bioavailability of newly manufactured versus aged tizanidine tablets, single dose crossover design	Single dose cross over (unlabeled drug) Tizanidine in plasma	No significant differences in bioavailability between new and aged tablets; absorption rapid (t _{max} = 2 h for parent drug); elimination half-life of parent drug t _{1/2} about 2 h between 3-12 h post dose
22	Dog/ Beagle	Male/ 8.5-11.1 kg Female/ 6.7-9.4 kg	3 (single group)	0, 0.03, 0.1 or 0.3 mg/kg/day for 6 weeks, iv (acetic acid, sodium acetate, sodium chloride, water, carbon dioxide, pH 4.6)	6-week intravenous toxicity study; plasma levels of unchanged tizanidine after first and last dose	Multiple doses, once a day for 6 weeks (unlabeled drug) Tizanidine in plasma	Plasma levels of parent drug lowered by 30-50% after chronic dosing; no effect of chronic dosing on plasma half-life of parent drug (t _{1/2} = 0.5 h between 0.25-3 h post dose); no sex differences

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TABLE
(Continued)

Antipyretic/Pharmaceuticals (Continued)

Reference	Species/ Strain	Sex/WT	No. Animals	Treatment Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration (Radiolabel) Radio measured	Study Results
7	Minkery/ Rhesus	Male/ 8.9-5 kg	3 ³	= 0.2 mg/kg (0.05 mg/kg) in solution for 4 h; vehicle (NS)	Single-dose pharmacokinetics in plasma of tizanidine versus clonidine, crossover design	Single dose cross over (radiolabel drug)/Tizanidine or clonidine in plasma	Distribution half-time similar for tizanidine and clonidine ($t_{1/2}$ = 3 h between 6-16 h post labeling); plasma levels lower for tizanidine (C_{max} = 18 ng/ml) than for clonidine (C_{max} = 20 ng/ml); tizanidine plasma clearance = 1.91 L/kg and volume of distribution = 7.8 L/kg; clonidine plasma clearance = 1.02 L/kg and volume of distribution = 4.4 L/kg

Protein Binding

Reference	Species/ Strain	Sex/WT	No. Animals	Treatment Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration (Radiolabel) Radio measured	Study Results
8	Rat/NR	Male (NS)	10	1.5 mg oral (generic; phosphate buffer)	In vitro plasma protein binding and whole blood distribution 2 h after single dose of [¹⁴ C] tizanidine	Single dose; [¹⁴ C] Total radioactivity; in vitro plasma protein binding and whole blood distribution 2 h after dose	Shaw, J. R. <i>et al.</i> of radioactivity the same as in <i>in vivo</i> studies. In Tizanidine studies have similar whole blood distribution and plasma protein binding as clonidine
9	Rat/NR	NA	NA	1-13,000 ng/ml; whole blood; 3-12,000 ng/ml; erythrocytes; 1-10,500 ng/ml; plasma	In vitro plasma protein binding; whole blood distribution and erythrocyte uptake of [³ H]- tizanidine	NA; [³ H] Total radioactivity; in vitro plasma protein binding; whole blood distribution and erythrocyte uptake	Whole blood distribution: 30% free, 10% bound to plasma protein, 60% in blood cells; erythrocyte uptake 60%; plasma protein binding 30%; constant over the concentration range tested
8	Can/NR	NA	NA	1-12,900 ng/ml; whole blood; 3-11,700 ng/ml; erythrocytes; 6-11,600 ng/ml; plasma; 3670- 261,000 albumin	In vitro bovine albumin and plasma protein binding; whole blood distribution and erythrocyte uptake of [³ H]- tizanidine	NA; [³ H] Total radioactivity; in vitro bovine albumin and plasma protein binding; whole blood distribution and erythrocyte uptake	Whole blood distribution: 30% free, 24% bound to plasma protein, 46% in blood cells; erythrocyte uptake 59%; plasma protein binding 40-50%; constant over the concentration range tested; no significant species differences; prediction of protein free drug albumin to plasma binding

5
TABLE 1
 (Continued)

Reference	Species/Strain	Sex/WT	No. Animals	Tizidines Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration [Radioisotope] /Radioactivity measured	Study Results
1	Mouse/OF-1	Male, Female/ 22-31 g	36 (3/sex/ admin. route/ sampling time)	4 mg/kg, intravenous (5% glucose soln)	Distribution of radioactivity following single dose of ^{14}C tizidine	Single dose [^{14}C] Total radioactivity in blood and tissues	The highest levels seen in kidney, liver, adrenals (4-10-fold higher than in blood); brain levels were lower than blood levels; rapid decline to negligible levels within 24 h in all tissues; no unusual retention of radioactivity; no sex differences
9	Mouse/ C57 BL	Male/ 22-30.5 g	22 (2/admin. route/sampling time)	7 mg/kg, intravenous (5% glucose soln)	Distribution of radioactivity following single dose of ^{14}C tizidine via whole body autoradiography	Single dose [^{14}C] Total radioactivity	No differences after oral and iv doses; the highest levels in gall bladder, stomach, retroperitoneal fat, kidneys, seminal vesicles; rapid decline to low levels within 24 h; some persistence in the peritoneal cavity (ova and uteri) at 48 h
2	Rat/Sprague Dawley - OFA	Male, Female/ 170-200 g	48 (3/sex/ admin. route/ sampling time)	8 mg/kg, intravenous (5% glucose soln)	Distribution of radioactivity following single dose of ^{14}C tizidine	Single dose [^{14}C] Total radioactivity in blood and tissues	iv dose; levels 2 h post oral and iv doses; the highest levels in kidney and liver; adrenals, 4-9-fold higher than in blood; brain levels lower than blood levels; with rapid decline within 24 h in all tissues; no unusual retention of radioactivity; no sex differences
10	Rat/Sprague Dawley - OFA	Male/ 180-200 g	20 (2/dosing schedule/ sampling time)	7 mg/kg, intravenous (5% glucose soln), single dose and chronic dosing (once a day for 10 days)	Distribution of radioactivity following single dose or 10 days of dosing with ^{14}C tizidine via macroautoradiography	1 or 10 days [^{14}C] Total radioactivity	No significant differences after single or repeated oral dosing; drug was absorbed; the highest levels seen in liver, bladder, kidney and GI tract; low levels 24-48 h post dosing; no tendency for accumulation
10	Rat/Sprague Dawley - OFA	Pregnant Female/ 300-400 g	10 (2/ sampling time)	7 mg/kg, intravenous (5% glucose soln)	Distribution of radioactivity following single dose of ^{14}C tizidine via macroautoradiography	Single dose [^{14}C] Total radioactivity	Radioactivity across the placenta; the highest levels 1-2 h post dosing seen in the stomach, bladder, liver, kidney; moderate levels seen in placenta (1 h) and umbilicus (2-3 h); distribution pattern and decline similar to male rats

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TABLE I
 (Continued)

Reference	Species/Strain	Sex/Wt	No. Animals	Tizimidine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration [Radiolabel] / Assay measured	Study Results
11	Rat/OFA	Lactating Female ~310 g	42 (7/sampling time)	1.5 mg. intubation (5% glucose soln)	Distribution of radioactivity in milk, blood and plasma following single intramammary injection of ¹⁴ C-tizimidine	Single dose [¹⁴ C] / Total radioactivity in plasma and milk	Radioactivity passes to the milk by passive diffusion; t_{max} = 2 h in plasma and t_{max} = 8 h in milk; milk AUC/plasma AUC (0-24 h) = 1.8
12	Rat/Wistar	Male/ 200-250 g	6	0.12 μCi (2.3 μCi/mg) intramammary bolus (buffered Ringer soln)	Placental transfer of ¹⁴ C-tizimidine following single intramammary injection	Single injection of [¹⁴ C] tizimidine and [³ H]- ¹⁴ C /	High degree of passage of unchanged tizimidine to the brain; the brain uptake index = 56%
13	Rabbit/New Zealand	Pregnant Female/ ~3.5 kg	15 (3/sampling time)	3 mg/kg/day, intubation (7% gelatin soln)	Distribution of radioactivity and placental transfer following administration of ¹⁴ C-tizimidine from day 6-18 of gestation	Dosing from day 6 to 18 of gestation [¹⁴ C] / Total radioactivity in blood and tissues	Radioactivity crosses the placenta; fetal tissue levels lower than maternal blood levels; upon chronic dosing decrease seen in the fetus and mammary fluid levels but not in maternal tissues; after final dose terminal half-life $t_{1/2} = 31-32$ h in maternal tissues, and shorter in umbilical and fetal tissues ($t_{1/2} = 16-25$ h); no indication of acetylation
Metabolism							
Reference	Species/Strain	Sex/Wt	No. Animals	Tizimidine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration [Radiolabel] / Assay measured	Study Results
14	Mouse/OF-1	Male/ 22-31 g	18 (3/sampling time)	4 mg/kg, intubation (5% glucose soln)	Metabolic pathway in plasma following single dose of ¹⁴ C-tizimidine	Single dose; [¹⁴ C] / Tizimidine and metabolites in plasma	Rapid metabolism; parent drug = 16% of plasma radioactivity at 0.25 h; metabolism mostly via oxidation of benzimidazole ring (major metabolite noracetyl tizimidine 2, 74% plasma radioactivity at 0.25 h; acetyl tizimidine 2, 8, also present), and imidazole ring (metabolite 9)

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TABLE I
 (Continued)

Metabolism (Continued)

Reference	Species/ Strain	Sex/Wt	No. Animals	Tizaniine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration (Radioabel) /Exity measured	Study Results
15	Rat/ OFA	Male/ 280-320 g	8 (2 for 5 mg/kg and 6 for 330 mg/kg doses)	5 or 330 mg/kg intubation (water)	Metabolic pattern in plasma and urine following single dose of ¹⁴ C-tizaniine	Single dose; [¹⁴ C]/Tizaniine and metabolites in plasma and urine	Very rapid metabolism; parent drug not detectable in plasma (1 h) and urine (0-48 h post); metabolism via oxidation of thiazolidine ring (metabolite 10 was the major metabolite in plasma (96%), and urine (77%)), benzox- ing (urinary conjugates 7 and 8) and imidazole ring (urinary metabolite 2,3,4+5)
15	Rat/ OFA	Male, bile duct cannulated/ 280-320 g	10	330 mg/kg, intubation (water)	Metabolic pattern in bile following single dose of ¹⁴ C- tizaniine	Single dose; [¹⁴ C]/Tizaniine and metabolites in bile	Very rapid metabolism; parent drug not detectable in bile (0-24 h post); detected products of metabolism at thiazolidine ring (metabolite 10), benzox- ing (conjugates 7 and 8) and imidazole ring (3, 4)
15	Rat/RS	NS	NA	200 mg ¹⁴ C-tizaniine; 30 min incubation with hepatocytes	Metabolic pattern in rat hepatocytes incubated with ¹⁴ C-tizaniine	NA; [¹⁴ C]/Tizaniine and metabolites	Metabolism via oxidation of benzox- ing (to monopropionic acid derivative 9, 10%) and imidazole ring (to metabolite 1, 69%)
3	Rat/ Winter OFA	Male/ 200 g	4	2 mg/kg, intubation (3% glucose soln)	Metabolic pattern in urine after single dose of ³ H- tizaniine	Single dose; [³ H]/Tizaniine and metabolites in urine	Trace of unchanged drug in urine (0- 24 h post); 10 different unidentified metabolites present
16	Rabbit/ Sera here	Male/ 2 kg	2	4 or 50 mg/kg, intubation (water)	Metabolic pattern in plasma and urine after single dose of ¹⁴ C-tizaniine	Single dose; [¹⁴ C]/Tizaniine and metabolites in plasma and urine	Very rapid metabolism; parent drug not detectable in plasma (0.5 h) and urine (0-24 h post); metabolism via oxidation of thiazolidine ring (to metabolite 10), benzox- ring (to glucuronide 1 (37%) and monopropionic 2 (30-20%), major metabolites in plasma and urine), and imidazole ring (to 3, 4)

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TABLE I
 (Continued)

Metabolism (Continued)							
Reference	Species/ Strain	Sex/ WT	No. Animals	Tizimidine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration [Radiolabel] /Activity measured	Study Results
17	Dog/ Beagle	NS/11 kg	3	3 or 4.5 mg/kg, inhalation (water)	Metabolic pattern in plasma and urine after single dose of ¹⁴ C-tizimidine	Single dose; [¹⁴ C]/Tizimidine and metabolites in plasma and urine	Rapid metabolism; parent drug detected in plasma (12%, 1-3 h post) and urine (3%; 8-24 h post) metabolism via oxidation of thiazolidine ring (to sulfone 18, 3% in plasma), benzimidazole ring (to 2, 2 and 2, sulfone 3 was major metabolite in plasma (23%), and imidazolidine ring (4+2 were major metabolites in urine (33%), 4 was abundant in plasma (23%))
3	Dog/ Beagle	Female, Male/ 10 kg	2	1 mg/kg, inhalation (5% glucose saline)	Metabolic pattern in urine after single dose of ³ H- tizimidine	Single dose; [³ H]/Tizimidine and metabolites in urine	Only 2% of unchanged drug seen in urine (8-24 h post); 10 different unidentified metabolites present

Excretion							
Reference	Species/ Strain	Sex/ WT	No. Animals	Tizimidine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration [Radiolabel] /Activity measured	Study Results
1	Monkey/ OF-1	Male/ 22-31 g	10 (5/female)	4 mg/kg, inhalation or iv (5% glucose saline)	Excretion of total radioactivity in urine and feces quantified up to 96 h after a single dose of ¹⁴ C- tizimidine	Single dose; [¹⁴ C]/Total radioactivity in urine and feces	Rapid elimination; 64% oral dose excreted in urine and 26% in feces within 96 h; most excreted within first 24 h; similar excretion pattern after iv dosing
2	Rat/ Sprague- Dawley OFA	Male/ 250-300 g	12 (6/female)	1.5 mg/kg, inhalation or iv (5% glucose saline)	Excretion of total radioactivity in urine and feces quantified up to 72 h after a single dose of ¹⁴ C- tizimidine	Single dose; [¹⁴ C]/Total radioactivity in urine and feces	Rapid elimination; 85% oral dose excreted in urine and 27% in feces within 72 h; most excreted within first 24 h; similar excretion pattern after iv dosing

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TABLE 5
 (Continued)

Reference	Species/ Strain	Sex/Weight	No. Animals	Treatment Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration (Radioisotope) /Radioisotope	Study Results
2	Rat/ Sprague- Dawley OFA	Male, bile duct cannulated/ 250-300 g	10 (Strone)	1.5 mg/kg, imbibition or iv (5% glucose soln)	Urinary, fecal and biliary excretion of total radioactivity in bile duct- cannulated rats up to 72 h after a single dose of ^{14}C - tizanidine	Single dose; ^{14}C /Total radioactivity in urine, bile and feces	^{14}C excretion (0-72 h) after oral dosing was 90% (61% in urine, 29% in bile, 1% in feces); rapid, extensive absorption; most excreted within first 24 h; similar excretion pattern after iv dosing
15	Rat/ OFA	Male/ 280-320 g	6	330 mg/kg, imbibition (water)	Urinary excretion (0-48 h) of parent drug and metabolites following single dose of ^{14}C -tizanidine	Single dose; ^{14}C /Tizanidine and metabolites in urine	Rapid metabolism and excretion; 45% of the dose excreted in urine (0-48 h post) in form of metabolites; parent drug was not detectable
15	Rat/ OFA	Male, bile duct cannulated/ 280-320 g	10	330 mg/kg, imbibition (water)	Biliary excretion (0-24 h) of parent drug and metabolites following single dose of ^{14}C -tizanidine	Single dose; ^{14}C /Tizanidine and metabolites in bile	Rapid metabolism and excretion; 29% of the dose excreted in bile and 36% in urine (0-24 h post) in form of metabolites; parent drug was not detectable
3	Rat/ Wistar OFA	Male/ 200 g	10 (Strone)	1.5 mg/kg, imbibition; 0.3 mg/kg, iv (5% glucose soln)	Excretion of total radioactivity in urine and feces quantified up to 96 or 120 h after single dose of ^3H -tizanidine	Single dose; ^3H /Total tizanidine in urine, non-volatile tizanidine in feces	Rapid metabolism and excretion; 63% oral dose excreted in urine and 20% in feces within 24 h; complete excretion after 96 h; similar excretion rates and patterns after iv dosing
3	Rat/ Wistar OFA	Male/ 200 g	4	2.0 mg/kg, imbibition (5% glucose soln)	Urinary excretion of parent drug and metabolites up to 24 h after a single dose of ^3H -tizanidine	Single dose; ^3H /Total tizanidine, tizanidine and metabolites in urine	Rapid metabolism, extensive metabolism; urinary excretion within 8 h (67%) or 24 h (74%) mostly in the form of metabolites; traces of unchanged drug only (0-24 h post)
10	Rat/ Sprague- Dawley OFA	Male/ 180-200 g	2 (single dose); 10 (chronic dosing)	7 mg/kg, imbibition (5% glucose soln), once a day for 10 days	Daily excretion of total radioactivity in urine and feces after a single dose and during 10 days of dosing with ^{14}C -tizanidine	10 days; ^{14}C /Total radioactivity in urine and feces	Within 24 h after the first dose, 55% dose excreted in urine and 23% in feces; no effect of chronic dosing on urine/feces excretion ratio

5
TABLE X
 (Continued)

Reference	Species/ Strain	Sex/WT	No. Animals	Tizanidine Dose, Route of Admin. (Vehicle)	Study Description	Treatment Duration (Radiolabel) /Excreted	Study Results
10	Rat/ Sprague Dawley OPA	Pregnant Female/ 300-400 g	2	7 mg/kg, intubation (5% glucose soln)	Excretion of total radioactivity in urine and feces up to 24 h after single dose of ¹⁴ C-tizanidine	Single dose; [¹⁴ C]/Total radioactivity in urine and feces	Excretion pattern similar to male rats: 56% excreted in urine and 7% in feces within 24 h post dosing
4	Rabbit/ New Zealand	Female/ 3.5 kg	6 (3/males)	1 mg/kg, iv; (2% gelatin) 3 mg/kg, intubation (saline)	Excretion of total radioactivity in urine and feces quantified up to 96 h after single dose of ¹⁴ C- tizanidine	Single dose; [¹⁴ C]/Total radioactivity in urine and feces	Rapid elimination; 64% oral dose excreted in urine and 23% in feces within 96 h; excretion the fastest within first 24 h; similar pattern after iv dosing
16	Rabbit/ Swiss hare	Male/2 kg	2	2 or 50 mg/kg, intubation (water)	Urinary excretion of parent drug and metabolites up to 74-48 h after a single dose of ¹⁴ C-tizanidine	Single dose; [¹⁴ C]/Total radioactivity, tizanidine and metabolites in urine	Rapid elimination, extensive metabolism; 37% dose (50 mg/kg) excreted in urine within 24 h, and 54% within 48 h; for 2 mg/kg dose, 40% excreted within 24 h; no parent drug detected in urine
3	Dog/ Beagle	Female (n=1), Male (n=2) 3.2-9.9 kg	3 ⁷	0.1 mg/kg, intubation or iv (5% glucose soln)	Excretion of total radioactivity in urine and feces quantified up to 96 h after single dose of ¹⁴ C- tizanidine	Single dose; [¹⁴ C]/Total radioactivity, tizanidine and metabolites in urine	Rapid elimination; no sex differences in excretion (83% in urine, 24% in feces within 96 h after oral dosing); excretion the fastest within first 24 h; similar pattern after iv dosing
3	Dog/ Beagle	Female (n=1), Male (n=2) 10 kg	3 ⁷	0.05 mg/kg, iv; 0.3 mg/kg, intubation (5% glucose soln)	Excretion of total radioactivity in urine and feces quantified up to 168 h after single dose of ³ H- tizanidine	Single dose; [³ H]/Total radioactivity, tizanidine and metabolites in urine and feces	Rapid and complete elimination (56% in urine and 15% in feces within 24 h post oral dosing); all excreted within 168 h; no sex differences; similar pattern after iv dosing

NS = not specified NA = not applicable Admin. = administration iv = intravenous ip = intraperitoneal soln = solution

- 1 Crossover design with 3-4 week washout interval
- 2 Crossover design with 3 week washout interval
- 3 Each animal received both drugs separated by 1-4 week washout interval
- 4 Animals were dosed on day 16 of gestation
- 5 Animals were tested 8-13 days after parturition
- 6 Same animals as used in study of absorption, see reference 1
- 7 Crossover design with 3-4 week washout interval

6
TABLE 17Inter-Species Comparison of the Biotransformation of Tizanidine
(% total radioactivity)

Tizanidine Metabolite	Species (Reference)				
	Mouse (94)	Rat (95)	Rabbit (96)	Dog (97)	Man (100)
Plasma (at Cmax)					
1 <i>Parent</i>	13.4	ND or trace	ND or trace	11.5	ND or trace
2	ND	ND	ND	ND	0-2.7
3	ND	ND	3.5	11.0	17
4	4.8	ND	1.0	23.3	14.7
5 ^a	ND	ND	ND	ND	ND
6 ^b	ND	ND	ND	ND	ND
7	0-6.1	ND	37	4.0	1.3
8	2.4	ND	2.1	33.2	2.7
9	64.3	ND	26.1	4.2	6.4
10	ND	>98	10.7	3.0	12.5
Urine (0-25 hr pool)					
1 <i>Parent</i>	NA	ND or trace	ND or trace	2.9	ND or trace
2	NA	6.8	ND	2.7	ND
3	NA	2.9	ND	5.4	5.5
4	NA	23.2 ^c	ND	31.7 ^c	11.4
5 ^a	NA	c	ND	c	ND
6 ^b	NA	ND	ND	ND	ND
7	NA	1.4	37.2	3.7	6.6
8	NA	ND	ND	ND	ND
9	NA	10.5	19.8	5.1	4.5
10	NA	37.4	ND	ND	11.6

The numbers are taken from original reports rather than from the summary report: Reference 15

NA = not analyzed

ND = not detectable

^a This metabolite was found in rat and dog urine but not in plasma. It can be formed from metabolite of 2 as an artifact of isolation procedure and might not be a true metabolite.

^b Metabolite 6 was not detected in any of the investigated species, but it is believed to be formed, as judged by the presence of its conjugates, metabolites 7 and 8

^c Sum of metabolites 4 and 5

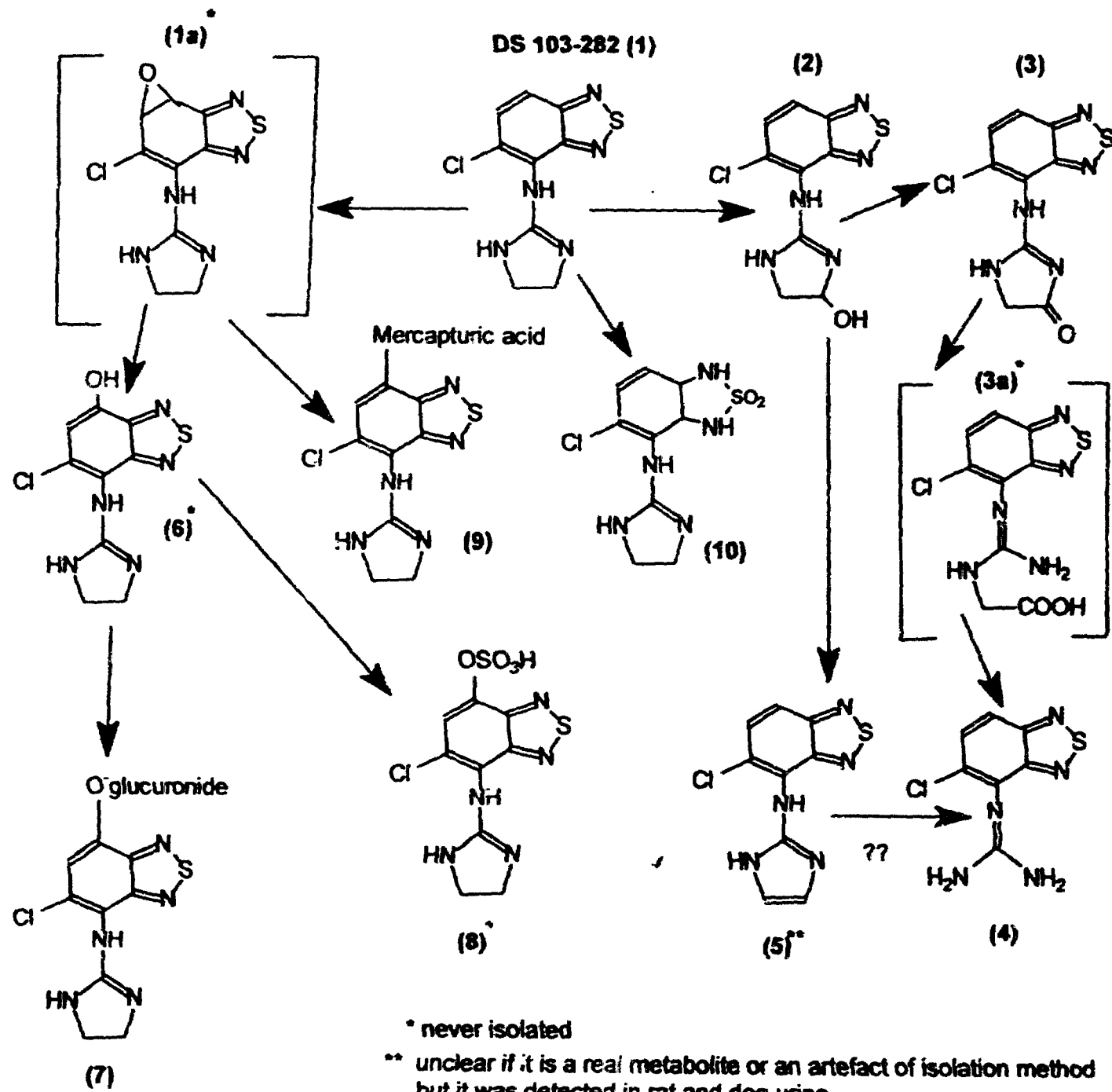


Table 7

Major Metabolites		Man	Rat	Mouse	Dog ^a	Rabbit ^a
3	Plasma	16.7	ND	ND	11	3.5
	Urine	5.5	3	*	5.4	ND
	Bile	*	7.4	*	*	*
4	Plasma	14.7	ND	4.8	23.3	1.0
	Urine	11.4	23.2	*	31.7	ND
	Bile	*	5.4	*	*	*
10	Plasma	12.5	> 98	ND	3	10.7
	Urine	11.6	37.4	*	ND	ND
	Bile	*	7	*	*	*
9	Plasma	6.4	ND	64.3	4.2	26.1
	Urine	4.5	10.5	*	5.1	20
	Bile	*	7	*	*	*

^a other major plasma metabolite in the dog is #8 (33.2%) and in the rabbit is #7 (37%).

ND not detectable at analytical assay's detection limit (NR).

The above values are percent of metabolites in plasma at C_{max} and 0-24 hr pooled urine.

Pharmacology:

Pre-clinical animal studies investigating the pharmacology and mechanism of action of tizanidine were conducted by Sandoz Pharma, Ltd. in addition to large number of published literature. The following tables (taken from the sponsor's submission) summarize all the pharmacology, mechanism of action studies, and other effects of tizanidine.

TABLE I
Studies Assessing the Muscle Relaxant Activity of Tizanidine

Direct Effects on Muscle or Neuromuscular Junction			Effects of Tizanidine		Effects of Reference Compounds
Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration		
1,2	Cal. chloralhydrate	Direct peripheral motor nerve stimulation (muscle twitch)	1-30 mg/kg iv	Tizanidine failed to inhibit muscle contraction at doses up to 30 mg/kg	Baclofen: similar lack of inhibition in same dose range. Dantrolene: ED ₅₀ = 2.0 mg/kg iv
1	Rat (in vivo)	In vitro phrenic nerve-diaphragm	In vitro bath application	Tizanidine had no effect on muscle response to direct or indirect stimulation except at extremely high concentrations (>> 100 and 77 µg/mL, respectively)	Liszapem: = 8x more effective (IC ₅₀ >> 10 and 11 µg/mL, respectively) Baclofen: similar effectiveness at 300 µg/mL for direct and indirect stimulation Dantrolene: highly effective at 1 µg/mL for direct and indirect stimulation

Effects on Reflex Activity in Whole Animal Models

Effects on Reflex Activity in Whole Animal Models			Effects of Tizanidine		Effects of Reference Compounds
Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration		
3	Rat, intact, decerebrate, acutely spinalized	Evoled hindlimb flexor reflex, EMG response	0.25, 0.5, 1.0 mg/kg ip	50% or greater inhibition of hindlimb flexor reflex activity in intact and decerebrate rats; with spinal effects 10-15 minutes post injection. Facilitation of response in acutely spinalized rats after 0.5 or 1.0 mg/kg ip antagonized by picrotoxin	Not done
3	Rat, intact	Evoled hindlimb flexor reflex, EMG response	0.75 mg/kg ip	Pre-treatment with yohimbine prevented tizanidine-induced flexor reflex suppression	Not done
1	Rabbit (conscious)	Teschendorfer model, tonic stretch reflex measurement	Increasing doses at 1 hr intervals iv	Tizanidine ED ₅₀ for inhibiting hindlimb tonic stretch reflex activity = 0.019 mg/kg iv	Diazepam: ED ₅₀ = 0.23 mg/kg iv Baclofen: ED ₅₀ = 0.3 mg/kg iv Dantrolene: ED ₅₀ = 20.0 mg/kg iv
1,2	Rabbit (conscious)	Teschendorfer model, tonic stretch reflex measurement	Days 1 & 14 = 0.02 mg/kg iv Days 2-13 = 2.0 mg/kg sc	No tolerance to tonic stretch reflex suppression	Not done
4	Rabbit (conscious)	Teschendorfer model, tonic stretch reflex measurement	0.03 mg/kg iv	Maximal extensor reflex suppression in conscious rabbit at 5 min., with activity half-life of 21 min	Not done

TABLE 1
(Continued)

Effects on Reflex Activity in Whole Animal Models (Continued)

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
1,2	Cat, chloralose anesthesia	Linguo-mandibular reflex	0.1-3.0 mg/kg iv	Tizanidine inhibited this reflex, ED ₅₀ = < 0.1 mg/kg iv	Baclofen: ED ₅₀ = 0.6 mg/kg iv
5,6	Cat, L ₁ spinalized	Supramaximal stimulation of peripheral motor nerves, ventral root recording	0.025-1.2 mg/kg cumulative, iv, iontophoretic	Dose-dependent inhibition of polysynaptic reflexes, complete abolition of spinal polysynaptic response at 0.05 mg/kg iv. Monosynaptic reflexes relatively insensitive	Not done
2	Cat, chloralose anesthesia; C ₁ spinalized	Mono- and polysynaptic spinal reflex response after stimulation of peripheral motor nerve	0.1 - 3.0 mg/kg iv	Inconsistent effects on mono- and polysynaptic reflexes in intact cat. Facilitation of both reflexes in spinalized animals at higher doses	Baclofen: caused dose-dependent inhibition of both reflexes
1,2	Cat, atlanto-occipital spinalized	Supramaximal dorsal root stimulation to measure mono- and polysynaptic ventral root reflexes	0.005-5.0 mg/kg iv	Tizanidine inactive	Baclofen: inhibited both reflexes at ≥ 0.1 mg/kg iv Dantrolene: facilitated monosynaptic reflexes, and weakly inhibited poly-synaptic reflexes at ≥ 1.0 mg/kg iv Dantrolene: ineffective at doses to 10 mg/kg iv
7	Mice (fasciolaris or arctoides) (conscious)	Peripheral motor nerve stimulation to evaluate flexor reflex	0.2-0.5 mg/kg iv, ip or im	Significant inhibition of polysynaptic cutaneous reflexes, abolished by yohimbine pretreatment	Not done

Single Unit Recordings in Whole Animal Spinal Cords

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
5,6	Cat, L ₁ spinalized	Single unit recording from dorsal horn neurons and Renshaw cells	0.025-1.2 mg/kg cumulative, iv, iontophoretic	Polysynaptic reflex ↓ dose-dependently after iv administration. Monosynaptic reflexes less sensitive. Similar effects with iontophoretic dosing. Less inhibition of excitatory amino acid-induced responses or evoked responses of Renshaw cells	Baclofen: iontophoretic administration more effective at ↓ monosynaptic, than polysynaptic inhibition

TABLE I
(Continued)

Single Unit Recordings in Whole Animal Spinal Cords (Continued)

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
6,8	Cat, chloralose anesthesia	Presynaptic inhibition, neuromuscular at dorsal cervical nuclei after limb or sensorimotor cortex stimulation	0.025-2.0 mg/kg iv	Low doses (0.025 - 0.10 mg/kg) suggested and higher doses (0.2 - 2.0 mg/kg) depressed peripherally and centrally mediated inhibition. Dorsal column reflex inhibited at all doses.	Diazepam: enhanced peripheral inhibition and dorsal column reflex at 0.25 - 3.0 mg/kg iv, but depressed centrally mediated inhibition at the same doses.
9	Cat, pentobarbital anesthesia	Spinal interneuron recording after peripheral nerve stimulation	iontophoretic application	Input-synaptic NMDA- and quisqualate excitation of interneuron response Input-synaptic excitation, but little effect on mono-synaptic excitation	2 amino-5-phosphorvaleric acid (APV) and <i>ctr</i> -2,3-piperidine dicarboxylic acid (2,3PDA) had similar effects
10	Cat, chloralose anesthesia	Measurement of Group I and Group II afferent field potentials	Iontophoretic application	Tizanidine induced strongest and most selective depression of interneuronal zone Group II (polysynaptic) neurons of spinal cord, with little effect on Group I neurons afferent response	NE agonists less potent than tizanidine on Group II afferent transmission. Serotonergic agonists selectively depressed Group II interneuron transmission

Effects on Spinal Reflexes *In Vitro*

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
11	Rat	<i>In vitro</i> hemisection spinal cord, immature animal	0.1-10 µM in bath	2 amino-5-phosphorvaleric acid (APV) sensitive long duration ventral root reflex decreased by tizanidine (EC ₅₀ = 13.5 µM). No effect on NMDA depolarization in the presence of tetrodotoxin; Depression of superior ganglion synaptic response complete, EC ₅₀ = 33 µM	Cyclothiazide: EC ₅₀ for 2 amino-5-phosphorvaleric acid (APV) sensitive reflex = 25.8 µM, diazepam EC ₅₀ = 114 µM Baclofen: induced depression of superior ganglion synaptic response to 75% control, EC ₅₀ = 29 µM Diazepam: no effect
12	Rat	<i>In vitro</i> , transverse slices of spinal cord	50-500 µM in bath	No effect on D-sergines, uptake or calcium-independent release; K ⁺ and veratridine-evoked D-sergines release decreased	Baclofen: No effect to 500 µM Morphine: No effect to 500 µM Glycine: No effect to 500 µM Serotonergic: No effect to 500 µM Norpip: 100% inhibition of D-sergines release at 500 µM
12	Frog	<i>In vitro</i> , hemisection spinal cord, evaluating NMDA and quisqualate inhibition	100 µM in bath	Tizanidine failed to affect excitatory amino acid depolarization or dorsal-ventral root potential	APV at 10 µM effective at blocking excitatory amino acid depolarization

TABLE 1
(Continued)

Effects in Models of muscle Rigidity

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
1,2	Rat	Droperidol/ fentanyl- (Thalamonal®) induced muscle rigidity	Increasing iv doses: given at 10 min. intervals: 2.5-2.5 mg/kg po	FD ₅₀ = 0.55 mg/kg iv; 0.48 mg/kg po	Diazepam: ED ₅₀ = 2.2 mg/kg iv; 4 mg/kg po Baclofen: ED ₅₀ = 4.5 mg/kg iv; 3.3 mg/kg po Dantrolene: ED ₅₀ = 7.1 mg/kg iv; >80 mg/kg po
1,2	Rat	Muscle rigidity after intercollicular decerebration	Increasing iv doses at 10-15 min. intervals	ED ₅₀ = 0.48 mg/kg iv	Baclofen: ED ₅₀ = 1.3 mg/kg iv Diazepam: ED ₅₀ = 3.3 mg/kg iv
6	Cat	Muscle rigidity after intercollicular decerebration or decortication	Increasing iv doses at 1 h intervals	Inhibition of tonic stretch reflexes at doses of 0.05 to 0.4; no effect on phasic stretch reflex	Not done

Mechanism of Action

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
12	Calf cortex tissue	Radioisland binding studies: α adrenergic receptor binding	Not applicable	α ₁ receptor binding: IC ₅₀ for clonidine displacement = 2.1 nM α ₁ receptor binding: IC ₅₀ for prazosin displacement = 4687 nM	α ₁ receptor binding: IC ₅₀ for clonidine displacement = 1.1 nM; α ₁ receptor binding: IC ₅₀ for prazosin displacement = 700 nM
2	Rat whole brain homogenates	Radioisland binding studies: various receptor types (α, β, adrenergic, cholinergic, dopaminergic)	Not applicable	EC ₅₀ for QNB (quinacridinyl benzylate) displacement = >100 μM; EC ₅₀ for DHA (dihydroalprenolol) displacement = >100 μM; EC ₅₀ for haloperidol displacement = 35 μM; EC ₅₀ for DBC (dihydroergocryptine) displacement = 2 μM	Diazepam: EC ₅₀ QNB = >100 μM; EC ₅₀ DHA = >100 μM; EC ₅₀ haloperidol = >100 μM; EC ₅₀ DBC = >100 μM Haloperidol: EC ₅₀ QNB = 30 μM; EC ₅₀ haloperidol = 0.001 μM Dopamine: EC ₅₀ DHA = >100 μM; EC ₅₀ haloperidol = 2.3 μM; EC ₅₀ DBC = 5 μM

TABLE I
(Continued)

Mechanism of Action (Continued)

Ref. No.	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
13	Cloned receptor subtypes	α_2 -adrenergic receptor subtype binding study	Not applicable	K_1 (α_2A) = 65 nM K_2 (α_2B) = 167 nM K_3 (α_2C) = 107 nM; non-subtype-selective	Clonidine also not subtype-selective Nerisapiprin α_2C -selective
14	Rat kidney membranes	Radioligand binding studies: α_2 and imidazole receptor binding	Not applicable	K_1 (imidazoles) = 4.17 nM K_2 (α_2) = 91.5 nM	Clonidine: K_1 (imidazoles) = 9.2 nM; K_2 (α_2) = 9.2 nM Epipristin: K_1 (imidazoles) = >10000 nM; K_2 (α_2) = 3.18 nM
15	Rat, chloralose anesthesia	Measurement of locus coeruleus (LC) neuron and flexor reflex activity	0.5 mg/kg ip; 0.25 mg/kg iv	Tizanidine decreased spontaneous locus coeruleus neuron and flexor reflex activity after peripheral stimulation with a parallel time course	Yohimbine reversed tizanidine effect on LC neuron activity
16	Rat, chloralose anesthesia	Measurement of norepinephrine in spinal cord perfusate after locus coeruleus stimulation	0.1, 0.3 mg/kg iv	Tizanidine decreased spontaneous NE release, but not increased NE release after LC stimulation	Clonidine had similar effects (0.03 and 0.1 mg/kg iv) Chloryperazine and prazosin (both at 1 mg/kg iv) did not affect NE content of the spinal perfusate
17	Rat, halothane anesthesia	Dorsal horn convergent neurons, evoked after iontophoretic DL-homocysteic acid	Iontophoretic application	Iontophoretic administration decreased neuronal discharge evoked by iontophoretic DL-homocysteic acid	Not done

Ref. No. = Reference number; po = oral; ip = intraperitoneal; iv = intravenous; sc = subcutaneous; min = minutes; NS = not specified; NE = norepinephrine; LC = locus coeruleus

TABLE 2
Antinociceptive Effects of Tizanidine

Antinociceptive Screening Models

Ref. No	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
1,2	Mouse	Chemical: induced writhing by ip injection of phenylbenzoquinone (PBQ)	0.1 - 0.32 mg/kg po	ED ₅₀ of response inhibition = 0.21 mg/kg	Diazepam: ED ₅₀ = <1.0 mg/kg. (Not dose-dependent) Baclofen: ED ₅₀ = 2.0 mg/kg Dantrolene: ED ₅₀ = >32 mg/kg (At low doses, potentiated response)
21	Mouse	Chemical: induced writhing by ip injection of acetic acid, PBQ or acetylcholine	Range not stated, po	Acetic acid ED ₅₀ = 1.07 µmol/kg PBQ ED ₅₀ = 0.861 µmol/kg Acetylcholine ED ₅₀ = 0.965 µmol/kg	Diazepam: Acetic acid ED ₅₀ = 12.6 µmol/kg Baclofen: Acetic acid ED ₅₀ = 3.15 µmol/kg; PBQ ED ₅₀ = 15.9 µmol/kg
22	Mouse	Chemical: induced writhing by ip injection of acetic acid	0.047-0.86 µmol/kg (0.014-0.250 mg/kg) sc	ED ₅₀ of response inhibition = 0.37 µmol/kg (0.078 mg/kg)	Clonidine: ED ₅₀ = 0.04 µmol/kg (0.011 mg/kg). (7.75% higher than tizanidine)
21	Mouse	Chemical: induced writhing by ip injection of acetic acid, PBQ or acetylcholine	Range not stated, sc	Acetic acid ED ₅₀ = 0.379 µmol/kg (0.110 mg/kg); PBQ ED ₅₀ = 0.316 µmol/kg (0.099 mg/kg); Acetylcholine ED ₅₀ = 0.379 µmol/kg	Morphine: Acetic acid ED ₅₀ = 1.55 µmol/kg; PBQ ED ₅₀ = 1.40 µmol/kg Acetylcholine ED ₅₀ = 0.879 µmol/kg
1	Mouse	Mechanical: tail pinch	1-3.2 mg/kg po	ED ₅₀ of response inhibition = 2.5 mg/kg	Not done
1	Mouse	Thermal: tail flick and hot plate Electrical: stimulation to the tail	Range not stated po	Tail flick ED ₅₀ of inhibition = 11.7 µmol/kg (3.4 mg/kg); hot plate ED ₅₀ of inhibition = 12.77 µmol/kg (3.7 mg/kg); electrical ED ₅₀ of inhibition = 15.2 µmol/kg (4.4 mg/kg)	Diazepam: oral tail flick ED ₅₀ = >28.1 µmol/kg Baclofen: oral tail flick ED ₅₀ = >28.1 µmol/kg Morphine: electrical ED ₅₀ = 728.1 µmol/kg
1	Mouse	Thermal: timed movement of tail from radiant heat, source	3.2-10 mg/kg po	ED ₅₀ of response inhibition = 4.8 mg/kg	Diazepam: no effect to 18 mg/kg po Baclofen: ED ₅₀ = 12 mg/kg Dantrolene: no effect to 100 mg/kg
23	Mouse 3 days after C ₅ -6 spinalization	Thermal: timed movement of tail from radiant heat, source	0.86 - 6.89 µmol/kg (0.250-2.0 mg/kg) sc	ED ₅₀ of response inhibition = 4.14 µmol/kg (1.2 mg/kg)	Clonidine: ED ₅₀ = 2.18 µmol/kg (0.58 mg/kg) Morphine: ED ₅₀ = 98.5 µmol/kg (44.4 mg/kg)
25	Mouse	Thermal: timed movement of tail from radiant heat source	17.2-68.9 nmol/mouse (0.25-1.0 mg/kg) icv	ED ₅₀ of response inhibition = 49.3 nmol/mouse (0.70 mg/kg) icv	Clonidine: ED ₅₀ = 9.38 nmol/mouse (0.125 mg/kg) icv

TABLE 2
(Continued)

Antinociceptive Screening Models (Continued)

Ref. No	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
21	Rat	Thermal: timed movement of tail from radiant heat source	Range not stated, po	ED ₅₀ of response inhibition = 19.0 µmol/kg (3.5 mg/kg)	Morphine: ED ₅₀ = 12.9 µmol/kg
24	Rat	Thermal: timed movement of tail from radiant heat source	0-25 µg/rat (0-75 µg/kg) iv, 5x daily doses of 25 µg/rat iv	Significant antinociception at 25 µg/rat; reduced effect of iv tizanidine at 25 µg/rat after 3 days	Clonidine: Significant antinociception at 25 µg iv/rat Morphine: Significant antinociception at 25 µg iv/rat
1,2	Monkey (rhesus)	Electrical: shock titration (self selected electrical shock avoidance)	3.2-10.0 mg/kg po	No effect on pain at 3.2 mg/kg; higher doses caused sedation and ataxia	Not done
6	Rat	Arthritis: mycobacterium butyricum injection into paw	Range not stated, po	ED ₅₀ of vocalization inhibition after foot flexion = 3.7 mg/kg po	Baclofen: ED ₅₀ = 12 mg/kg Dantrolene: ED ₅₀ = 21 mg/kg Morphine: ED ₅₀ = 46 mg/kg Acetylsalicylic acid: ED ₅₀ = 140 mg/kg

Mechanism of Action

Ref. No	Species	Test Model/Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
22	Mouse	Timed movement of tail from radiant heat source	0.5, 1.0 mg/kg sc	Prolonged latency of response at both doses	Dopaminergic, serotonergic, GABA system antagonists had no effect on tizanidine effectiveness Yohimbine, not prazosin, effective at blocking tizanidine effectiveness
22	Mouse	Timed movement of tail from radiant heat source	0.86 - 6.89 µmol/kg (0.250-2.0 mg/kg) sc	ED ₅₀ of response inhibition = 1.79 µmol/kg (0.5 mg/kg)	Clonidine: ED ₅₀ = 0.93 µmol/kg (0.25 mg/kg) Serotonergic system: No effect of 3,5-dihydroxytryptamine or cyproheptadine Catecholaminergic system: No effect of methyltyrosine, diethylthiocarbamate, 6-hydroxydopamine or haloperidol Phenothiazines, phentolamine and yohimbine, not prazosin, reduced antinociceptive effect of tizanidine and clonidine

TABLE 3
Gastrointestinal Effects

Ref. No.	Species	Test Model/ Test System	Dose & Route of Admin	Effects of Tizanidine	Effects of Reference Compounds
29	Mouse	Gastrointestinal transit time	5, 50 mg/kg po	At 5 mg/kg, 19.2% decrease in transit time 30 minutes after dose	5 mg/kg more effective than 30 mg/kg morphine at reducing GI transit time
30	Mouse	Gastrointestinal transit time	0.0-10 mg/kg ip	ID ₅₀ = 0.8 mg/kg	Loperamide (opioid agonist) ID ₅₀ = 0.2 mg/kg
31	Mouse	Gastrointestinal transit - effects of α 2-adrenergic agonists, antagonists and castor oil	2, 4, 12 mg/kg ip	Dose-dependent decrease in gastrointestinal transit time; 12 mg/kg decreased castor oil diarrhea 1.6x controls	Effect of clonidine on gastrointestinal transit time at 1 mg/kg equivalent to 12 mg/kg tizanidine; 1 mg/kg clonidine decreased castor oil diarrhea 2.8x control
29	Rat	Spontaneous gastric movement	0.3-1.0 mg/kg iv	Reduced spontaneous movement at 0.3 and 1.0 mg/kg iv	Not done
32	Rat	Peripheral (bethanechol, histamine, vagal nerve) and central (2-deoxy-D glucose (2 DG), icv TRH)-gastric acid stimulation	0.5-10 mg/kg sc	At higher doses, stimulated gastric acid secretion after administration of peripheral secretagogues, and suppressed centrally acting secretagogues (2 DG and TRH) stimulated gastric secretion. TRH effect suppressed by yohimbine	Clonidine at least 10x more effective
33	Rat	Indomethacin, aspirin, or stress-induced gastric ulcer	5, 10 mg/kg sc	Inhibited indomethacin and aspirin-induced lesions, not stress-induced ulcers	Clonidine at least 10x more effective in suppressing all three types of ulcers
29	Guinea pig	Spontaneous movement of ileum	0.1-0.3 mg/kg iv	Inhibited movement at 0.3 mg/kg	Not done
20	Guinea pig tissue	Guinea pig ileum <i>in vitro</i> preparation	10^{-7} - 10^{-5} M	Decrease in contraction ($pD_2=7.49\pm 0.12$), inhibitable by yohimbine, not atropine, or diphenhydramine or tetrodotoxin	Clonidine more effective ($pD_2=8.12\pm 0.13$) than tizanidine, otherwise similar pattern of response
30	Guinea pig tissue	Guinea pig ileum <i>in vitro</i> preparation	Range not stated	pIC_{50} for inhibition of ileal muscle = 7	Loperamide (opioid agonist) pIC_{50} inhibition of ileal muscle = 9

35

225

74

TABLE 4
Genitourinary Activity

Ref. No.	Species	Test Model/ Test System	Tizanidine Dose, Route of Administration	Effects of Tizanidine	Effects of Reference Compounds
1,2	Rat, conscious	Bladder catheterization	0.1-30.0 mg/kg po	Dose-dependent ^{urinary} decrease in water and electrolyte excretion (0.3-3.0 mg/kg), less effect higher doses	Not done
1,2	Dog, Inactin anesthesia	Bladder catheterization	0.1, 1.0 mg/kg iv	Dose-dependent ^{urinary} decrease in water and transient increased electrolyte excretion (0.1 mg/kg), less effect higher dose (1.0 mg/kg)	Not done

Cardiovascular Effects:

Similar to other α_2 agonists, tizanidine caused a transient pressor/hypertensive response that is believed to be peripherally mediated, and a longer-lasting, dose-dependent depressor/hypotensive response that is centrally mediated. The CVS effects of tizanidine were tested in the rat (intact and pithed), dog, and cats using both in vivo and in vitro preparations. The doses tested ranged between 0.1-5 mg/kg p.o. (also 0.035% in feed), and 0.1 ug/kg to 1 mg/kg i.v. (upto 18.7 mg/kg cumulative). In general, tizanidine was less effective than clonidine in its pressor and hypotensive effects (10-50x less effective than clonidine). The CVS effects were more pronounced after i.v. administration than after oral tizanidine specifically the transient hypertension in rats that was not observed after oral dosing. The CVS responses were observed at doses higher than those required for muscle relaxation (significant effect was not seen in rats at 1 mg/kg p.o. or less) (See table 3 in Executive Summary section).

Drug Interactions:

Interaction of tizanidine with acetaminophen, diazepam, imipramine, and haloperidol was evaluated in 4 studies (see attached table). The following pharmacological responses were tested in mice or rats: anticonvulsant activity (diazepam), locomotor activity (imipramine), catalepsy (haloperidol), and toxicity (acetaminophen). The results did not show any drug interactions at the doses tested.

Physical Dependence:

Potential physical dependence of tizanidine was assessed in rats and monkeys using standard tests. Doses tested in rats ranged between 0.02-0.32 mg/kg i.p. and in monkey 1 ug/kg i.v. for 5 wks to 64 mg/kg p.o. for 5 wks (table 4 Executive Summary). The only effect of tizanidine was in monkeys where 3/4 monkeys injected with 3.2 ug/kg i.v. self-administered tizanidine and all 4 animals self-administered the drug at 10 ug/kg (marked increase in lever pressing). Saline administration after tizanidine caused a decline in lever pressing but there was no signs of withdrawal. Physical dependence was evaluated in monkeys for 5 wks by automatic oral dosing of the drug every 12-hr. Doses were 10, 18, and 32 mg/kg twice daily. Tizanidine at the HD only, exhibited withdrawal in all 4 animals (increased locomotion, body twitching, and aversive behavior toward the examiner). These withdrawal signs could not be reversed by naloxone.

PHARMACOKINETICS

1. Pharmacokinetics in mice/Sandoz Switzerland 1980/Report# 303-015/vol 1-19
Batch# RA 425-1
Purity: by TLC >98%

Methods: ^{14}C -tizanidine (at carbon #2 of imidazolin ring) was administered to mice as a single oral or i.v. 4 mg/kg in 5% aqueous glucose solution. Male mice were used for the excretion study and both sexes were used for the distribution study (OF-1 Sandoz; 21-32 g weight). Drug-blood level was measured from 3 male mice/time interval. Excretion of radioactivity in urine and feces was determined in 10 male mice and samples were quantitatively and separately collected for 4 days. For the distribution studies, 36 mice (18/sex) were administered oral doses and another 18/sex were given an i.v. dose. Three mice/sex were sacrificed at specific time intervals, small samples of organs/tissues (5-15 mg) were also removed and weighed. Radioactivity reflective of drug-blood level, was determined as F-value which is equivalent to conc. (dpm/gm blood or tissue) divided by dose (dpm/g body wt.). For a 4 mg/kg dose, an F-value of 1.0 corresponded to 4 μg equivalent of intact drug per gm blood or wet tissue.

Results:

Oral: the drug appeared in the blood within 0.25 hr postdose with mean peak concentration reached at 0.75 hr postdose. At this time, mean F-value was 0.2 corresponding to an equivalent drug concentration of 0.8 μg equiv/g blood. Half maximum peak levels were reached within 2-3 hr and the drug was eliminated from the blood by 24 hr (F-value= 0.003). The drug was widely distributed, high radioactivity was detected in kidneys and liver with moderate levels upto 3 hr postdose. Small amount was detected in the brain within 0.5 hr which declined to trace amount by 24 hr (0.004-0.005).

i.v.: the mean drug concentration at 0.25 hr was ~ 2 μg equivalent/g of whole blood with mean F-value of 0.47. Mean maximum concentration was 2.6 μg equiv/g whole blood reached at 0.5 hr postdose and mean F-value at this time was 0.64. By 24 hr postdose, only trace amount of radioactivity remained (F-value of 0.002 corresponding to 0.01 μg equivalent/g whole blood). The drug was widely distributed, brain levels were maximum by 0.5 hr postdose and remained detectable upto 24 hr postdose. High radioactivity was also detected in the following organs/tissues: kidney>liver>salivary glands>pancreas>thymus. Radioactivity was very low in any one organ/tissue by 24 hr (F-value <0.01).

Following either route of administration, tizanidine was excreted predominantly in urine (64-65% total radioactivity) and small amount eliminated in feces (23-26% of total radioactivity) (see attached summary PK table/provided by the sponsor). About 88-91%

of total radioactivity was eliminated in urine + feces by 96 hr postdose.

Summary/Conclusion:

¹⁴C-Labelled tizanidine was administered to mice at 4 mg/kg single oral or i.v. dose. The drug was rapidly absorbed and appeared in plasma within 0.25 hr of dosing. Peak levels reached within 0.5-0.75 hr with mean concentration range of 0.8-2.6 µg equivalent/g whole blood. The drug was distributed to various organs/tissues following either route of administration. Trace radioactivity was still detected 24 hr postdose. The drug was excreted mainly in urine (64-65%) and in feces (23-26%) with 88-91% of total radioactivity eliminated from the body by 96 hr postdose.

Table 5. Calculated pharmacokinetic parameters of ¹⁴C-DS 103-282-ch in mice after oral and intravenous administration (4 mg/kg) (means ± SD). *single*

Parameters		oral	intravenous
β (6-24 h)	hrs ⁻¹	0.1324	0.1284
t _{1/2} β	hrs	5.2	5.4
B: intercept of back extrapolated β -slope (t=0)	F-values	0.072	0.043
Blood level C _{max}	F-value	0.184 ± 0.023	
Blood t _{max}	hrs	0.83 ± 0.14	
AUC (0-24 h) total radio-activity	F-values x h	1.026 ± 0.299	1.438 ± 0.198
AUC p.o./AUC i.v.	%	71.3	
Urine (0-96 h) total radio-activity	%	64.4 ± 4.5	65.3 ± 8.3
Faeces (0-96 h) total radio-activity	%	26.3 ± 2.3	22.8 ± 2.4
Urine p.o./Urine i.v.	%	> 100	

Study # 303-915

¹⁴C-103-282: ADE STUDIES IN MICE

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NDA-020397

FIRM: ATHENA NEUROSCIENCES

5 OF 7

TRADE NAME: ZANAFLEX ORAL TABS. 4MG

GENERIC NAME: TIZANIDINE HCL

2. Pharmacokinetics in rats/Sandoz Switzerland 1979/Report# 303-007/vol 1-19
Batch# RA 425-1
Purity: by TLC >98%

Methods: absorption, blood and tissue distribution, and excretion (bile, urinary, and fecal) all were studied in intact and bile-duct cannulated rats following administration of ¹⁴C-tizanidine. Listed below is the type of experiment:

	oral	i.v.
	----	----
Dose (excretion study)	1.5mg/kg	1.5mg/kg
Dose (distribut. study)	8mg/kg	8mg/kg
no. of intact rats	6	6
no. of bile-fistula rats	5	5
no. of rats in distribution study	24	24

For excretion studies male rats were used (250-300 g), and for distribution studies both sexes (170-200 g), of SPF Sprague-Dawley rats of OFA strain were used. The drug was administered in 5% aqueous glucose solution and freshly prepared. Similar to the mouse study above, drug levels were represented as F-values. For 1.5 mg/kg dose (p.o. and i.v.) and the 8 mg/kg (p.o. and i.v.), an F-value of 1 corresponded to 1.5 µg equivalents and 8 µg equivalents respectively of intact drug/g blood or wet tissue.

Results:
oral: the drug was rapidly absorbed and appeared in the blood within 0.25 hr postdose. Mean maximum blood level was reached at 0.75 hr with an F-value of 0.62 corresponding to an equivalent drug concentration of ~1 µg/g. The drug also rapidly disappeared from the blood by 24 hr postdose with mean F-value of 0.003. Most radioactivity was eliminated by 72 hr postdose in the urine (58±5% of total radioactivity) and some in feces (27±4%). Half of the drug was eliminated by 24 hr and the total excretion (urinary + fecal) amounted to 85±6% of the oral dose. In the bile-fistula rats, 29% of radioactive dose was eliminated through the bile within 24 hr postdose and the total cumulative values excreted in urine and feces were 61 and ~1% respectively. The drug was distributed to various organs with peak radioactivity reached by 2 hr postdose and increased in the following order in males and females: kidney>liver>pancreas>thyroid>bone marrow>salivary glands>thymus. The F-values in these tissues ranged from 0.17 to 0.91 which are 0.3-1.5x higher than the mean peak plasma levels.

i.v.: similar to the oral dosing, radioactivity was detected within 0.25 hr postdose and peak level reached at 0.75 hr with a mean F-value of 0.54 corresponding to an equivalent drug concentration of 4.3 µg/g blood. The drug rapidly disappeared from the blood by 24 hr with mean F-value of 0.002. Most radioactivity was eliminated

by 72 hr in urine (59±7% of total radioactivity) and less in feces 25±2%. Total radioactivity (urine + feces) amounted to 83±8%. In the bile-fistula rats, 32±3% of radioactivity was eliminated through the bile within 72 hr postdose and the total cumulative values excreted in urine and feces were 60 and 2% respectively. The drug was distributed to various organs with peak radioactivity reached by 2 hr postdose and increased in the following order in males and females: kidney>liver>thyroid>adrenals>salivary glands>lung>pancreas>bone marrow. The F-values in these tissues ranged from 0.55 to 2.5 which are

about 1-5x higher than the mean peak plasma levels. Within 24 hr postdose, radioactivity was markedly reduced from all tissues following either route of administration.

The attached PK table shows that drug elimination appears to be biphasic with $t_{1/2}$ of radioactivity elimination of 1.5 hr for both routes (calculated only for the β phase).

Summary/Conclusion:

¹⁴C-labelled tizanidine was administered to rats at 1.5 and 8 mg/kg single oral or i.v. dose. The drug was rapidly absorbed and appeared in plasma within 15 min of dosing by either route. Peak levels reached within 0.75 hr with mean concentration range of 1-4.3 μ g equivalent/g whole blood for the oral and i.v. routes respectively. The drug was distributed to various organs/tissues following either route of administration. Trace radioactivity was still detected 24 hr postdose. The drug is excreted mainly in urine (58-59%) as well as in feces (25-27%) and % of total radioactivity was eliminated from the body by 72 hr postdose. From the bile-fistula rat studies it is clear that small amount is excreted by the bile. Elimination half life was calculated at 1.5 hr.

study # 303-007

Table 9. Calculated pharmacokinetic parameters of ¹⁴C-DS 103-282-ch in rats after oral and intravenous administration of 1.5 mg/kg (p.o. and i.v.).

Parameters		oral	intravenous
A (3-7 h)	hrs ⁻¹	0.467	0.505
t _{1/2} β	hrs	1.5	1.4
B: intercept of back extrapolated A-slope (t=0)	F-values	0.409	0.691
Blood level C _{max}	F-value	0.619	
Blood t _{max}	hrs	0.75	
AUC (0-72 h) total radio-activity	F-values x h	1.506	1.693
AUC p.o./AUC i.v.	%		89
Urine (0-72 h) total radio-activity	%	58.1 ± 5.4	58.6 ± 7.4
Faeces (0-72 h) total radio-activity	%	26.7 ± 3.8	24.8 ± 2.1
Urine p.o./Urine i.v.	%		99
Amount absorbed (urine + bile)	%	89.9	

3. Pharmacokinetics in rats and dogs/Sandoz Switzerland
 1976/Report# 303-001/vol 1-19
 Batch# RA 299-2 and RA 299-3
 Purity: by TLC >98%

Methods: Absorption, blood levels, urinary and fecal excretion, and metabolic profile were studied in male rats (Wistar SPF-OFA) and dogs (m+f beagles) after oral intubation and i.v. dosing of ³H-DS 103-282. The metabolites were not structurally identified in this study. All studies were conducted with a single dose as follows:

i.v. 0.3 mg/kg (5 rats), 0.05 mg/kg (3 dogs)
 p.o. 1.5 mg/kg (5 rats), 0.3 mg/kg (3 dogs)
 p.o. for metabolic studies: 2 mg/kg (4 rats), 1 mg/kg (2 dogs)

In the dog, the same animals were used for the i.v. and p.o. dosing with 4-wk washout period between routes. The radioactive and unlabelled drug were dissolved in 5% w/v glucose solution. Blood, urine, and feces samples were collected at specified time intervals postdose. Levels of radioactivity in blood and plasma were expressed similar to the studies in rats and mice reported above, as F-values. The latter is calculated as the ratio of specific radioactivity (dpm/g) sample to the specific radioactive dose (dpm/g) times body weight (g).

Results:

Rat:

The drug was rapidly absorbed following oral dosing with blood levels detected within 0.5 hr postdose. Mean peak blood level was 0.1 ± 0.015 (F-value) within 1 hr of oral and 0.3 ± 0.05 within 0.5 hr of i.v. dose. Total cumulative % of administered ³H-activity excreted in urine by 96 hr was about 63% and 65% following i.v. and p.o. dosing respectively, and for feces the values were 19 and 23% respectively. Within 24 hr, 64% of orally administered radioactive dose was excreted in the urine and 20% in feces. Very little drug was excreted unchanged <1% (0-24 hr) in urine. The rate of metabolism in the rat was determined at 0-8 and 8-24 hr in addition to the overall metabolism at 0-24 hr. Quantitative analysis of metabolites in urine showed a total of 4 metabolites in the rat with metabolite I constituting 82%, and 3 minor metabolites: II 8%, and V and VIII each 1% of total radioactivity at 0-24 hr analysis. It was found that there were no qualitative differences between the urine fractions but there were quantitative differences for metabolite I and II. The rate of formation of metabolite I and II at 0-8 hr were 86 and 4% respectively, whereas in the 8-24 hr fraction the corresponding values were 29 and 50%.

Dog:

The drug was rapidly absorbed following oral and i.v. dosing with blood levels detected within 3 min postdose with an F-value of 0.62 ± 0.21 for i.v. dose and 0.01 ± 0.01 for the p.o. Mean peak blood level (F-value) for both routes was 0.3 ± 0.04 within 5 hr postdose.

The blood levels were flat increasing gradually indicating possible slow absorption or/and slow metabolism. Cumulative % excretion of radioactivity in urine following p.o. and i.v. was approximately 58% and in feces 19% at 24-48 hr period; total of 99% was excreted by 168 hr postdose. Similar to the rat, little drug was excreted unchanged in urine (2% at 0-24 hr) with mean total excretion of 49% during the 1st day. The drug was metabolized to 10 metabolites with metabolites I and V composing the majority of the label (39 and 22% respectively at 0-24 hr) (attached table), the rest were minor metabolites varying greatly in polarity and are found at trace amounts.

In both the rat and dog, high radioactivity (10-20%) was determined and assumed to be tritiated water (hot). The content of this hot material was calculated by measuring the volatile ³H-activity in urine by lyophilization. Based on a 75% water content of human body, the amount of water formed was calculated by extrapolating back to t=0. The sponsor concluded that water (hot) formation was an analytical artefact and not a metabolic process but the result of instability in the label of some of the formed metabolites.

Summary/Conclusion:

³H-DS 103-282 was administered as a single dose to rats and dogs by the oral and i.v. routes to determine absorption, blood levels, excretion profile, retention, and metabolism. Tritiated compound was used, blood, urine, and feces were collected at specific time periods. In both species the drug was well absorbed and there appear to be no drug accumulation. Absorption may be slow in the dog since concentration increased very slowly with time. Following oral dosing radioactivity was detected by 0.5 hr to 3 min in the rat and dog respectively, peak blood levels (F-values) were 0.10 to 0.3 within 0.5-1 hr and 0.3 within 5 hr postdose in the rat and dog respectively. Most of the drug was metabolized and excreted mainly in urine. There were 10 metabolites in the dog with 2 major ones and a total of 4 in the rat with 1 major metabolite. Almost all drug was recovered by 168 hr postdose in either species. The identity of the metabolites was not determined.

Study # 303-001 *AK*

Table 7

Quantitative analysis of metabolites in urine of dogs and rats
 The amount of each metabolite is given in % of the total radio-activity excreted in the corresponding urine fraction.

Animal and urine fraction	Metabolites									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Dog 0 - 8 h	50 %	9 %	2 %	1 %	19 %	2 %	1 %	12 %	1 %	1 %
Dog 8 - 24 h	45 %	10 %	4 %	7 %	26 %	2 %	1 %	1 %	1 %	1 %
Dog 0 - 24 h	39 %	8 %	3 %	4 %	22 %	2 %	1 %	5 %	1 %	1 %
Rat 0 - 8 h	86 %	4 %	-	-	2 %	-	-	1 %	-	-
Rat 8 - 24 h	29 %	50 %	-	-	7 %	-	-	4 %	-	-
Rat 0 - 24 h	82 %	8 %	-	-	1 %	-	-	1 %	-	-

Pharmacokinetic studies with *Tizolidin*
 H-DS 103-262

page 2 of 4

4. Pharmacokinetics in dogs/Sandoz Switzerland 1979/Report# 303-008/vol 1-19
Batch# RA 425-1
Purity: by TLC >98%

Methods: Absorption, blood levels, urinary and fecal excretion of radioactivity were investigated in dogs after oral and i.v. dosing of 0.1 mg/kg (1f and 2m/route; wt 3-9.9 kg); 19 and 21 plasma determinations/animal at specified intervals). The same animals were dosed orally and i.v. with 3-4 wk period between doses.

Results: The drug was almost completely absorbed with estimated oral bioavailability of 88-97% calculated as the ratio of urinary AUC p.o./i.v. After oral dosing, mean peak drug concentrations (F-values) were reached at 2.25 hr in blood (0.37) and 2.5 hr in plasma (0.49) (F-value= concen of blood or plasma(dpm/g) per dose (dpm/g body wt)). These values corresponded to an equivalent drug concentration of 38 ng/g blood and 52 ng/g plasma respectively. One half maximum F-value of radioactivity was reached at 6-7 hr in blood and plasma. About 72% of radioactivity was eliminated in urine and 24% in feces by 96 hr postdose (total of 96%). Most of urinary radioactivity was eliminated by 24 hr after dosing (68% p.o. and 77% i.v.). Following i.v. dosing, mean peak concentrations (F-values) were 0.7 in whole blood and 0.67 in plasma reached within 5 min of dosing. Half maximum levels (F-value) were reached between 3-5 hr postdose and small radioactivity was left by 96 hr (0.03-0.04%). The drug was excreted mainly in urine (82%) and small amount in feces 24% by 96 hr (total excreted was 106%). Half lives of elimination were calculated only for the terminal beta phase (24-96 hr) and were 110±33 hr (p.o) and 93±19 hr (i.v.), the mean AUC for the blood is 6.7 (p.o.) and 7 (i.v.) at t=0-96 hr. PK data are summarized in the attached table provided by the sponsor. Elimination half life ranged between 93-110 hr depending on sampling time.

Summary/Conclusion:

C14-DS-103-282 was administered at 0.1 mg/kg single oral and i.v. doses to dogs. Plasma/blood levels, absorption and excretion profiles were determined. The drug was well absorbed with oral bioavailability of 88-97%. Peak levels of 0.4-0.5 (F-values) were reached by 2-2.5 hr p.o. and declined rapidly within 24 hr. Peak level after i.v. dosing was 0.7 and were reached within 5 min. The drug was eliminated mainly in urine (72 and 82% p.o. and i.v. respectively) and some in feces. Total radioactivity excreted by 96 hr was 100% by 96 hr. Elimination half lives were 93-110 hr (these values changed with sampling time). Based on recovery data, the drug does not appear to accumulate in the body following single administration.

2.

Comment:

In a separate study, the relative bioavailability of DS-103-282 was compared in the dog using newly manufactured and aged (3.25 yr) 4 mg tablet (Sandoz-NJ 1983/Report# DM-1-7/26/83/vol 1-19) (Batch# PRD-Ao-6-162 for aged and PRD-CR-2-112 for new tablets). Six male beagle dogs (wt 8.5-12 kg) were used and each dog received single oral tablet. Following 3-wk wash-out period, each dog in a cross-over design received another single oral tablet. Plasma was sampled at specified times from each dog upto 48 hr postdose and drug concentration was determined by radioimmunoassay. The results for the aged tablet showed lower Cmax (13%), lower AUC (11-19%), and longer Tmax (15%) than the corresponding parameters in the newly synthesized tablet. These differences were contributed to slower dissolution rate. Although statistically insignificant, in vitro dissolution profiles showed at t=45 min, the new tablet released 96% of drug substance compared with 81% for the aged tablet, a 15% difference which is similar to the differences in Cmax and AUC reported above.

Table 7. Calculated pharmacokinetic parameters of ¹⁴C DS 103-282-ch in dogs after oral and intravenous administration. Means ± SD (n=31). *0.1mg/kg dose*

Parameters	oral	intravenous
β (24-96 h) hrs ⁻¹	0.0067 ± 0.0023	0.0077 ± 0.0017
t _{1/2} β hrs	110 ± 33	93 ± 19
B: intercept of back-extrapolated -slope (t=0)		
F-values	0.061 ± 0.037	0.060 ± 0.005
Blood level C _{max} F-values	0.375 ± 0.019	0.689 ± 0.182
Blood t _{max} hrs	2.2 ± 0.3	0.08
AUC (0-96 h) total radio-activity: F-values x n	6.734 ± 3.005	6.951 ± 0.568
AUC p.o./i.v. 1		97
Urine(0-96 h) total radio-activity 1	72.2 ± 1.4	81.9 ± 4.5
Faeces(0-96 h) total radio-activity 1	23.6 ± 2.4	24.2 ± 3.5
Urine p.o./i.v. 1		88

¹⁴C-DS 103-282-ch: Pharmacokinetic Studies in Dogs Page 18 of 21
Study 303-008

5. PK studies of tizanidine HCl and clonidine HCl in rhesus monkeys/Sandoz 1985/Report# 303-040/vol 1-19

Methods:

Compound's purity and batch# were not provided. Drug concentrations were determined by a RIA with detection limit of 0.25 ng/ml for tizanidine and 50 pg/ml for clonidine. The sponsor indicated that there was no "important cross-reactions" with the known metabolites and tizanidine; details were not provided.

Tizanidine and clonidine were administered each to 3 rhesus monkeys (sex not identified) by an i.v. infusion over 4 hr at 0.05 mg/kg/h or 0.2 mg/kg. Blood was collected before and upto 16 hr post administration.

Results and Summary:

The following tables present plasma levels for both drugs and the attached table shows PK data. Animal C56 dosed with tizanidine showed an unusual rebound at 8 hr postdose which could not be explained by analytical means it could be a metabolite, but this was not confirmed. Tizanidine blood levels and AUCs were lower than those of clonidine at all collection times however, elimination half life remained the same (about 3 hr). Mean maximum concentration of tizanidine was >18 ng/ml compared with 4.5 ng/ml in man and that for clonidine was 29 ng/ml. Tizanidine tissue distribution phase was short reflecting the low plasma levels and high plasma clearance of about 2 l/hr/kg vs. 1 l/hr/kg for clonidine. Mean Vd was larger for tizanidine vs clonidine and man indicating good and wide distribution (7 vs. 4.4 and 2 l/kg respectively). Hepatic plasma Cl of tizanidine in monkey and man were comparable with corresponding hepatic blood flow (ratios of plasma Cl/hepatic flow 0.6 and 0.63 for man and monkey respectively).

It was concluded that tizanidine after a 4 hr i.v. infusion to monkeys produced lower plasma levels than clonidine given under the same experimental conditions and same dose. Such finding was not explained and may be related to rapid distribution or extensive metabolism and excretion. Elimination half lives however, were comparable with higher plasma Cl of tizanidine than that of clonidine in monkey and in man.

Report # 303-040 PK

Table 2 Plasma concentrations of tizanidine (ng/ml) after i.v. infusion of 0.2 mg/kg over 4 hours to 3 rhesus monkeys

Time animal	0	2	3.0	4.0	4.5	5.0	6.0	8.0	12.0	14.0	16.0
C 56	0	20	25.0	28.0	21.6	16.30	11.50	29.50	7.50	0.79	0.84
B69	0	15	14.8	-	-	17.70	11.00	5.91	2.92	2.09	1.27
D 24	0	15	18.6	17.1	13.6	9.53	5.78	2.40	0.62	0.16	0.08

Table 3 Plasma concentrations of clonidine (ng/ml) after i.v. infusion of 0.2 mg/kg over 4 hours to 3 rhesus monkeys

Time animal	0	2	3.0	4.0	4.5	5.0	6.0	8.0	12.0	14.0	16.0
C 56	<0.1	19.7	30.6	23.9	20.9	23.1	21.8	15.6	6.4	4.4	3.4
D 24	0.2	17.6	24.1	28.5	25.2	22.4	19.0	8.3	3.0	2.0	0.7
D 64	<0.1	20.5	26.3	27.5	19.9	18.6	17.0	12.4	4.2	2.2	1.6

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Report # 303-240 PK

Table 3 Comparison of the pharmacokinetics of tizanidine and clonidine in rhesus monkeys

Parameters	Units	Clonidine in monkey				Tizanidine in monkey				Tizanidine in man***
		C 56	D 24	D 64	mean $\pm$ S.D.	C 56	D 24	869	mean $\pm$ S.D.**	
Weight	kg	8.1	9.5	9.1	8.9 $\pm$ 0.7	8.0	9.5	9.0	9.3 $\pm$ 0.4	70 (assumed)
Dose	μ g/kg	200	200	200	200	200	200	200	200	7.14 (bolus)
cp max	ng/ml	30.6	28.5	27.5	29 $\pm$ 2	28	18.5	> 18	> 18.3 $\pm$ 0.5	4.5 $\pm$ 1.3
β	h^{-1}	0.187	0.237	0.239	0.24 $\pm$ 0.05	-	0.385	0.196	0.29 $\pm$ 0.13	0.44 $\pm$ 0.08
t _{1/2}	h	3.7	2.4	2.9	3.0 $\pm$ 0.7	-	1.8	3.5	2.7 $\pm$ 1.2	1.7 $\pm$ 0.4
AUC 16	(ng/ml)h	217	168	183	189 $\pm$ 25	230	86	> 120	103 $\pm$ 24	-
AUC	(ng/ml)h	235	171	190	198 $\pm$ 33	144*	86	126	106 $\pm$ 28	7.8 $\pm$ 2.0
Cl p	l/h/kg	0.85	1.17	1.05	1.02 $\pm$ 0.16	1.79*	2.32	1.58	1.95 $\pm$ 0.52	0.88 $\pm$ 0.53
Cl _{area}	l/kg	4.6	4.1	4.4	4.4 $\pm$ 0.3	4.8*	6.0	8.1	7.0 $\pm$ 1.5	2.3 $\pm$ 0.7

* With an elimination constant assumed equal to 0.29 h⁻¹ after 6 hours (without rebound)

** Mean without animal No. C 56

*** E. Neesch / Biostatistik: Bioverfügbarkeitsstudie Sirdalud i.v./i.m. 5.3.1985 (10 subjects)

6. Comparison of PK parameters in man and animals/Sandoz-Switzerland 1986/Report# 303-049/vol 1-19

Attached table (produced by the sponsor) presents percentage of parent and metabolite concentrations in plasma (Cmax), urine and bile in man and animals and the diagram shows the three major metabolic pathways of tizanidine. Tizanidine is rapidly absorbed after single oral administration, peak plasma radioactivity in man, rat, mouse, and rabbit was reached by 1 hr (0.75 hr in mouse); slower absorption rate noted in the dog (2.2 hr). Based on cumulative urinary excretion data, 70% of administered oral dose is absorbed in man and mice and >90% in rat, dog, and rabbit. Distribution was biphasic in man and animals with half lives in man of 2.5 and 22 hr; the drug was widely distributed to various organs. Half lives were short in mice (5 hr), and rats (1.5 hr) after p.o. and i.v. administration and in the dog half life was 93 and 110 hr after i.v. and oral dosing respectively (values were dependent on time of sampling). The drug both in man and animals showed low protein binding (23-30%). Drug distribution was sex independent in rats and mice. A milk/plasma AUC ratio of 1.8 was reported in lactating rats. The drug was extensively metabolized in all species through one or more of 3 major pathways: oxidation at imidazoline ring, oxidation at the benzene ring, or oxidation of the sulfur atom. The drug undergoes extensive first pass (50-80%) with <2% of parent drug appearing in urine and only 6% in plasma; oral bioavailability was 34%. The major plasma metabolites: in man are 3, 4, and 10 (17, 15, 13% respectively), in the rat 10 (>98%), in the mouse metabolite 9 (64%), in the dog metabolites 3,4,8 (11, 23, 33% respectively), and in the rabbit 7,9,10 (37, 26, 11% respectively). The drug was eliminated mainly in urine (70%) and some in feces (30%) in all animal species and man, large amount of radioactivity was eliminated by 24 hr. (attached Table presents disposition parameters of DS 103-282; it is noted that half life in the dog was 10 hr compared to 110 hr reported above. The 10 hr is based on re-analysis of blood data in report# RA 425-1 with new half lives between 48 and 96 hr and calculations made on samples collected between 6 and 24 hr. None of this information was referenced or indicated in a separate memo.

The parent drug represented less than 2% of the dose in human urine and only 6 % of the radioactivity in human plasma (pool 0-24 h), consequence of a high first pass effect (50-80%). Accordingly an absolute bioavailability of about 34 % was determined.

The following table compares the percentage of the different metabolites in the plasma at Cp(max) and in 0-24 h pooled urine, in order to facilitate the inter-species comparison of metabolism.

Metabolites		man	rat	dog	mouse	rabbit
(Sirdalud)	plasma	Little interspecies difference: either				
1	urine	not detectable (N.D.) or at trace levels.				
	bile					
	plasma	0-2.7	N.D.	N.D.	N.D.	N.D.
2	urine	N.D.	6.8	2.7	*	*
	bile	*	N.D.	*	*	*
	plasma	16.7	N.D.	11	N.D.	3.5
3	urine	5.5	2.9	5.4	*	N.D.
	bile	*	7.4	*	*	
	plasma	14.7	N.D.	23.3	4.8	1.0
4	urine	11.4	23.2	31.7	*	N.D.
	bile	*	5.4	*	*	*
	plasma	N.D.	This metabolite was found in rat and			
5	urine	N.D.	dog urine but not in plasma, and is			
	bile		thought to be a degradation product			
			of 2 rather than a true metabolite.			
	plasma	has not been found in any species but is				
6	urine	certainly formed as shown by the presence				
	bile	of its glucuronide 7				
	plasma	1.3	N.D.	4.0	0-6.1	37
7	urine	6.6	1.4	3.7	*	37.2
	bile	*	10.9	*	*	*
	plasma	2.7	N.D.	33.2	2.4	2.1
8	urine	N.D.	N.D.	*	*	N.D.
	bile	was never isolated (assignment by HPLC with				
		the synthetic reference compound)				
	plasma	6.4	N.D.	4.2	64.3	26.1
9	urine	4.5	10.5	5.1	*	19.8
	bile	*	6.9	*	*	*
	plasma	12.5	>98	3	N.D.	10.7
10	urine	11.6	37.4	N.D.	*	N.D.
	bile	*	6.9	*	*	*

N.D. = Not Detectable,

* = sample not analysed

Study #
303-049

not true
mouse →

plasma 30.0
urine 11.4
bile 5.4

Table 1: Summary of disposition parameters of DS 103-282

Parameter (oral dose)	Man	Rat	Mouse	Dog	Rabbit
<u>Absorption:</u> amount absorbed (% dose) rate of absorption	> 70 fast	90 fast	> 70 fast	90 fast	90 fast
<u>Plasma levels of radioactivity:</u> C_{max} (P-value) time to peak level (h)	0.805 1.0	0.750 0.75	0.197 0.75	0.375 2.2	0.335 1
<u>Distribution:</u> $t_{1/2}$ α -phase (h) highest radioactivity levels in plasma protein binding (%)	2.5 30	short K,L 23	short K,L	short	2.5
<u>Biotransformation:</u> fraction metabolized first-pass effect main metabolites in plasma % of parent drug at or near peak time	> 90% 50 to 80% 4, 3, 10 6.0 *	> 90% 10 0.0	> 90% 2 13.1	> 90% 2, 1, 2 11.5	> 90% 2, 2 0.0
<u>Elimination:</u> excretion $t_{1/2}$ β -phase (h) $t_{1/2}$ percent drug (h)	= 70 20-30 22 (61) 3-5	61 1 29 2	64 26 5	72 24 10	64 22 45

* 0-24 h plasma pool

K = kidney
L = liver

7. Whole-body autoradiography in pigmented mice by p.o., i.p., and microtome/Sandoz-Switzerland 1980/Report# A11/vol 1-20 Batch# RA 425-3 for ¹⁴C-tizanidine, 99% purity.

Methods:

Male C57 BL mice (10-12 mice 8-wks old, 22-31 g) were orally dosed with 7 mg/kg ¹⁴C-labeled tizanidine and sacrificed at specific times after dosing up to 48 hr.

Results:

Total radioactivity (parent and metabolites) was slowly excreted with label still detectable in the liver, skin, and eyes up to 48 hr post administration. The pattern of distribution was similar after the oral and i.p. dosing.

i.p. at 0.5 hr postdose: very high levels of radioactivity was found in the gall bladder>stomach>retroorbital fat tissue>salivary glands>kidneys>seminal vesicles>other parts of the eye>nerve endings of olfactory nerve>s.c fat tissue. High levels noted in liver>GI wall>brain>fat tissue>bone marrow>prepuccial gland>muscles>testes/seminal vesicles>lungs>skin>heart muscle. Medium levels detected in blood>stomach wall, low levels in the eye and traces in bones. At 48 hr radioactivity was still detectable in the outer part of the eye, s.c. fat, and liver.

p.o at 1 hr post dose: very high levels detected in stomach lumen>gall bladder>outer parts of the eye>olfactory nerve endings>salivary gland>kidneys>retroorbital fat, high levels in liver>GI wall>lungs>skin>bone marrow. Medium levels in muscles>heart muscle>prepuccial gland>brain>seminal vesicle>blood, low levels in the eyes>testes; the bones seems to be free of radioactivity. By 48 hr, traces were detected in the outer parts of the eye, liver, s.c. fat, and olfactory nerve endings.

It is concluded that the drug tissue distribution was similar after p.o. and i.p. dosing with the exception of higher radioactivity in seminal vesicles after i.p. Also the drug was not completely excreted by 48 hr after dosing. The mouse excretes the radioactivity slower than does the rat but the pattern is similar. The results also indicate that tizanidine has high affinity for parts of the eye and skin which could not be detected in the albino rat. The sponsor assumed that the radioactivity is localized in the pigment-containing cells of the choroid plexus. They could not explain the high levels of radioactivity in nerve endings of the olfactory system.

8. Macroautoradiography* in male rats after single and chronic administration and in pregnant rats after single administration/Sandoz-Switzerland 1979/Report# A12/vol 1-20 Batch# RA 425-2 for the ¹⁴C-tizanidine

* Method of Kalberer 1966.

Methods:

SPF Sprague-Dawley (OFA strain) were used, the male rats weighed 180-200 g, the pregnant females weighed 300-400 g and these females were on gd 16 at study initiation. The animals, 2/time period, were sacrificed at given times up to 48 hr post dose. For all the experiments, the labeled drug was dissolved in 5% glucose solution and the dose was 7 mg/kg (1 ml/kg) equivalent to 100 uCi/kg*. In the chronic study, the drug was administered daily for 10 days. The drug was administered as a single dose to the males and pregnant females and repeated dosing for 10 days was done in males. * page 110 of the report/table 1 shows doses 1 and 4 mg which equal to 5-20 mg/kg doses (based on 200 g rat) it is unclear which is the correct dose.

Single administration: 1 hr post dose radioactivity was highest in the stomach>small intestine>bladder, medium levels were found in the liver and kidneys. Low amount was detected in the lungs, blood, intestinal wall, spinal cord, and muscles. No radioactivity was detected in the brain, eyes, fat tissue, heart, or testicles. After 24 hr, radioactivity was detected in the bladder and the GIT, only traces were present in the liver; no radioactivity was detectable in any other organ. Radioactivity distribution after 48 hr was similar to that after 24 hr.

Chronic administration: 1 hr postdose distribution of radioactivity was similar to that after single dosing with high levels in the stomach, GIT and bladder. Medium radioactivity levels were found in the kidneys and liver and only low amounts in the lungs, stomach, and intestinal wall. No radioactivity was detected in the brain, eyes, fat tissue and testicles. After 24 hr, high levels of radioactivity were found in the GIT and low levels in the liver and outer part of the kidneys. By 48 hr, low radioactivity remained detectable in the GIT and liver, traces in the kidneys and no radioactivity detected in any other organ.

Single dosing to pregnant rat: 1 hr post dose, high levels found in the stomach, bladder, liver, and kidneys (outer part less than the inner). Medium levels noted in the lungs, blood, intestine, skin, lacrimal and salivary glands, placenta, and cartilagenous slives between the vertebrae. Low radioactivity was present in muscles and bone marrow and only traces in the brain and fetus. No radioactivity was detected in the eyes or bones. Post 24 hr, high levels were present only in the GIT and low radioactivity still detected in the liver, and traces in the amnion. The drug was completely eliminated from other organs. Similar distribution was found in the 48 hr samples.

Excretion: 78% of radioactivity (55% in urine, was eliminated 24 hr after the single dose in male rats and 63% (44% in urine) after the chronic dosing. Similarly, pregnant females excreted 61% of radioactivity by 24 hr with 55% excreted in the urine.

It is concluded that tissue distribution is similar after single or repeated dosing in the rat and no difference in distribution pattern between males and females. The wide distribution indicates good absorption of the drug. Radioactivity was high in the liver, GIT, kidneys, and bladder. The drug crossed the placenta and was detectable after 1 hr of dosing and upto 48 hr traces were detectable in the amnion. The drug is mainly excreted in the urine and does not appear to accumulate.

9. Passage into the rat milk/Sandoz-Switzerland 1979/Report# 303-006/vol 1-20

Batch# 425-1 for the ¹⁴C-labeled drug./99% pure.

Methods:

¹⁴C-tizanidine was orally administered to lactating rats at 1.5 mg/rat dose. These rats (OFA strain) weighed on the average 310 g and were tested 8-13 days after parturition. Milk was collected (1 ml/rat) after 1, 2, 4, 6, 8, and 24 hr (7 rats/time) and radioactivity was determined; blood and plasma were collected immediately after the milk sampling.

Results:

Tizanidine was transferred through the milk in lactating rats. Total radioactivity appeared in milk shortly after dosing and presented below as means (range) in ng equivalents/ml:

	1 hr	8 hr	24 hr
milk	402(321-497)	958(650-1176)	67(29-160)
blood	708(338-1071)	356(205-475)	26(16-36)
plasma	610(312-898)	351(214-456)	27(19-38)

Blood and plasma total radioactivity were higher than that in milk during the 1st hr, the reverse was true during the 8 and 24 hr sampling times. Peak concentration reached within 2 hr in plasma and 8 hr in milk. Milk/plasma ratio of 24-hr AUC was about 2 and the transport mechanism appears to be via non-ionic passive diffusion (using pH values and pKa and Henderson-Hasselbach equation). Below are tizanidine concentrations (total radioactivity) expressed in ug equivalents/ml or g tissue:

<u>Tissue</u>	<u>2 hr</u>	<u>24 hr</u>
milk	0.56	0.07
plasma	0.82	0.03
blood	0.92	0.03
plasma*	0.74	0.06
blood*	0.88	0.06
kidney*	5.43	0.31
liver*	5.00	0.58

* results from previous study at 7 mg/kg dose (Report# 303-007) used for comparison.

Although the drug appeared in milk, concentrations were about 10x higher in kidney and liver. The author estimated the amount of tizanidine that could be consumed by an infant of a nursing mother. Human plasma concentration lower than 20 ng/ml have been measured after a single oral dose of 5 mg (0.08 mg/kg). If milk/plasma ratio is assumed to be 1.8, the maximum amount of tizanidine an infant could ingest would be 36 ug or 0.7% of the adult dose (based on consuming 1 l of milk per day).

10. ¹⁴C-tizanidine distribution in pregnant rabbits during multiple dosing/Sandoz-Switzerland 1985/Report# 303-039/vol 1-20 Batch# 1038-236-25 for the ¹⁴C-compound; >98% pure.

Methods:

Mature female New Zealand white rabbits (mean wt 3.5 kg) were used. The dose of 3 mg/kg was selected because it was minimally toxic (decrease in B.wt without teratogenicity). The labeled drug was orally administered to pregnant rabbits on gd 6 through 18. Rabbits (3 per time point) were sacrificed after 2 hr of dosing on gd 10, 14, and 18, and additional rabbits were sacrificed 24 and 48 hr postdosing on gd 19 and 20 respectively. Blood, liver, kidneys, amniotic fluid, fetuses, placentas, ovaries, corpora lutea, and uterus were also isolated and analyzed.

Results:

After 2 hr following the 5th dose (gd 10), radioactivity was detectable in all tissues with the highest level of 17.2 ug equiv/g found in the liver followed by the kidneys at 6 ug equiv/g and the blood at 657 ng Eq/ml (attached table). Radioactivity although slightly lower than that in the blood was detected in corpora lutea, uterus, placenta, ovaries, and fetus. The radioactivity was stable/constant when measured at 2 hr on gd 10, 14, and 18 in all these tissues except for the fetus with values declining about 70% on gd 18 (439 vs. 133 respectively). The level declined markedly on gd 20 in all tissues except the liver radioactivity remained high (though was 37% less than that on gd 10). The ovaries at 48 hr (gd 20) had an unusually high levels (711 vs. 78 ng equiv/g on gd 19) which was attributed to contamination of the sample. It was indicated that the 2 hr blood levels were lower than those recorded after single dosing. This was related to perhaps a difference in t_{max} in single vs. repeated dosing. After cessation of dosing, radioactivity declined biexponentially with similar half lives (calculated for the 24 and 48 hr) ranging between 31 hr for blood and 52 hr for the liver. These values were consistent to those calculated after single dose. The half lives in amniotic fluid and fetuses were shorter: 16 to 25 hr.

It is concluded that oral dosing of pregnant rabbits on gd 6-18 at 3 mg/kg/d showed reasonably stable radioactivity levels in blood and tissues of the mothers with slightly lower levels in reproductive organs but high values in liver and kidneys (highly perfused excretory organs). Radioactivity in fetus and amniotic

fluid decreased with fetal:placenta ratios of 1 and 0.31 on gd 10 and 18 respectively, the corresponding ratios for amniotic fluid:placenta were 0.33 and 0.27 respectively. This decline in radioactive level with time maybe related to increased clearance by the fetus and/or limited transport at these later stages of pregnancy. Half lives of elimination were similar in maternal tissues and fluids but shorter in amniotic fluid and fetuses.

DN-1-2/8/85

CONFIDENTIAL-TRADE SECRET

pk action
study # 303-039 vol. 1-20
TABLE 2

DISTRIBUTION OF RADIOACTIVITY DURING AND FOLLOWING MULTIPLE ORAL ADMINISTRATION OF ^{14}C (3 mg/mg/day) IN PREGNANT RABBITS.
Tizanidine

Tissue	ng Bq/mL or g, Mean $\pm$ SD ¹				
	Day Post Conception ²				
	10 (5th dose)	14 (9th dose)	18th (13th dose)		
	2 h	2 h	2 h	24 h	48 h ³
Blood	657 $\pm$ 183	767 $\pm$ 161	714 $\pm$ 88	131 $\pm$ 19	77
Liver	17180 $\pm$ 4635	22790 $\pm$ 1652	20580 $\pm$ 3150	8697 $\pm$ 2164	6333
Kidneys	5934 $\pm$ 1366	6078 $\pm$ 919	6123 $\pm$ 1918	654 $\pm$ 63	376
Uterus	452 $\pm$ 69	410 $\pm$ 61	412 $\pm$ 72	96 $\pm$ 24	55
Ovaries	440 $\pm$ 151	444 $\pm$ 73	400 $\pm$ 65	78 $\pm$ 19	711
Corpora Lutea	517 $\pm$ 181	563 $\pm$ 57	514 $\pm$ 49	96 $\pm$ 26	58
Amniotic Fluid	146 $\pm$ 30	138 $\pm$ 53	114 $\pm$ 19	58 $\pm$ 16	30
Placentas	445 $\pm$ 67	414 $\pm$ 44	419 $\pm$ 84	95 $\pm$ 25	97
Fetuses	439 $\pm$ 54	74 $\pm$ 14	133 $\pm$ 104	59 $\pm$ 18	21

¹n=3
²Dosing started on day 6 post conception
³n=2

Biotransformation:

In all of the following studies the detection limit of the analytical methods were not reported.

1. Metabolism in Mice/Sandoz-Switzerland 1980/Report# 303-021/vol 1-20
Batch#RA425-3 for the 14C label and RA483-1 for the unlabelled compound.

Methods:

OF-1 male mice (22-31 g) were individually housed and orally dosed with 4 mg/kg of radioactive tizanidine (¹⁴C at position 2 of the imidazoline ring). Blood was collected at specific times starting at 0.25 hr and upto 3 hr postdose and metabolites were separated and identified by HPLC and NMR/MS analyses. These same animals were used for the absorption, distribution, and excretion studies.

Results:

The major metabolite is #9 (mercapturic acid derivacive) with 55-74% of radioactive dose (tables 1&2). At 0.75 hr postdose, metabolite 4 and the parent constituted 5 and 13% respectively, of radioactivity in plasma. Percentage of the parent declined to 8.6% by 1.5 hr (samples were not analyzed after this time period). None of metabolites 2,3, or 6 were detectable in plasma (Fig 1 for metabolite pattern in plasma as determined by HPLC) (urine samples were not analyzed for metabolites). However, the sponsor indicated that based on data from other species, it can be postulated that these metabolites are also present in mice. Based on the identified metabolites and biotransformation studies in other species including man, it can be concluded that tizanidine in the mouse is brokendown by 2 main pathways. One is oxidation of the imidazoline ring and the 2nd is the oxidation of the benzene ring. The postulated metabolites, 1a (epoxide) and 3a (amino acid) seemed valid since epoxides of type 1a are known intermediates in formation of mercapturic acid derivatives and a similar amino acid was reported to be a metabolite of clonidine.

1 mouse

Table 3. Percentages of identified metabolites in plasma of mice at different times after administration of a single oral dose of [¹⁴C]DS 103-282 (4 mg/kg)

Time (h)	Radioactivity F-value*	Metabolite					total accounted for
		<u>1</u>	<u>4</u>	<u>7</u>	<u>8</u>	<u>9</u>	
0.25	0.192	15.5	2.7	traces	traces	73.8	92.0
0.5	0.149	12.7	4.3	5.1	1.7	63.7	87.5
0.75	0.197	<u>13.4</u>	<u>4.8</u>	traces	2.4	<u>64.3</u>	84.9
1.0	0.160	13.1	2.7	6.1	2.6	70.5	95.0
1.5	0.170	8.6	3.3	traces	4.7	55.2	71.8
3.0	0.078	**	**	**	**	**	**

* F-value = $\frac{\text{concentration (dpm/g of plasma)}}{\text{dose (dpm/g body weight)}}$ (approx.; based on [3])

F = 1.0 corresponds to 4000 ng-equiv./ml plasma

** not determined, =ols decomposed

MC-DS 103-282: Metabolism in mouse

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study # 303-21 vol. 1-20

MOUSE

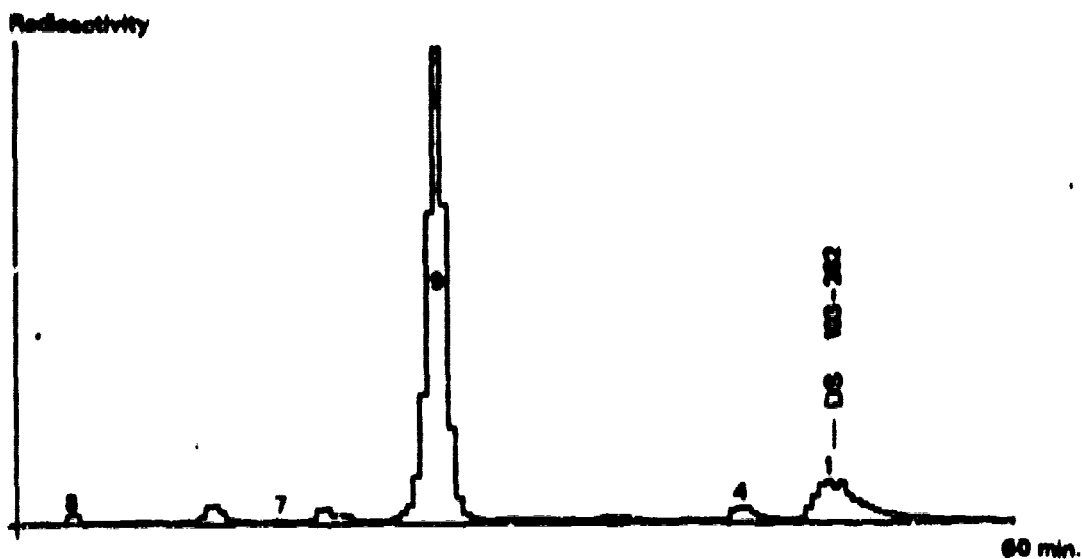
Table 8. Plasma levels (ng/ml) of DS 103-282 and its metabolites after a single oral dose of 4 mg/kg

Metabolite	Molecular weight	Time (h)					
		0.25	0.5	0.75	1.0	1.5	3.0
1 (103-282)	253.71	119	76	106	84	59	*
4 (201-341)	227.68	19	23	34	16	20	*
7	445.84	traces	53	traces	69	traces	*
8	349.78	traces	14	26	23	44	*
9	414.90	927	621	828	736	614	*

* not determined, sample decomposed

HPLC

Fig. 1. Metabolite pattern in mouse plasma 0.25 h after an oral dose of ¹⁴C/DS 103-282 (4 mg/kg)



2. Metabolism in Rats/Sandoz-Switzerland 1980/Report# 303-027/vol
1-20
Batch#RA425-3 for the ¹⁴C label.

Methods:

Intact and bile-fistula OFA male rats (280-320 g) were used. The labeled drug was administered by gastric intubation at 5 or 330 mg/kg. biological fluids were collected as follows: urine and bile 0-24 and 24-48 hr and plasma was collected 1 hr post dose presumed peak level from previous pk study in rats.

Results:

The cumulative urinary excretion in bile duct was 36% after 24 hr of administration and the biliary excretion in the same period was 29%; these values are in agreement with the values found in the PK studies. The only plasma metabolite and main urinary metabolite is #10 (attached table and HPLC figures/>98 and 37% respectively). Traces of metabolite 3 were detected only in urine (3%) and none were detected in bile or plasma. Metabolite 4 was detected in bile (5%) and urine (23%) but none in plasma. The metabolite pattern was also studied in rat hepatocyte; the major metabolite was the imidazole #5 and the minor compounds: glucuronide #7, mercapturic acid derivative #9, metabolite #2, and the parent drug.

It is concluded that 3 major metabolic pathways may function in the rat: oxidation of the sulfur atom to produce sulfone derivative (#10), oxidation of the imidazoline ring to produce 2,3,4, and 5 or oxidation and subsequent conjugation of the aromatic ring to produce #6,7, and 9. It is noted that metabolites 1a or 3a are neither isolated nor detected they are hypothesized based on the detection of metabolites 7,9, and 4 and that a metabolite similar to 3a has been detected in clonidine metabolism and the knowledge that epoxides of type 1a precede the formation of mercapturic acid conjugates.

Rat

Table 9 Proportions (%) of the metabolites in biological samples after single oral doses of [¹⁴C]DS 103-282

Sample	Dose (mg/kg)	Metabolites							Total accounted for (% dose)		
		<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>7</u>	<u>9</u>	<u>10</u>			
plasma 1.0 h	5								>98	98	
urine 0-48 h pool	330	6.8	2.9	23.2		1.4	10.5	37.4	82	(38)	
bile 0-24 pool	330		7.4	5.4		10.9	6.9	6.9	38	(13)	
hepato- cyte incubation	c. e. 2.3.5.	3.7			69.4*	traces	10.5				

*includes traces of parent drug

Study # 303-27

[¹⁴C]-DS 103-282 : Metabolism in rat

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Study #303-27 Vol. 1.20

¹⁴C-DS 103-282 : Metabolism in rat

Fig. 1 Metabolite pattern in rat plasma one hour after an oral dose of [¹⁴C]DS 103-282 (5 mg/kg) (NPLC conditions I)

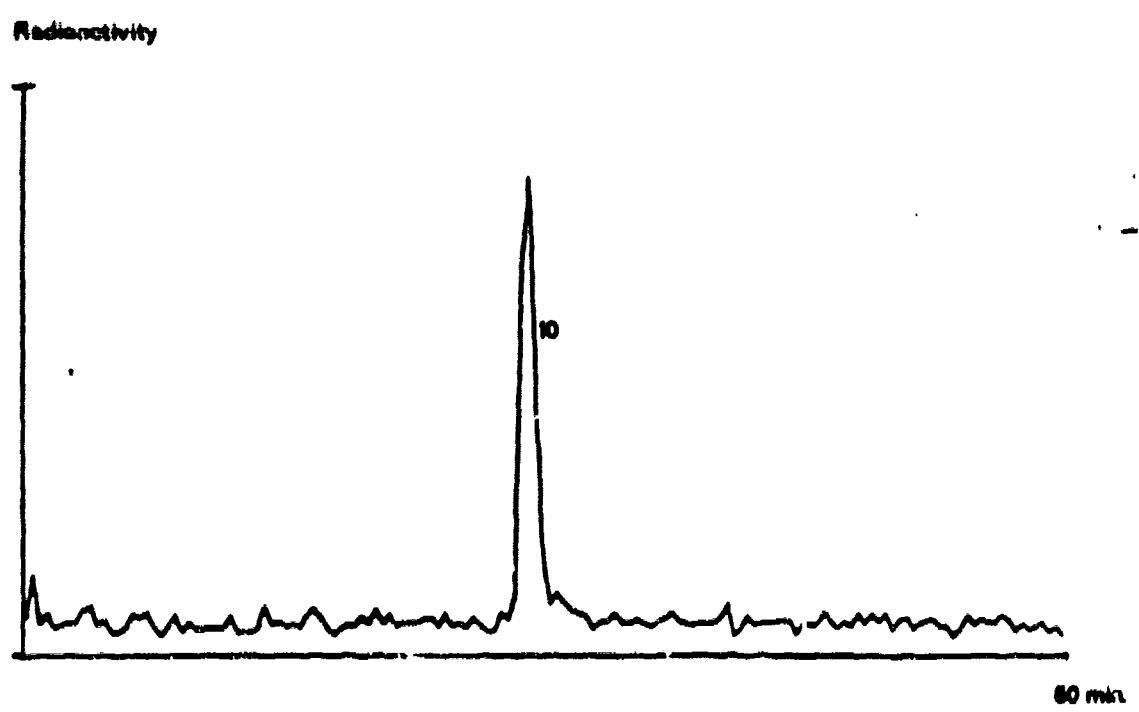


Fig. 2 Metabolite pattern in rat urine (0-24 h) after an oral dose of [¹⁴C]DS 103-282 (330 mg/kg) (HPLC conditions I)

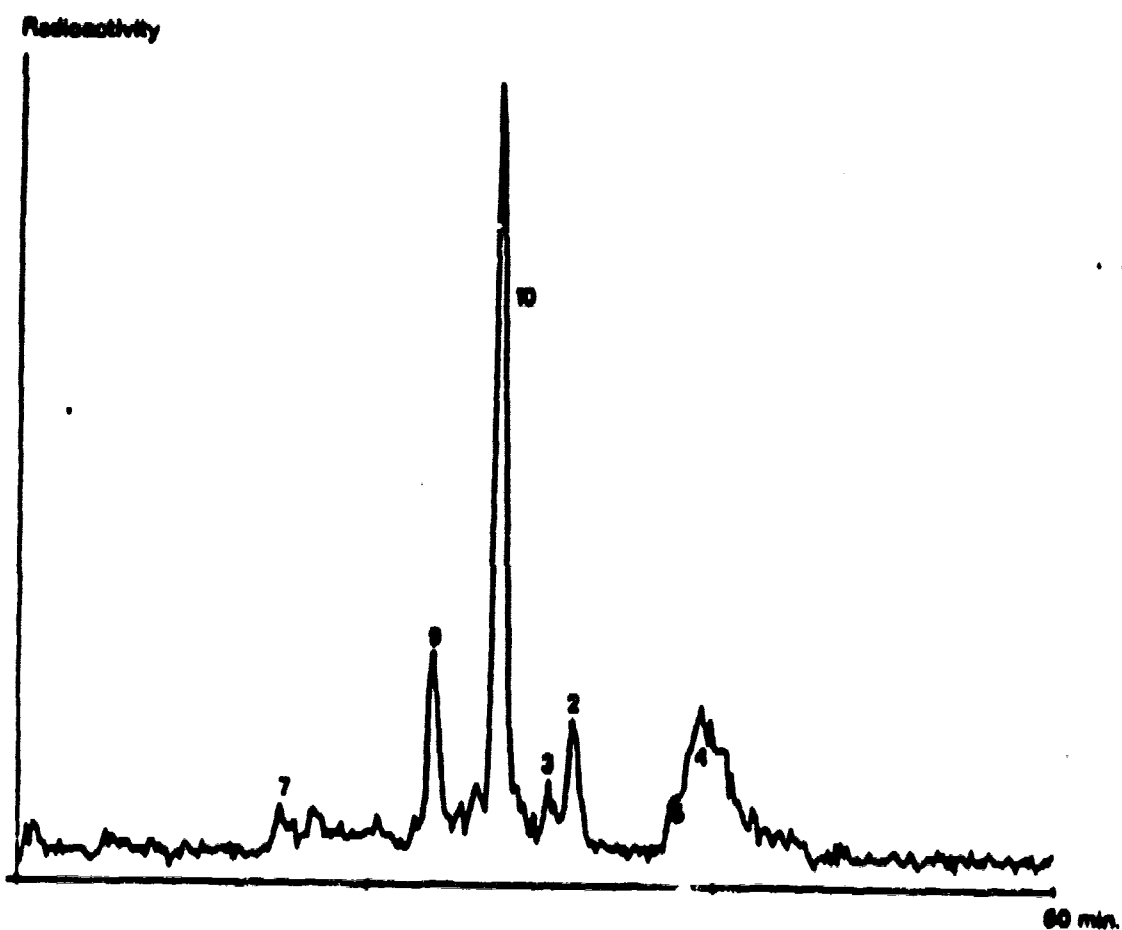


Fig. 1 Metabolite pattern in rat bile (0-24 h) after an oral dose of (¹⁴C)DS 103-282 (330 mg/kg) (HPLC conditions I)

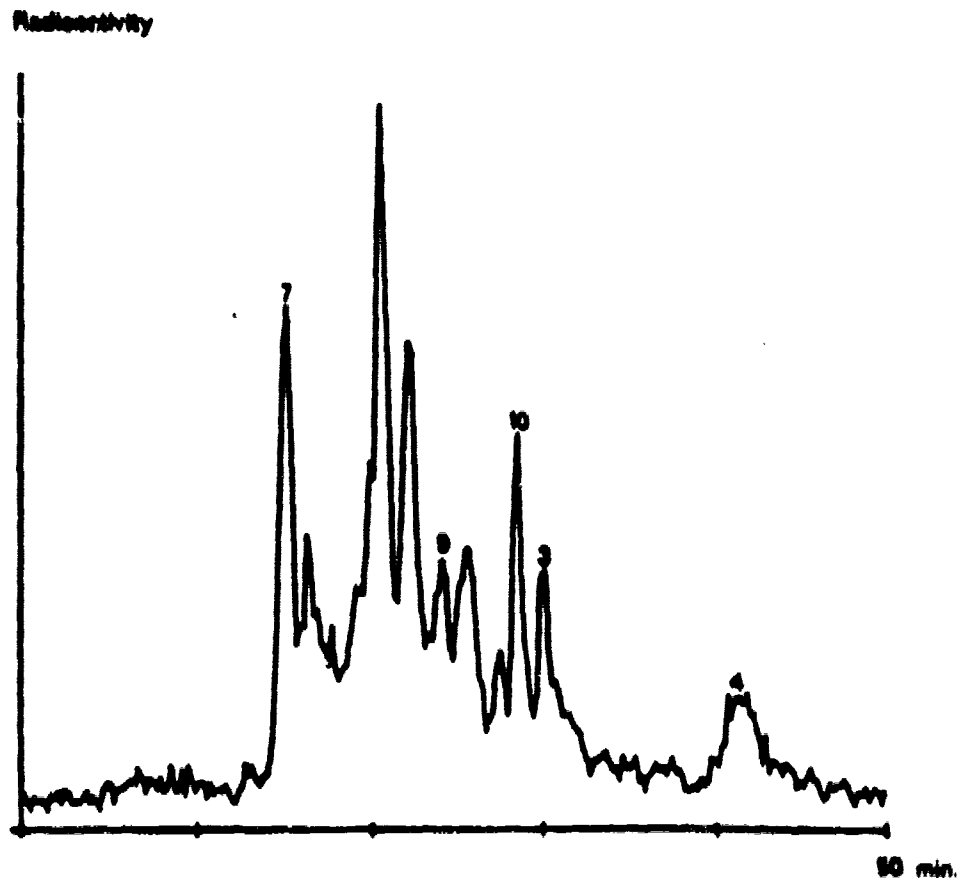
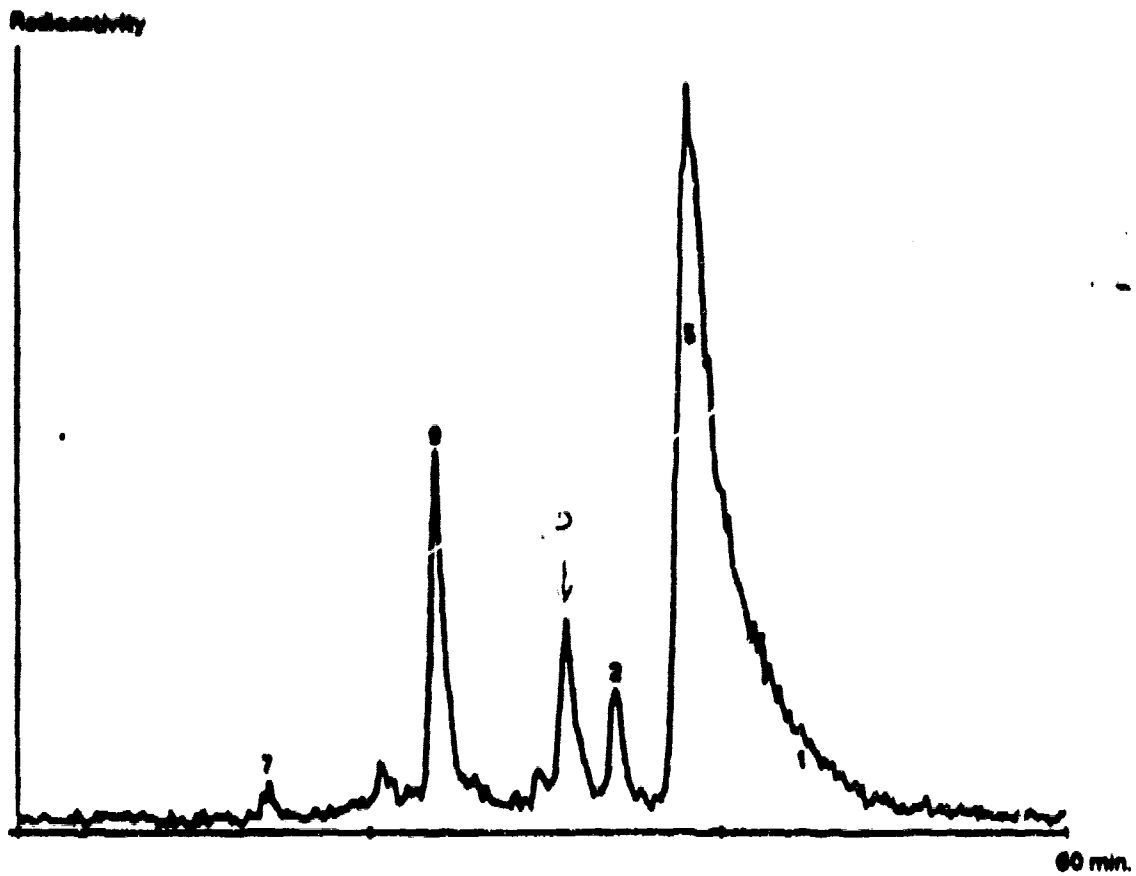


Fig. 4 Metabolite pattern of [^{14}C]DS 103-282 in the rat
hepatocyte incubation medium; c.f. 2.3.8.1.
(HPLC conditions I).



3. Metabolism in Dogs/Sandoz-Switzerland 1980/Report#303-025/vol
1-20
Batch#RA425-3 for the ¹⁴C label.

Methods:

Beagle dogs (mean body wt 11 kg; sex NR) were orally dosed with ¹⁴C-tizanidine at 3 or 4.5 mg/kg. Blood was collected at 1, 2, and 3 hr postdose and 24-hr urine samples were also collected. Quantitation and identification of metabolites were done similar to the other biotransformation studies in rodents, by HPLC and NMR/MS.

Results:

Following 3 mg/kg dose, 60±15% of total radioactivity was eliminated in urine. The parent compound was detected in plasma (12%) and urine (3%) (table 1). Two main metabolites were detected in plasma: metabolite 8 (33%) and 4 (23%), the former however, could not be isolated but its chromatographic properties were compared with those of the synthesized compound. Metabolite 8 could not be detected in urine but #4 accounted for 32% of radioactive dose. Metabolite #3 was present in plasma at low levels of 11% and urine at 5%. Only trace amount of metabolite #10 (3%) was detected in plasma; none in urine. It was indicated that #10 could not be isolated due to the insolubility of the compound therefore, the chemical structure remained unknown. Total plasma radioactivity (1-3 hr pool) accounted for 90% of administered dose and the urine (0-24 hr) accounted for 52%. In terms of concentration the following was calculated in plasma: metabolite 8 131 ng/ml, #4 60 ng/ml, and for #3 and parent, the F value was 33 ng/ml (table 2). The pattern of metabolites in dog plasma is presented in fig. 1 as determined by HPLC.

It is concluded that after single oral administration of radioactive tizanidine to the dog it is metabolized by either oxidation of the imidazoline ring and produce metabolite #4 in plasma, or oxidation of the aromatic ring and production of metabolite #8 (sulfate conjugate). These biotransformation pathways are similar to those proposed in rodents.

1 DOZ
Table 3 Percentages of the different metabolites of DS 103-282 in the plasma and the urine of dogs after oral doses of the radiolabelled drug

	Dose mg/kg	Metabolite										total accounted for
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>		
Plasma 1 - 3 h pool	4.5	11.5	--	11.0	23.3	--	4.0	33.2	4.2	3.0	90.2	
Urine 0 - 24 h pool	3.0	2.9	2.7	5.4	31.7		3.7	--	5.1	--	51.5 (31% dose)	

14-C-08 103-282 : Metabolism in dog

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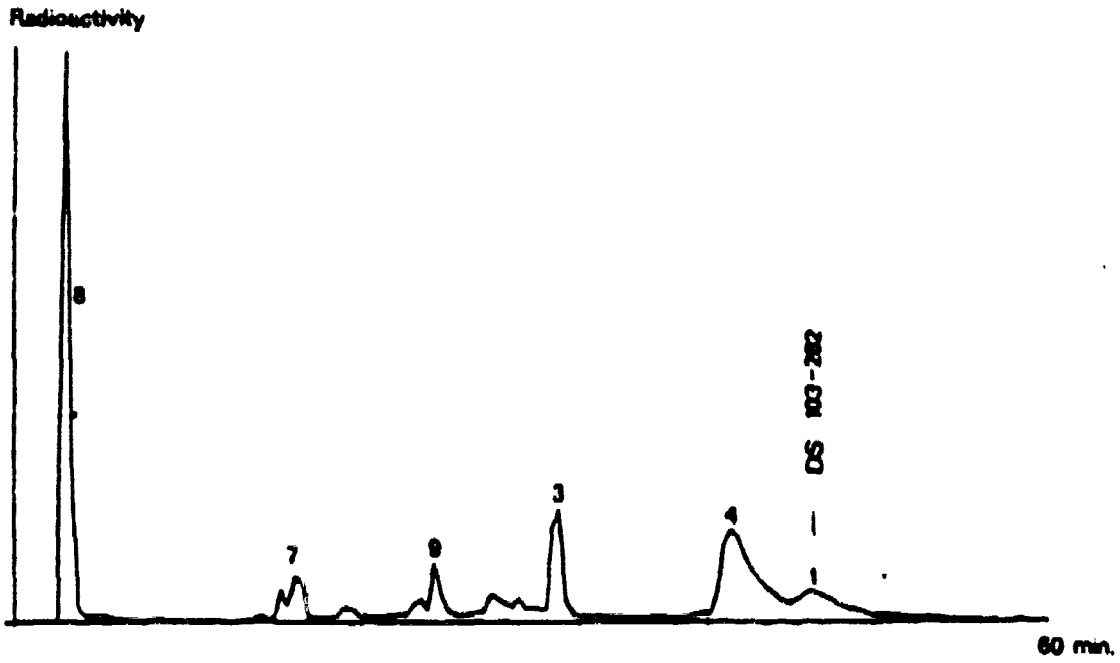
2
 Table 10 Concentration of DS 103-282 and its metabolites in dog plasma and urine after single oral doses of [¹⁴C]DS 103-282 (for doses c.f. Table 9)

Metabolite	Molecular weight	4.5 mg/kg	3 mg/kg
		Plasma (ng/ml)* (1-3 h pool)	Urine (µg/ml) (0-24 h pool)
<u>1</u> (103-282)	253.71	33.0	8.3
<u>2</u> (200-715)	269.71	----	8.2
<u>3</u> (200-717)	267.70	33.3	16.4
<u>4</u> (201-341)	227.68	60.0	
<u>5</u> (200-716)	251.70	----	81.6.
<u>7</u>	445.84	20.2	18.7
<u>8</u>	349.78	131.4	----
<u>9</u>	414.90	19.7	23.9
<u>10</u>	253.71	8.6	----
tot. radioactivity		287 ng-equiv./ml*	15.77 µg-equiv./ml

*) F-value = $\frac{\text{concentration (dpm/g plasma)}}{\text{dose (dpm/g body weight)}} = 0.064$

HPLC

Fig. 1 Metabolite pattern of (¹⁴C)DS 103-282 in dog plasma (1-3 h pool) after an oral dose of 4.5 mg/kg



4. Metabolism in Rabbits/Sandoz-Switzerland 1980/Report#303-025/vol 1-20
Batch#RA425-3 for the 14C label.

Methods:

Two male rabbits (Swiss hase) (mean body wt 2 kg) were orally dosed with 14C-tizanidine at 2, 4, or 50 mg/kg. Blood was collected after 0.5 hr postdose and 0-24 hr urine samples were also collected. Identification and quantification of metabolites were done by HPLC and NMR/MS.

Results:

Cumulative urinary excretion reached 54% after 48 hr. (dose 50 mg/kg) and 40% after 24 hr (dose 2 mg/kg). There were 2 main plasma and urine metabolites: metabolite 7 with 37% of radioactivity in plasma and urine and metabolite 9 at 26% in plasma and 20% in urine. The concentrations of these 2 metabolites in urine were 415 and 205 ug/ml. In plasma only, these other metabolites were detected: #10 at 11%, #3 at 4%, #4 at 1%; these metabolites were found after 4 mg/kg dose.

It is concluded that tizanidine undergoes 2 metabolic transformations: the major one is aromatic ring oxidation to produce metabolites #7 and 9 in plasma and urine, and a minor pathway e.g. oxidation of imidazoline ring to produce small amounts of metabolites 3 and 4 in plasma only. In general, the metabolic pattern of tizanidine in the rabbit is similar to that in other species.

Plasma Protein Binding:

Sandoz-Switzerland 1979/Report# 303-004/vol 1-20
Batch# RA 299-3 for 3H- and RA 425-1 for 14C-label.

Methods:

3H-labeled tizanidine was used for in vitro and 14C-labeled was used for in vivo. The drug was dissolved in isotonic phosphate buffer to give concentrations ranging between 20 ug/ml to 2 ng/ml and unlabeled compound was added in some cases to achieve concentrations up to 500 ug/ml. For the in vitro assays, freshly heparinized blood was collected from rats and cattle and fresh blood from humans. For the in vivo assay, blood was collected from 10 rats 2 hr post oral dose of 1.5 mg/rat (mean radioactive concentration in these samples was 0.57 ug equiv/ml in plasma and 0.86 ug equiv/ml in blood. The binding and distribution in blood were studied by equilibrium dialysis.

Results:

Distribution of tizanidine in blood-in vitro experiment, did not show species differences and was not affected by total drug concentration in the range of 13 ug/ml and 1 ng/ml. In whole blood free fraction of tizanidine averaged 30% in plasma water, 60% in

blood cells, and only 10% in plasma proteins. In the in vivo study, distribution of tizanidine was similar to that in vitro. No differences noted in plasma protein binding in humans and rat (about 30%), higher values in bovine (40-50%) may reflect higher protein concentration. No differences in plasma protein binding was found between the in vivo and in vitro assays indicating similar binding affinities of tizanidine and its metabolites in plasma.

It is concluded that protein binding is low (at therapeutic concentrations of <20 ng/ml 30% was bound in human plasma). At high concentrations protein binding was reduced indicating saturation of binding sites. There was no differences in binding between species. The drug uptake into RBCs was independent of concentration. The in vivo results were similar to those in vitro indicating that both the drug and its metabolites have similar binding affinities to plasma proteins.

Summary of PK Studies:

Tizanidine ADME was studied in the mouse, rat, dog, and rabbit by the oral and parental routes of administration. Doses ranged between 0.03 to 8 mg/kg except for 2 metabolism studies that used 50-330 mg/kg (the clinical dose is 0.72 mg/kg). There were no sex differences in PK parameters in any of these species. Orally, tizanidine was well absorbed with absolute bioavailability range of 70-110% calculated using AUC values after oral and i.v. dosing. Following oral administration the drug was detected within 0.25 hr with mean peak plasma levels of total radioactivity of 0.1-0.64 (F-value) after oral or i.v. dosing. These maximum blood levels were reached at 0.75 hr (T_{max}) in the mouse and rat and at 2.25-3 hr in the dog. After an i.v. infusion of 0.2 mg/kg to monkeys, mean maximum plasma tizanidine was 20 ± 5.5 ng/ml. This value was lower than that of clonidine administered at the same dose and by the same route (29 ± 1.5 ng/ml). Tizanidine is weakly bound to plasma proteins (30% for the rat and 40-50% in bovine plasma proteins). Because of this weak binding, tizanidine is not expected to displace other drugs that are highly plasma protein bound i.e. low drug-drug interaction. Binding appeared to be saturable at high plasma levels (>300 ng/ml). From radiolabelled in vivo and in vitro rat studies it was found that both the parent and metabolites have similar plasma protein binding properties.

The drug is widely distributed to tissues with concentration range (F-value) of 0.17-0.91 after oral and 0.55-2.5 after i.v. dosing. There was no sex difference in tissue distribution. Highest radioactivity was in the liver and kidneys measuring upto 1.5x higher than plasma levels at a given time. Whole-body autoradiography in pigmented mice showed very high to high radioactivity in nerve endings of olfactory nerve, brain, liver, kidneys, eyes, skin, and seminal vesicles; pattern of distribution

was similar after i.p. and p.o. dosing. Radioactivity remained detectable at 48 hr specifically in olfactory nerve endings, eyes, s.c. fat, and liver. The high radioactivity in olfactory nerve endings could not be explained. Macroautoradiography of single dose ¹⁴C-tizanidine was tested in pregnant rats (gd 16) at 7 mg/kg and repeated 10-day dosing in males at the same dose. Radioactivity after the single and repeated dosing was highest in stomach, bladder, kidney, and liver; medium levels of radioactivity were detectable within 1 hr in lungs, blood, placenta and other tissues, and only trace levels in fetus and brain. After 24 hr of dosing, low levels were detectable in the liver and traces in the amnion and high levels remained in the GIT. Tissue accumulation did not occur. In another study, tizanidine was found in rat milk following oral dosing to lactating rats (8-13 day post parturition). Peak levels of total radioactivity were reached at 8 hr in milk compared with 2 hr in plasma and were higher in milk at 8 and 24 hr periods than those in blood or plasma (the reverse was true at 1 hr). The milk/plasma ratio of 24 hr AUC was 2 and transport appeared to occur via non-ionic passive diffusion. It is noted that drug levels in milk were 10x lower than those in kidneys and liver. The sponsor estimated maximum intake of tizanidine by an infant to be 0.7% of adult dose based on milk/plasma ratio of 1.8 and milk intake of 1 liter/day). Pregnant rabbits were orally administered 3 mg/kg ¹⁴C-tizanidine during gd 6-18. Highest radioactivity of 17 ug equiv/g was measured after 2 hr of dosing (gd 10/5th dose) in the liver and 6 ug equiv/g in kidneys and in the blood the value was 0.657 ug equiv/g. Lower levels were detected in corpora lutea, uterus, placenta, ovaries and fetus. Except for the fetus, radioactivity was stable on gd 14 and 18 (fetus levels declined 70% on gd 18). Elimination half lives were calculated as 31 hr for the blood and 52 hr for the liver, shorter in amniotic fluid and fetus at 16-25 hr. Fetal to placenta ratios were 1 and 0.31 on gd 10 and 18 respectively, and the corresponding values for amniotic fluid to placenta were 0.33 and 0.27. This decline in radioactivity with time may be related to more efficient clearance in the fetus and/or decrease in transport of the parent drug and/or its metabolites across the placenta. It is clear from these studies that tizanidine and/or its metabolites crosses the placenta into the fetus and appear in milk. Tizanidine was shown to readily cross the BBB in rats in vivo with high extraction across the cerebral capillaries.

Tizanidine is mainly eliminated in the urine. About 50-70% of total radioactive dose was eliminated in urine at 24 hr and 11% in feces. Some excretion (29% at 0-72 hr) occurred via the bile as determined in bile-fistula rats. Elimination was almost complete (>95%) by 96-168 hr postdosing. Plasma elimination half lives ranged between 1.5-5 hr in mouse, rat, and rabbit but was long in the dog upto 110 hr; the half life in humans is 22 hr.

Tizanidine biotransformation involves one or more of the following metabolic pathways (attached fig.):

1. Oxidation of the aromatic ring to form metabolites:
 - #6 (hydroxy derivative)
 - #7 glucuronide conjugate of #6
 - #8 sulfonate derivative (never isolated)
 - #9 mercapturic acid derivative

2. Oxidation of the imidazoline ring to form metabolites:
 - #2 (hydroxy derivative)
 - #3 (keto derivative)
 - #4 (guanidine derivative)
 - #5* (imidazol-amino derivative)

3. Oxidation of the sulfur atom to form metabolite**:
 #10 (sulfone derivative)

* isolated from rat hepatocyte preparation and detected in rat urine. It is unclear if this compound is a real metabolite or a degradation product of #2 which is a chemically labile compound that can be dehydrated to form metabolite #5.

** In early studies (report#303-027 1980) this metabolite could not be isolated due to rapid polymerization and instability in alkaline solutions (pH 8) and neither NMR nor MS could detect it. In a more recent report (#303-045 Sandoz 1986), more stable conditions allowed isolation of metabolite #10 from rat urine without degradation. Male Wistar rats were orally dosed 100 mg/kg of 14C-labelled tizanidine, blood collected 1 hr postdose (maximum radioactivity in plasma) and urine was collected for 48 hr. NMR/MS-IR spectroscopy were used for structure elucidation. Two-step process was involved in S-oxidation: intermediate sulfoxide 10a and introduction of a 2nd oxygen to form the sulfone metabolite 10.

It was concluded that in addition to the 2 oxidation pathways (#102 above), tizanidine undergoes a 3rd S-oxidation pathway. This pathway was shown to be the major biotransformation pathway in rats and an important one in humans.

Attached tables (from the sponsor) compare tizanidine metabolites in various animal species and humans.

The following are plasma levels of the parent and metabolites measured after a single oral dose in mice and dogs:

Metabolite	C _{max} (ng/ml)
<u>Mouse:</u> Dose 4 mg/kg	
1	119
4	34
7	69
8	44
9	927

Dog Dose 4.5 mg/kg

1	33
3	33
4	60
7	20
8	131
9	20
10	9

Comments on PK Data:

There was not enough detailed information in any study and the reporting of results was poor. For example detection limit of the analytical methods was not reported, plasma levels in almost all studies were expressed as ug equiv/g blood instead of the usual unit of mass per volume, some inconsistencies between text data and data in tables, some HPLC peaks were not identified.

Toxicology

Acute Toxicity Studies:

Table below (from the sponsor) summarizes all single dose studies.

Acute Toxicity Studies Performed with Tizanidine

Toxicology

Acute Toxicity Studies:

Table below (from the sponsor) summarizes all single dose studies.

Species/ Strain/ Source	Route of Admin.	No. Animals [Age]	Dose Range (mg/kg/day) [Volume]	Vehicle	LD ₅₀ (95% CI) (mg/kg)	Dose (mg/kg)	Time of Death	Deaths M F	Toxic Signs	Ref. No./ Laboratory
Mouse/ OF1/ Sandoz	gavage	30M/20F [NS]	100-420/ [25 mL/kg]	2% gelatin solution	24h: 271 (229-337) 7d: 235 (201-278)	420 300 240 180 130 100	5 min - 2 days 5 min - 2 days 8 min - 2 days 12 min 18 h - 3 days NA	5/5 5/5 5/5 2/5 3/5 0/5 1/5 0/5 2/5 0/5 0/5 0/5	Anaemia, convulsions, dyspnea, hypotension, heparin, motor excitation, mydriasis, epithelium, piloerection, tremors	43/Sandoz, Beul
Mouse/ OF1/ Sandoz	iv	20M/20F [NS]	30-75/ [25 mL/kg]	Distilled Water	24h: 52 (43-62)	75 56 42 30	30 sec - 2 min 40 sec - 3 days 50 sec - 2 min 4 min	5/5 5/5 5/5 1/5 3/5 0/5 1/5 0/5	Convulsions, drowsiness, dyspnea, heparin, piloerection	43/Sandoz, Beul
Rat/OFA/ Sandoz	gavage	30M/20F [NS]	240-1000/ [10 mL/kg]	2% gelatin solution	24h: 859 (738-1133)	1000 750 560 420 300 240	30 min - 2 days 1 hr - 3 days 1.5 h - 7 days 2 days NA NA	3/5 5/5 2/5 5/5 2/5 4/5 1/5 1/5 0/5 0/5 0/5 0/5	Aggressiveness, blood clotted nostrils, convulsions, cerebral opacity, drowsiness, dyspnea, hypocoelivision, hepatobulimia, motor excitation, tremors	43/Sandoz, Beul
Rat/OFA/ Sandoz	iv	20M/20F [NS]	18-100/ [10 mL/kg]	Distilled Water	24h: 48 (34-69) 7d: 46 (33-62)	100 56 20 18	30 sec - 1 min 1 min - 3 days 2 min - 10 min 10 min	5/5 5/5 3/5 2/5 3/5 0/5 1/5 0/5	Convulsions, drowsiness, dyspnea, hypocellia, heparin, piloerection	43/Sandoz, Beul
Rabbit/ Silver Fox	gavage	9M/9F [NS]	56-180/ [5 mL/kg]	2% gelatin solution	24h: 122 (74-372) 7d: 98 (66-154)	180 100 56	3 h - 2 days 6 h - 2 days 18 h	3/3 3/3 1/3 1/3 1/3 0/3	Drowsiness, dyspnea, mydriasis, piloerection, prnas position, sedation, tremors	43/Sandoz, Beul
Rabbit/ Silver Fox	iv	9M/9F [NS]	18-30/ [1 mL/kg]	Distilled Water	24h: 23 (20-25) 7d: 77 (20-25)	30 24 18	1.5 h - 12 h 7 h - 24 h NA	3/3 3/3 1/3 3/3 0/3 0/3	Anaemia, convulsions, drowsiness, dyspnea, hypocoelivision, heparin, mydriasis, epithelium, piloerection, prnas position, sedation, tremors	43/Sandoz, Beul
Dog/ Beagle/ Marshall	iv	1 either sex	0.03-1.0/ (0.005-0.167 mL/kg)	Placebo	NA	NA	NA	none	No effect at 0.03 mg/kg, dose- dependent sedation, piloerection, bradycardia. Prolonged PQ interval at 1 mg/kg	44/Sandoz, Beul

CI = confidence interval; M = male; F = female; iv = intravenous; h = hour; d = day; sign. = significant; NS = not significant in report

Subchronic Toxicity Studies:

Attached table (from the sponsor) presents all subchronic multiple dose studies and their results.

TABLE 2
Subchronic/Chronic/Carcinogenicity Studies Performed with Tizanidine

6 Week Intraperitoneal - Rat ¹ (Reference 45)					
Dose (mg/kg/day)	Clinical Examination	Clinical Pathology	Macroscopy	Histopathology	
0.3	Wet genital area	No relevant findings ¹	No relevant findings ¹	No relevant findings ¹	
1.0	Wet genital area, slight mydriasis, slight piloerection, distinct sedation	Glucose in urine (3/8 females)	No relevant findings ¹	Hemosiderin in pulmonary macrophages	
3.0	Death of 1 animal; slight inhibition of weight gain and food intake (males), weight loss (females); wet genital area, severe sedation, piloerection, slight mydriasis, slight hypersalivation, slight exophthalmos, irregular breathing; reduced eye movements, dry cornea	Glucose in urine, slightly lower urine volume	No relevant findings ¹	Hemosiderin in pulmonary macrophages, congestion of pulmonary blood vessel, bronchial exudation	
6-Week Intravenous - Dog ¹ (Reference 46)					
Dose (mg/kg/day)	Clinical Examination	Clinical Pathology	Macroscopy	Histopathology	
0.03	Dry mouth, hypersalivation, slight sedation and equilibrium disturbance, sporadic emesis (1/5 animals)	No relevant findings ²	No relevant findings ²	No relevant findings ²	
0.1	Dry mouth, hypersalivation, pale mucous membranes, distinct sedation, equilibrium disturbance, abnormal posture, sporadic emesis (2/6 animals)	No relevant findings ²	No relevant findings ²	No relevant findings ²	
0.3	Dry mouth, hypersalivation, pale mucous membranes, prolapse of the tongue, distinct sedation, equilibrium disturbance, abnormal posture, sporadic emesis (4/6 animals)	Slightly elevated SGPT	No relevant findings ²	No relevant findings ²	

¹ Findings were reversible during the 4 week recovery period
² No relevant findings as compared to the control animals
³ No symptoms in recovery animals as of first day

TABLE 9
(Continued)

13-Week Oral - Rats¹ (Reference 47)					
Dose (mg/kg/day)	Clinical Examinations	Clinical Pathology ²	Necropsy	Histopathology	
1.7	Slight inhibition of weight gain and food intake in females.	No relevant findings ²	No relevant findings ³	Increased activity of salivary glands, possible hypoplasia of mammary tissue, slightly decreased activity in thyroid tissue.	
8	Distinct inhibition of weight gain and food intake. Slight miosis (f-males). Slight pilorecression (females).	Slight decrease in blood glucose, slight increase in BUN	No relevant findings ³	Increased activity of salivary glands, possible hypoplasia of mammary tissue, slightly decreased activity in thyroid tissue, increased incidence of prostatic.	
40	Death of 1 animal, premature sacrifice of another (poor health). Severe inhibition of weight gain (males), weight loss (females). Inhibition of food intake. Miosis, wet perineal region, aversion to touch, occasional convulsions (some females), dermatitis, corneal opacity (2/3 females)	Slight reduction of lymphocytes, corresponding increase in neutrophils. Slight decrease in blood glucose, slight increase in BUN, increased SGPT.	Skin defects (3 males).	Increased activity of salivary glands, possible hypoplasia of mammary tissue, slightly decreased activity in thyroid tissue, increased incidence of prostatic, focal and single cell necrosis in heart and liver (some animals).	
13-Week Oral - Dogs (Reference 48)					
Dose (mg/kg/day)	Clinical Examinations	Clinical Pathology ²	Necropsy	Histopathology	
0.3	Slight slowing of the heart rate 2 hours after administration, persisting, in some cases, for 24 hours	No relevant findings ²	No relevant findings ³	No relevant findings ³	
1	Slight sedation during week 1 - 10, slight reduction in body temperature, slight slowing of heart rate. ECG: slightly prolonged QRS and QT intervals	No relevant findings ²	No relevant findings ³	MGI inflammatory infiltrations in liver (2/4 dogs)	
3/4 ⁴	Sedation, occasional vomiting, slight stasis, reduced body temperature, markedly reduced heart rate, reduced CNS responsiveness. ECG: slightly prolonged QRS and QT intervals.	Slightly increased alkaline phosphatase (1/4 dogs). SGPT at upper limit (1/4 dogs).	No relevant findings ³	MGI inflammatory infiltrations in liver (3/4 dogs)	

¹ Findings were reversible during the 4 week recovery period

² No relevant findings as compared to the control animals

⁴ Since toxicity was no longer observed after week 10, the dose was increased from 3 to 4 mg/kg/day

Chronic Toxicity Studies:

Only one chronic toxicity study was conducted. A 52-week oral dog study tested tizanidine at 0.15, 0.45, and 1.5 mg/kg dose. There were no significant gross or histopathological changes at any dose and most of the clinical signs occurred in HD (see Dr. Wilk's review in Appendix A).

CARCINOGENICITY

Mouse Carcinogenicity:

Study# 197M vol 1.12

Lab: Sandoz/Basle Switzerland/Report# 203-019/Mar 1980.

Species/No./sex: OF-1 (Sandoz SPF breed)/8-wk old/50/sex/dose/body wt. males: 23-39 g; females 19-27 g.

Dose/duration: 0, 1, 4, 16 mg/kg/d* for 78 wks.

Batch/lot#: 74901/analysis No. 7460102

* basis for dose selection was not provided; a 3-month dose-range finding or any other subchronic mouse study was not conducted.

Methods: mice were individually housed in type I Macrolon cages with sawdust bedding. The drug was mixed with feed and concentration was adjusted weekly. A separate study was done to accurately measure drug intake expressed as mg/kg/d.

The following parameters were assessed: general examination (daily), clinical signs and behavior (daily 1st wk, then weekly), visible/palpable masses (weekly), body wt (weekly), and at study end: hematology and necropsy. Histopathology was done on: lung, stomach, thymus, mediastinal and mesenteric lymph nodes, liver, spleen, ovaries, uterus, testes, prostate, urinary bladder, brain, pituitary, and any tumor-suspected tissue. Drug-exposure were not measured at any time period during the carcinogenicity assay.

Statistics: Fisher's exact test and the method of Peto et al. (1980) were used to assess differences between types of tumors, and percentage differences were calculated for the more commonly occurring tumors based on numbers of organs in each group submitted to histological examination.

Comment: Food intake, urinalysis, ophthalmoscopy, and clinical chemistry were not conducted.

Results:

Mortality: (table below from the sponsor): no difference in mortality rate or onset was found between treated and control groups.

Animals which died spontaneously or were killed due to poor general condition.

Week	Controls		DS 103-282 mg/kg/day					
	♂	♀	♂	♀	♂	♀	♂	♀
1 - 10					1			
11 - 20				1				
21 - 30		1	1					1
31 - 40	1	1	3		1	2	1	2
41 - 50	2	5	1	5	3	3	4	1
51 - 60	8	2	4	2	3	9	3	5
61 - 70	3	6	8	10	6	5	7	7
71 - 80	9	10	9	10	3	3	2	9
dead animals	23	25	26	28	17	22	17	25
%	46	50	52	56	34	44	34	50
Total dead animals	48		54		39		42	
%	48		54		39		42	

There was no drug dependent influence on the mortality rate

Clinical signs: none at 1 and 4 mg/kg. At 16 mg/kg the following signs were contributed to the drug: piloerection (end of wk 1), and self-inflicted wounds (end of wk 1) in 7m and 9f (wounds healed in 12/16 animals by treatment wk 18). Corneal opacities (wk 4) and ear necrosis (wk 13) occurred in both treated and control groups. Corneal opacities were more prominent in males than in females (table below). A dose-dependent increase in the frequency of these lesions was noted when these lesions were combined in m and f.

Total number of animals affected throughout the experiment:

Group	Corneal Cloudiness				Ear necrosis			
	K	A	B	C	K	A	B	C
Males	17	26	23	26	11	7	5	3
Females	6	4	11	12	4	3	6	5

Body weight: no drug effect at 1 and 4 mg/kg. Males in HD had lower body weight than the corresponding controls throughout the study but this decrease was not significantly different (figures attached).

Hematology/ (conducted on 10/sex/dose): extensive leukocytosis was found in 2HD (1m and 1f) mainly due to an increase in lymphocytes. In one mouse (HDm) there was also an increase in neutrophils and monocytes, and agranulocytosis in the HDf mouse. In both mice, the lymphocytes were partially polymorphous or immature forms and many Gumprecht's shadows. One control mouse although had normal leukocyte count, had few neutrophils, and slight reticulocyte increase (10%). Some animals in all three treated and control groups had slight to moderate anemia. Other changes included a significant 12% increase in Hct of HDm and a high but nonsignificant increase (168%) in WBC was observed in HDf (SD in both the control and HD was very high) (value ranges in control m 2-14 and f 2-9; the corresponding ranges in treated HDm 3-78 and f 2-67). The following are the incidences of anemia and leukocytosis:

	control	LD	MD	HD
anemia	5/10	2/10	2/10	1/10
leukocytosis	0/10	3/10	1/10	3/10*

* two of these animals had severe lymphocytic leukocytosis.

Gross Morphology: no findings.

Histopathology: the sponsor stated that answers to the following 5 questions would allow evaluation of the carcinogenic potential of the drug:

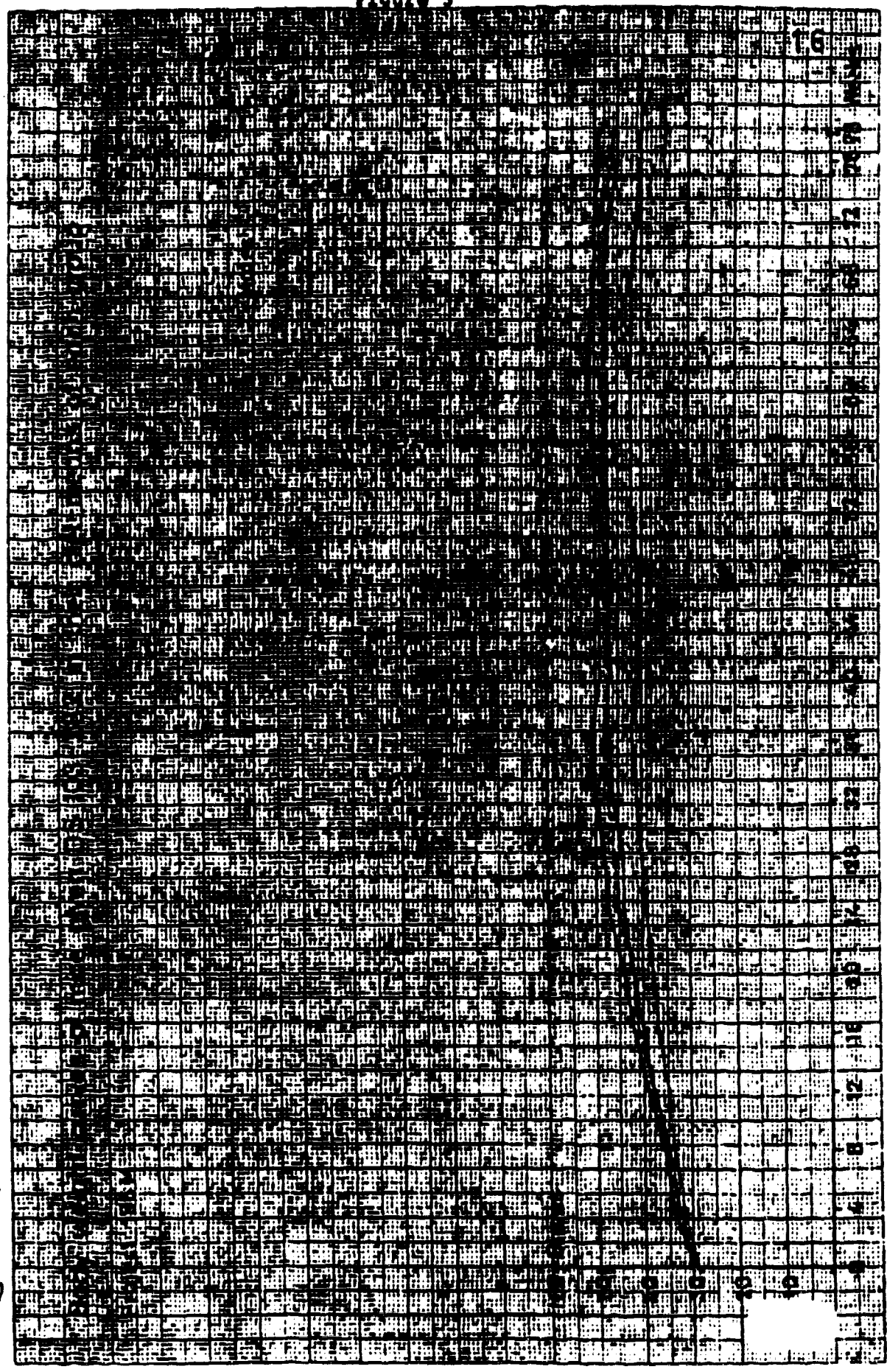
1. is there an increased incidence of tumors in treated mice?
2. do tumors in treated mice occur earlier than in controls?
3. are the tumors in treated mice not present in controls (tumor spectrum)?
4. were there any non-tumor findings that interfered with tumor evaluation?
5. is the species/strain suitable for this study?

Answers to these questions concluded that 103-282 is not a carcinogen in mice. Tumors were assessed in mice that died during the study, killed at end of study, and the cumulative incidences. The type of tumors most commonly found included: lymphoreticular>pulmonary>liver (tables 1&2). Total number of mice with lung tumors (adenomas) was higher in all three male mice groups relative to the control (tables 3-6). Tumors found in treated but not in control mice (except as noted) are:

Tizanidine NOA 20 - 377 mouse carcinogenicity study

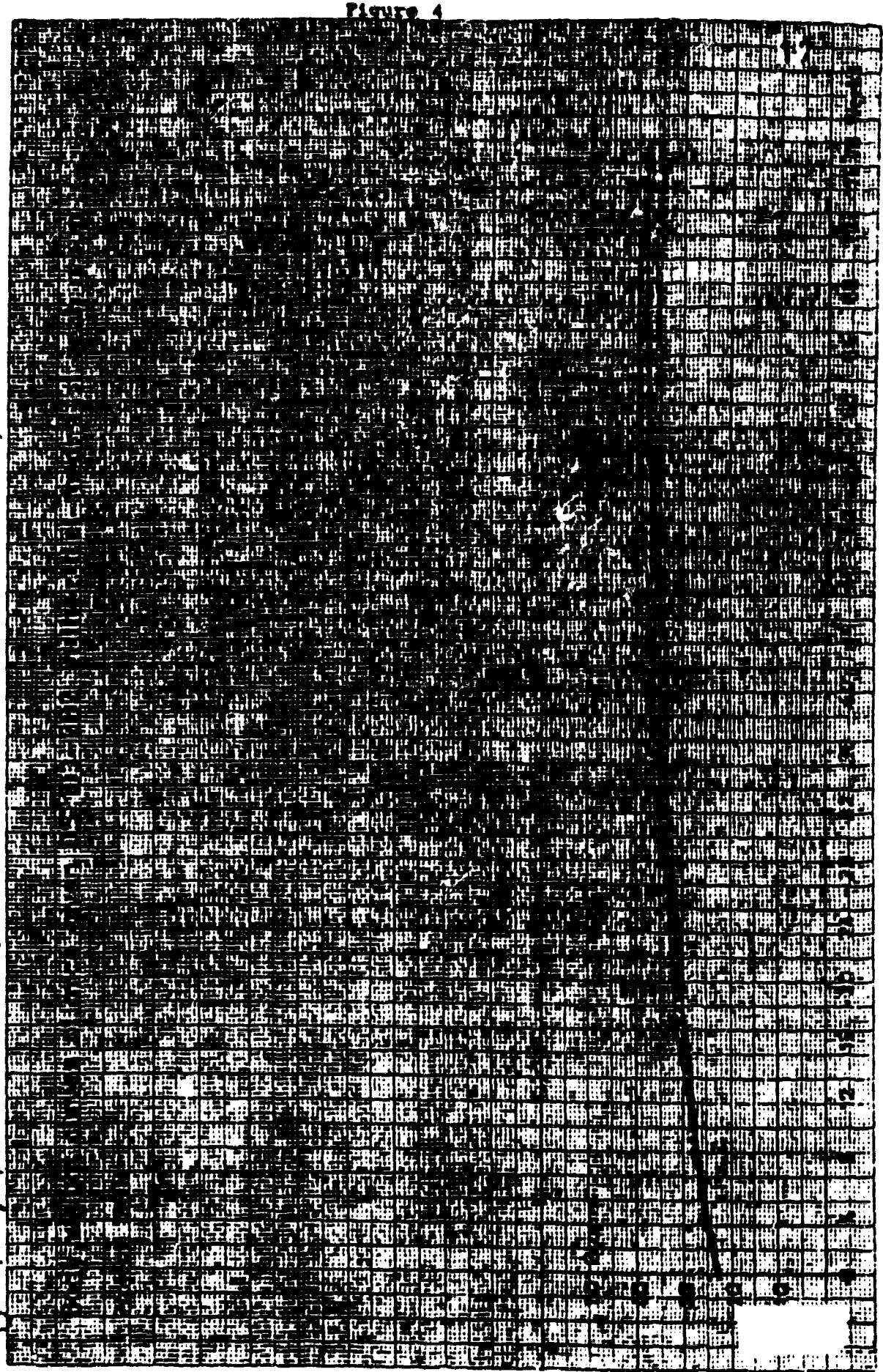
Body wt. of male mice given 103-282 in diet for 78 wks.

FIGURE 3



T1201idine NDA 20-397 mouse carcinos. study

Body wt. of female mice given 103-282 in diet for 78 wks-



	LD	MD	HD
Mammary gland adenocarcinoma	2f	2f	1f
Lacrimal gland adenocarcinoma	1f	-	-
Jejunum adenocarcinoma	-	1m	-
Bone hyperplasia	1m/3f	3m/1f*	7f
Pituitary hyperplasia	-	1f	-
Forestomach papilloma	1m	-	-
squamous cell carcinoma of the stomach	-	-	1m

* 2f control group

Historical data were not provided. The sponsor however, indicated that the overall tumor incidence in the present study was slightly higher than the historical data obtained from a previous study. But the sponsor indicated that the incidence and types of tumors in the control group were similar to those reported for mouse strains used in carcinogenicity studies (supportive data were not presented).

Statistical Analysis by the Sponsor:

The sponsor re-analyzed and re-represented the carcinogenicity data for mice and rats (see the rat study to follow) after the comments from the Canadian Health Protection Branch (NDS HN-8281 June 1981). The Health Protection Branch requested summary tables of a specific format of all neoplastic and pre-neoplastic lesions. In the mouse study, the sponsor re-examined slides and raw data were re-analyzed specifically those for hepatic proliferation and incidence of hyperplastic lesions. Hyperplasias were not reported in the original study but were found by the pathologist during examination of the raw data. Also, malignant liver tumors were confirmed after re-examining data from 15 control males. The lesions and combinations of lesions that were statistically analyzed included:

- Lung (pulmonary tumors)
- Hematopoietic system (all tumors and all tumors + lymphoid hyperplasia)
- Liver (hepatocellular and hepatocellular tumors + hyperplasia)
- Bone (hyperplasia)

Statistical analyses of mortality and lesion incidence in rats and mice were presented in a subsequent report by Sandoz in Dec 1984 (84-SAS023-702 vol. 1.15). For mortality analysis, Cox's test for homogeneity between groups was used and Tarone's test for trend was also used. The pathology data were analyzed by Peto method. Also single pair-wise comparison of control and HD mice was done. Results showed no significant difference in mortality incidence of either sex. A statistically significant difference in bone hyperplasia of HDf mice against the controls was found ($p < 0.027$) and a positive trend was also calculated ($p < 0.043$). A significant positive trend ($p = 0.043$) was found in bone hyperplasia in females

and a significant difference was also noted in incidence between the HD and control group ($p=0.027$). The sponsor indicated that since bone hyperplasia was not found in male mice and no osteosarcoma was detected in the mouse or the rat studies, the bone hyperplasia in female mice may not be a true drug effect. The reviewer is not in agreement with this argument and does not rule out a possible drug-related effect.

SUMMARY/CONCLUSION(■):

The basis for dose selection was not stated since a dose-range finding study was not conducted, and it is unknown why the study did not continue for recommended 2-yr duration.

Male and female mice were administered 103-282 by feed admixture at 1, 4, and 16 mg/kg/d for 78 wks. There were no clinical signs or any other drug-related changes at 1 and 4 mg/kg therefore, 4 mg/kg is considered a NOEL for general toxicity. At 16 mg/kg dose, piloerection and self-inflicted wounds were noted. A dose-dependent increase in the frequency of ear necrosis and corneal opacities was found when these lesions were combined in m and f. No change in body weight occurred in any group; food consumption was not determined. Extensive leukocytosis was found in 2HD (1m and 1f) mainly due to an increase in lymphocytes. In one mouse (HDm) there was also an increase in neutrophils and monocytes, and agranulocytosis in the HDf mouse. In both mice, the lymphocytes were partially polymorphous or immature forms and many Gumprecht's shadows. Other hematological findings were random and occurred in both control and treated groups. Tumors that were analyzed included lymphoreticular, pulmonary (lung adenomas), liver, and bone hyperplasia (perhaps pre-neoplastic) with incidences slightly higher (nonsignificant except for bone hyperplasia) than historical control data. Lesions found in treated but not control mice included adenocarcinomas of the mammary gland, lacrimal gland, and jejunum, forestomach papilloma, and squamous cell carcinoma of the stomach. Statistical analysis of the tumors revealed a significant positive trend in bone hyperplasia and a significant difference between HD and control group. However, the sponsor indicated that this is not a true drug effect since this lesion was not found in male mice and osteosarcoma was not detected in the mouse or the rat carcinogenicity studies.

From these data the sponsor concluded that 103-282 is not carcinogenic in mice at these doses. The reviewer however, can not rule out a drug-related effect for the bone marrow findings specially since historical data were not provided and that some hematology changes were found in males and females. It is noted that statistical analyses of tumors have not yet been conducted by the Agency because the sponsor is unable to provide the raw data on a disk for the Agency. As stated earlier, dose-ranging study was not done and from the general toxicity profile in this study, it seems that higher doses could have been tested in this bioassay.

Re-representation of neoplastic lesions & pre-neoplastic
for mice Sunday Research Report May 1984 (94)

Table 1
DS 103-282 78-weeks study in mice
Table of tumours and hyperplasias (males)

Numbers of mice with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 4 mg/kg/day		Group 4 16mg/kg/day	
	D	T	D	T	D	T	D	T
LUNG:								
-pulmonary tumour	5	10	8	13	3	21*	3	14
HEMATOPOIETIC SYSTEM								
-lymphoret. tumour	6	-	10	-	4	1	10	-
-lymphoma, lymphocytic	2	2	5	1	6	-	2	1
-reticulum cell sarcoma	3	4	2	8	2	8	1	5
TOTAL	11	6	17	9	12	9	13	6
-lymphoid hyperplasia	2	-	-	1	-	1	1	3
LIVER:								
-spatocellular tumour	6	10	6	13	1	13	-	10
-angioma	-	1	-	-	-	-	-	-
-hyperplasia	-	-	-	1	-	-	-	-
SKIN/SUBCUTIS:								
-infiltrative tumour	-	-	-	-	1	-	-	-
-sarcoma	1	-	-	-	-	-	-	-
KIDNEYS:								
-proximal cell adenoma	-	-	-	-	-	-	-	1
TESTES:								
-interstitial cell tumour	-	-	-	-	-	1	-	-
-Sertoli cell tumour	-	-	-	-	-	-	-	1
-hyperplasia	-	-	-	-	-	1	-	-
PROSTATE:								
-hyperplasia	-	-	-	1	-	-	-	-
STOMACH:								
-papilloma	-	-	1	-	-	-	-	-
-squamous cell carcinoma	-	-	-	-	-	-	1	-
-adenomatoid gastric hyperplasia	7	23	4	21	-	31	1	30

D=animals died or killed in extremis T=animals killed at termination
*statistically significant p < 0.05

Table 1 cont.
DS 103-282 78-weeks study in mice
Table of tumours and hyperplasias (males)

Numbers of mice with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 4 mg/kg/day		Group 4 16mg/kg/day	
	D	T	D	T	D	T	D	T
<u>INTESTINE:</u> -adenocarcinoma	-	-	-	-	1	-	-	-
<u>ABDOMINAL CAVITY:</u> -tumour (autolytic)	1	-	-	-	-	-	-	-
<u>BONE:</u> -hyperplasia	-	-	-	1	-	3	-	-
<u>MATL:</u> -indle cell sarcoma	-	-	-	1	-	-	-	-
Total number of mice with tumours	17	18	24	22	13	30	14	22
Total number of mice with malignant tumours	13	6	17	9	12	10	14	6
Total number of animals	23	27	26	24	17	33	17	33

D=animals died or killed in extremis T=animals killed at termination

Part of experiment on response to various + PL2-neoplastic data
for mice

Sandoz Research Report May 1984

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Table 1 cont.
DS 103-282 78-weeks study in mice
Table of tumours and hyperplasias (females)

Numbers of mice with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 4 mg/kg/day		Group 4 16mg/kg/day	
	D	T	D	T	D	T	D	T
<u>CERVIX:</u> -leiomyosarcoma	-	-	-	1	-	-	-	-
<u>VAGINA:</u> -leiomyosarcoma	2	-	1	-	-	-	-	-
<u>PITUITARY:</u> -hyperplasia	-	-	-	1	-	-	-	-
<u>STOMACH:</u> papilloma	-	-	-	-	-	-	-	1
-adenomatoid gastric hyperplasia	3	24	4	21	2	28	3	22
<u>BONE:</u> -hyperplasia	1	1	2	1	1	-	2	5
<u>EARS:</u> -hyperplasia	-	1	-	-	-	-	-	-
<u>EYES:</u> -adenocarcinoma (prob. lacrimal)	-	-	1	-	-	-	-	-
Total number of mice with tumours	22	16	23	16	20	18	23	13
Total number of mice with malignant tumours	20	12	21	10	20	14	21	9
Total number of animals	25	25	28	22	22	28	25	25

D=animals died or killed in extremis T=animals killed at termination

2

Table 4
 DS 103-282 78-weeks study in mice
 Table of tumours and hyperplasias (females)

Numbers of mice with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 4 mg/kg/day		Group 4 16mg/kg/day	
	D	T	D	T	D	T	D	T
<u>LONG:</u> -pulmonary tumour	2	4	8	5	-	7	5	6
<u>HEMATOPOIETIC SYSTEM</u> -lymphoret. tumour	6	-	8	-	11	-	11	-
-lymphoma, lymphocytic	2	2	5	-	3	-	3	2
-reticulum cell sarcoma	11	9	5	9	7	10	6	6
TOTAL	19	11	18	9	21	10	20	8
-lymphoid hyperplasia	2	1	4	1	-	1	2	6
<u>LIVER:</u> -hepatocellular tumour	1	2	1	-	1	2	1	-
<u>SKIN/SUBCUTIS:</u> -keratoacanthoma	1	-	-	-	-	-	-	-
-spindle cell sarcoma	-	-	-	-	-	-	1	-
<u>MAMMARY GLAND:</u> -adenocarcinoma	-	-	2	-	-	2	-	1
<u>PITUITARY:</u> -hyperplasia	-	-	-	1	-	-	-	-
<u>OVARIES:</u> -theca cell tumour	-	2	1	3	-	1	1	-
-granulosa cell tumour	-	-	-	1	-	1	-	-
-sarcoma	-	-	-	-	-	1	-	-
-hyperplasia	-	1	-	-	-	-	-	-
<u>UTERUS:</u> -leiomyosarcoma	-	-	2	-	-	-	-	-
-fibroma	-	-	-	1	-	-	-	-
-endometrial cystic hyperplasia	16	24	15	19	10	27	16	24

D=animals died or killed in extremis T=animals killed at termination

Mouse Carcinomas - NDA 20-397

DS 103-282 Mice, Died During Experiment

Project 196M

LUNG TUMORS

Lung Tumor Bearing Mice	Mice Bearing Single Adenoma	Mice Bearing 2 to 5 Adenomas	Mice Bearing 6 to 10 Adenomas	Total No. of Lung Tumor Bearing Mice in this Group
Dose K ♂	4, 20, 39	47	18	5
Dose K ♀	54, 73	-	-	2
Dose A ♂	111, 115, 123, 135, 142, 145	143	137	8
Dose A ♀	151, 160, 167, 172, 182, 190, 199	-	175	8
Dose B ♂	206, 247	233	-	3
Dose B ♀	-	-	-	0
Dose C ♂	302, 338, 345	-	-	3
Dose C ♀	351, 353, 376, 397	356	-	5

Table 5
3

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Mouse Lungs - NDA 20-397

DS 103-282 Mice, Died During Experiment

Project 196M

GRADING OF TUMORS

Lung Tumor Bearing Mice	Grade of Tumor 1	Grade of Tumor 2	Grade of Tumor 3	Grade of Tumor 4	Grade of Tumor 5
Dose K ♂	20, 39	4, 47	-	18	-
Dose K ♀	54, 73	-	-	-	-
Dose A ♂	111, 121, 142, 145	115, 123, 143	-	137	-
Dose A ♀	151, 167, 172, 182, 190, 199	160	-	175	-
Dose B ♂	206	233, 247	-	-	-
Dose B ♀	-	-	-	-	-
Dose C ♂	338, 345	302	-	-	-
Dose C ♀	353, 397	351, 366, 376	-	-	-

Table 6

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House Carcinog. NCA 02-97

DS 103-282 Mice, Killed at End of Experiment

Project 196M

LUNG TUMORS

Lung Tumor Bearing Mice	Mice Bearing Single Adenoma	Mice Bearing 2 to 5 Adenomas	Mice Bearing 6 to 10 Adenomas	Total No. of Lung Tumor Bearing Mice in this Group
Dose K ♂	3, 6, 14, 21, 27, 35	2, 31, 43, 44	-	10
Dose K ♀	64, 69, 70	52	-	4
Dose A ♂	106, 109, 113, 117, 118, 119, 124, 133, 150	105, 112, 125	127	13
Dose A ♀	158, 164, 171, 198	185	-	5
Dose B ♂	204, 207, 211, 213, 216, 222, 224, 230, 232, 234, 235, 236, 238, 245	226, 243, 244, 246	217, 242, 250	21
Dose B ♀	269, 274, 275, 298	258, 280	277	7
Dose C ♂	301, 304, 306, 309, 313, 319, 322, 328, 330, 331, 337, 342, 348	-	318	14
Dose C ♀	357, 365, 381, 393, 392	-	398	6

Table 5

Mouse Carcinoma - NDA 20-397

DS 103-282 Mice, Killed at End of Experiment

Project 196M

GRADING OF LUNG TUMORS

Lung Tumor Bearing Mice	Grade of Tumor 1	Grade of Tumor 2	Grade of Tumor 3	Grade of Tumor 4
Dose K ♂	14, 21, 27	2, 3, 6, 31, 35, 44	43	-
Dose K ♀	52, 69	70	64	-
Dose A ♂	106, 117, 118, 119, 133, 150	109, 113, 124, 125	112, 127	105
Dose A ♀	158, 171, 198	185	164	-
Dose B ♂	204, 207, 211, 224, 226, 230, 235	213, 216, 222, 232, 234, 236, 238, 243, 245, 246	244	217, 242, 250
Dose B ♀	258, 274	269, 275, 280, 298	-	277
Dose C ♂	309, 319, 322, 331, 348	302, 304, 306, 313, 328, 342	330, 337	318
Dose C ♀	365, 381, 393, 357	392	-	398

Table 8

Graded according to: Roe F.G.C. et al - The British Journal of Cancer 24, 107-120; 1970

Mouse carcinog.
NDA 20-397

DS 103-282 Mice Died During Experiment

Project No. 196 M

*
Numbers and percentage incidence of tumors

	Dose K ♂		Dose K ♀		Dose A ♂		Dose A ♀		Dose B ♂		Dose B ♀		Dose C ♂		Dose C ♀	
	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()	Mice with this pathol. ()	As % of ()
Mice bearing lympho-ret. tumours	11	(22) 50%	19	(24) 79%	17	(24) 70%	18	(24) 75%	12	(15) 80%	21	(21) 100%	13	(16) 81.2%	20	(24) 83%
Mice bearing liver tumours	6	(22) 27.3%	1	(25) 4.0%	6	(26) 23.1%	1	(26) 3.8%	1	(15) 6.7%	1	(21) 4.8%	0	(26) 0%	1	(24) 4.2%
Mice bearing lung tumours	5	(23) 21.7%	2	(24) 8.3%	8	(23) 34.8%	8	(26) 30.8%	3	(17) 17.6%	0	(20) 0%	3	(17) 17.6%	5	(25) 20%
Mice bearing other tumours	2	(23) 8.7%	3	(25) 12.0%	1	(26) 3.8%	5	(26) 19.2%	2	(17) 11.8%	0	(21) 0%	1	(17) 5.9%	2	(25) 8.0%

Table 2

* based on # of organs examined

K = control

A = low dose

B = mid dose

C = high dose

Mouse carcinog. NDA 20-397

DS 103-282 Mice Killed at End of Experiment
 Numbers and percentage incidence of tumors

Project No. 196 M

	Dose K ♂		Dose K ♀		Dose A ♂		Dose A ♀		Dose B ♂		Dose B ♀		Dose C ♂		Dose C ♀	
	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()
Mice bearing lympho-ret. tumours	6	(27) 22.2%	11	(25) 44.0%	9	(24) 37.5%	9	(22) 40.9%	9	(32) 28.1%	10	(28) 35.7%	6	(32) 28.7%	8	(21) 31.3%
Mice bearing liver tumours	11	(27) 40.7%	2	(25) 8.0%	13	(24) 54.2%	0	(22) 0%	13	(32) 40.6%	2	(28) 7.1%	10	(32) 31.2%	0	(25) 0%
Mice bearing lung tumours	10	(27) 37%	4	(25) 16%	13	(24) 54.2%	5	(22) 22.7%	21	(32) 56%	7	(28) 25.0%	14	(32) 43.7%	6	(25) 24%
Mice bearing other tumours	0	(27) 0%	2	(25) 8%	1	(24) 4.2%	5	(22) 22.7%	1	(32) 3.1%	4	(28) 14.3%	2	(32) 6.2%	2	(25) 8%

* statistically significant 2P<0.05

Table 3

Mouse carcinog. NDA 20-397

DS 103-282 Mice Cumulative

Project No. 196M

Numbers and percentage incidence of tumors

	Dose K ♂		Dose K ♀		Dose A ♂		Dose A ♀		Dose B ♂		Dose B ♀		Dose C ♂		Dose C ♀	
	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()	Mice with this pathol.	As % of ()
Mice bearing lympho-ret. tumours	17	(49) 34.7%	30	(49) 51.2%	26	(48) 54.2%	27	(46) 58.7%	21	(47) 44.7%	31	(49) 63.3%	19	(48) 39.6%	28	(48) 58.3%
Mice bearing liver tumours	17	(50) 34.0%	3	(50) 5.0%	19	(50) 38.0%	1	(48) 2.1%	14	(47) 29.8%	3	(49) 6.1%	10	(48) 20.8%	1	(49) 2.0%
Mice bearing lung tumours	15	(50) 30%	6	(49) 12.2%	21	(47) 44.7%	13	(48) 27.1%	24	(49) 49.0%	7	(48) 14.6%	17	(49) 34.7%		(50) 22.0%
Mice bearing other tumours	2	(50) 4.0%	5	(50) 10.0%	2	(50) 4.0%	10	(48) 20.8%	3	(49) 6.1%	4	(49) 8.2%	3	(49) 6.1%	4	(50) 8.0%

Table 4

Rat Carcinogenicity:

Vol. 1.12-1.15

Study# 80/SAS004/391/Sandoz Report# 203-021/Oct 1980.

Lab:

Species/No./sex: CD strain of remote Sprague-Dawley origin/60/sex/dose/5-wk old/body wt range for males 135-136g and for females 121-123g.

Dose/duration: 0, 1, 3, 9 mg/kg/d* for 104 wks administered as admixture in feed.

Batch/lot#: 74901

* doses were selected based on a 13-wk rat toxicity study reviewed by Dr. Wilk (Appendix A) and summarized in the attached table.

Methods: rats were housed in fives in polypropylene cages with stainless steel mesh floors and lids. After 85 wks of treatment and due to increased incidence of granuloma-like lesions in HD, all males in this group were housed in Type RCl high density propylene body and solid floor with stainless steel lid. Drug concentration in diet was calculated weekly for the first 24 wks and monthly thereafter.

The following parameters were assessed:

general examination (daily), clinical signs and behavior (daily), visible/palpable masses (weekly), body wt and food intake (weekly), water intake (daily visual inspection/due to urinalysis results on wk 50, quantitative measurements were done for 3 consecutive days on wk 55 and over 5 days on wks 77 and 101), hematology (predosing, and during wks 12 and 25 from the control and HD rats, and from all groups on wks 51,78, 102), blood chemistry (predosing, during wks 11 and 25 from control and HD, from all groups after wks 51, 78, 102), urinalysis (predose, wks 11 and 24 from control and HD and from all groups on wks 50, 77, 101), ophthalmoscopy (pre-treatment, on wks 12,24,50,76,101 for HD and controls; after the results in HD rats, examination was extended to LD and MD), and at study end: complete necropsy and organ weights. Histopathology was done on a variety of tissues and organs, initially only control and HD groups were examined microscopically, but because of results in the brain and eyes, these tissues were examined in LD and MD. Livers from all groups were examined, 1 liver section from each rat in control and HD and 2 sections from each rat in LD and MD.

Statistics: Chi square test or Fisher's exact test were used to assess intergroup distribution of signs, mortality, and macro- or microscopic findings. Student's t-test used for all other parameters.

Multiple Dose Studies

Rat

	13 Week
Strain	OFA (SPF, Sandoz) 10/sex/group 5/sex MD+HD recovery
Doses	0, 1.7, 8, 40 mg/kg (diet)
Signs	<u>Daily</u> <u>MDF</u> : slight piloerection and miosis. <u>HD</u> : Miosis, perianal wetting, piloerection, sensitivity to touch, dermatitis, bleeding injuries due to scratching, corneal clouding, convulsions (In F).
Mortality	2 HD; 1 bleeding from biting, scratching, 1 unknown in week 12.
Weight gain/food consumption	Fig 1+2: Sign. decrease in MD and HD. Corresponding decrease in food consumption.
Hematology	<u>6+13 weeks</u>
Blood Chemistry	Slight dec. glucose at 6+13 weeks in <u>MDF</u> . Sign. decrease in glucose at 6+13 weeks in <u>HD</u> . Increase in SGPT at 6 weeks in M and 6+13 weeks in M+F <u>HD</u> .
Urinalysis	<u>6+13 weeks</u>
Gross Pathology	<u>HD</u> : skin lesions, ulcers.
Organ Weights	Decrease mean absolute and relative liver weights. Increase in mean relative heart and adrenal weight in <u>HD</u> .
Microscopy	<u>HD Heart</u> : slight increase in focal necrosis. <u>Liver</u> : focal & single cell necrosis. <u>Eye</u> : Corneal ulcers. <u>Skin</u> : ulcers
NOEL Min. EL	1.7 mg/kg 8 mg/kg Dec. weight gain (-10%) piloerection.
EL	40 mg/kg convulsions Vasoconstriction Elevated SGPT Organ changes: Liver necrosis (focal+single cell) Heart (single cell necrosis) (All Reversible)

Results:

Mortality: rats died throughout the study; the only drug-related deaths were those associated with pedal granulomas. Mortality distribution was as follows:

Dose (mg/kg)	total weeks 1-107 m/f
0	40/32 (3) *
1	32/34
3	37/34
9	35 (3) */30

* died as a result of blood sampling.

Attached table shows mortality distribution throughout the study duration. Statistical analysis was conducted using Cox's test for homogeneity and Tarone's for linear trend. There was no difference in mortality distribution for either sex or inter-group differences.

Clinical Signs: The following signs were observed in control and treated groups; some signs occurred at higher incidence in treated groups: hyperactivity/hypersensitivity, piloerection/sparse coat, clonic convulsion, salivation, violent tremor with occasional exophthalmia, granuloma-like lesion, ocular opacity sometimes with ptosis and swollen eye lids/keratitis, hair loss in abdomen and limbs.

Body wt/Food Consumption/Water Intake: body wt was reduced significantly during the first year in HD rats starting from wk 13 in males and females (see attached figures), a less severe reduction was noted in MD rats. During the 2nd year, body weights of MD rats were comparable (females) or greater (males) than the weights of the corresponding control rats (note that the higher wt in males was partially due to poor growth of the control group). However, body wt of HD rats remained significantly lower than the corresponding control wts till study end (table below). There was no drug-related effect on water intake except during treatment wk 55 where HD m drank significantly more water than the control (118%) whereas all three female groups drank significantly less than their control counterparts (77-86%). Food intake of HD m and f was slightly reduced relative to the corresponding controls throughout the study but this decrease did not reach statistical significance. During wks 14-24 there was a dose-related increase in food-conversion ratios in m (calculated as the amount of food consumed per unit body wt gain; calculated upto wk 24). This was contributed to poor growth in these animals during this period. Body weight change (g) throughout the study and as % of control values:

TABLE 1

Mortality distribution

Group : 1 2 3 4
 Compound : Control --- DS 103-282 ---
 Dosage (mg/kg/day) : 0 1 3 9

Group & sex	Week of treatment									Total Weeks 1-107
	1-13	14-26	27-39	40-52	53-65	66-78	79-91	92-104	105-107 [†]	
1 ♂	0	1	0	0	1	6	12	18	2	40
2 ♂	1	1	0	2	1	3	10	13	1	32
3 ♂	0	0	2	1	1	4	14	12	3	37
4 ♂	0	2	1	3	1	4	12	12	0	35(3)
1 ♀	2	2	1	2	1	4	10	9	1	32(3)
2 ♀	0	0	2	1	3	6	9	13	0	34
3 ♀	0	0	0	2	1	6	12	13	0	34
4 ♀	0	0	1	0	4	3	5	16	1	30

Figures in parentheses indicate numbers of animals that died as a result of routine blood sampling procedures.

[†] Died while awaiting terminal sacrifice.

weeks		cont.	LD	MD	HD
0-26	m	500	504/101%	483/97%	384/77%
	f	221	221/100%	213/96%	188/85%
27-52	m	104	127/122%	108/104%	88/85%
	f	79	82/104%	72/91%	48/61%
53-78	m	65	101/155%	93/143%	84/129%
	f	93	87/94%	95/102%	74/80%
79-104	m	-20	-1	7	11
	f	52	26/50%	55/106%	52/100%

Ophthalmoscopy:

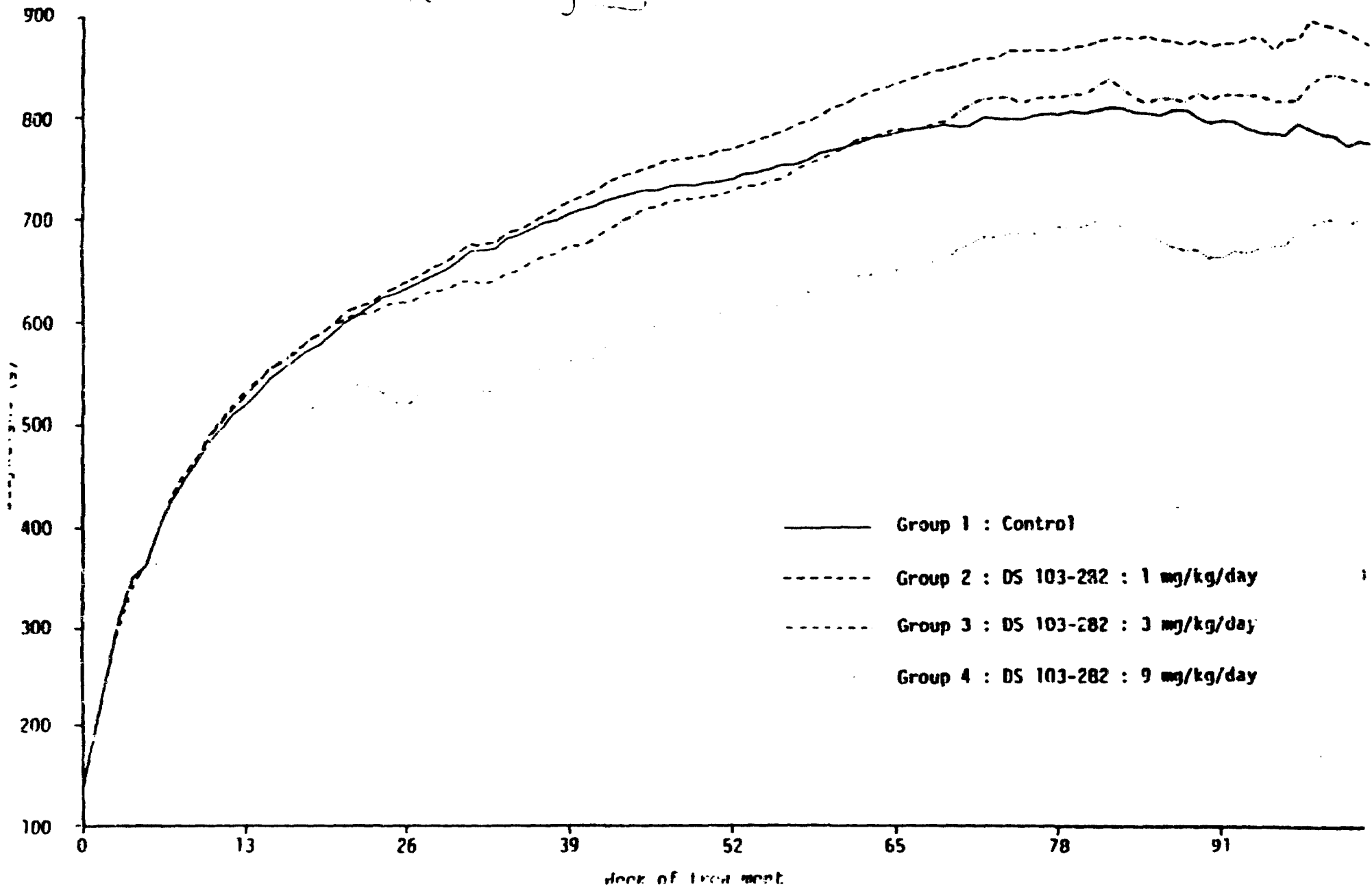
Effect	week(s)	Dose Group
no changes	12 & 24	all
corneal damage/keratitis/ ± vascularization	50 76	HDm all treated m groups showing dose-relationship (0/52, 2/52, 4/53, 24/48 cont., LD, MD, HD respectively); none in f except 4/52HDf.
	101	most HDm (21/28); some HDf (5/32); some MDm (11/28) *
collapsed eyeballs	1-101	3HDm

* absence of lesions in LDm was explained by the sponsor as due to the large number of deaths in this group. However, from the ophthalmoscopy data in table 7H p131 vol.12, number of animals surviving was similar in all groups at this time period. Therefore, the sponsor's explanation is not valid.

FIGURE 4

Bodyweights - males

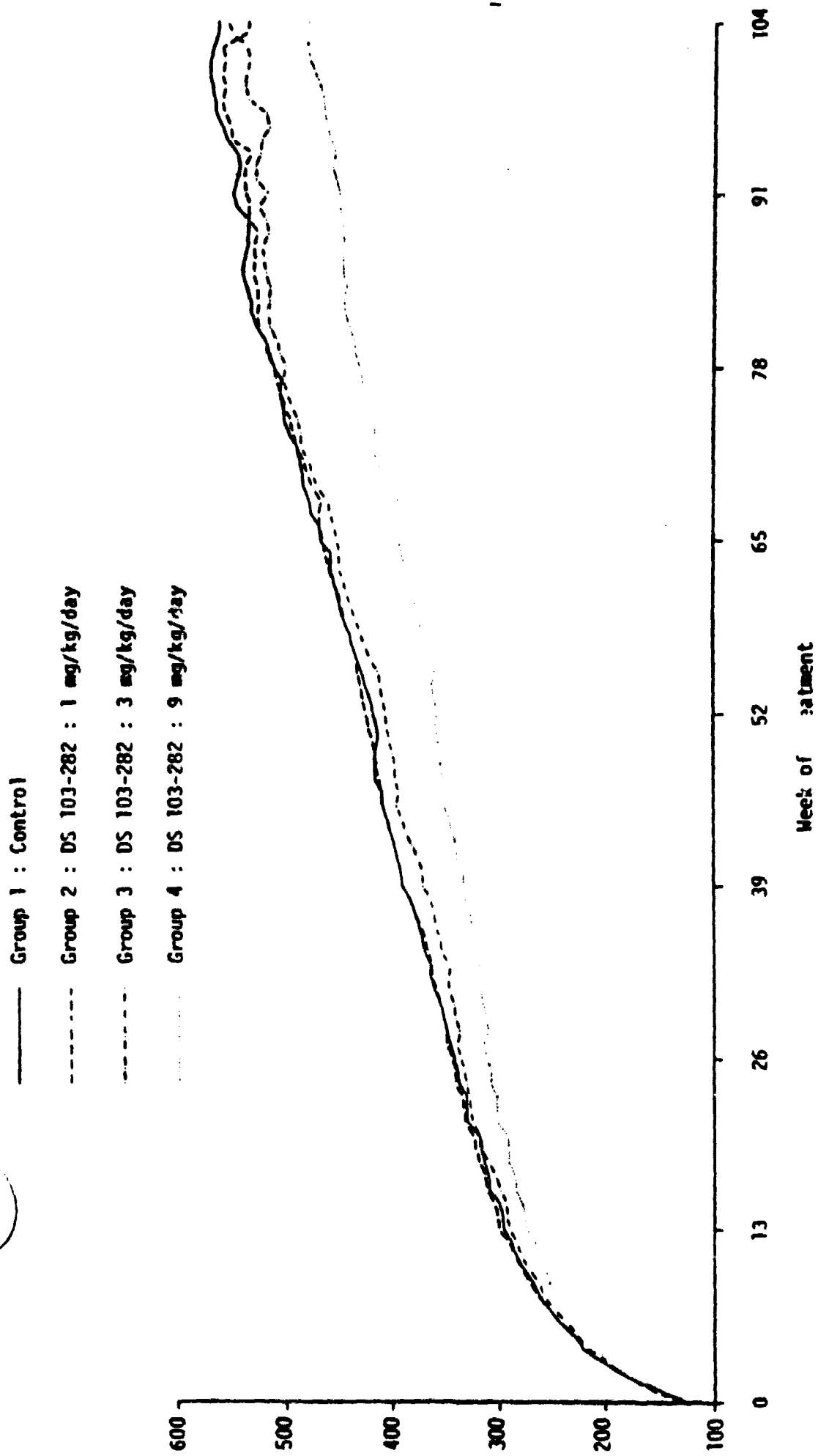
Tizandine N90-397
Rat carcinogenicity



Tizanidine N20-397 Rat carcinosy.

FIGURE 5

Bodyweights - females



Hematology: there were no consistent or dose-dependent changes in any of the tested hematology parameters. The following effects showed statistical significance from the control value:

Weeks	Parameter	Dose Group
12	total WBC ↑	HDm (30%)*
25	total WBC ↑	HD m(19%; due to 2x increase in neutrophils); HD f (3x cont)
51	neutroph ↑	HD m 1.5x cont
	RBC ↑	MD & HD m and f (5-10%)
	PCV ↑	HD f (5%)
	Hb ↑	HD f (4%)
	MCV ↓	MD & HD m and f (3-6%)
78	neutroph ↑	HD m (1.5x cont)
	RBC ↑	HD f (8%)
	Hb ↑	HD f (6%)
102	RBC ↑	MD m (14%)
	RBC ↓	HD f (14%)
	PCV ↑	MD & HD m (15-18%)
	Hb ↑	MD m (16%)
	Hb ↓	LD & HD f (10-12%)
	MCV ↑	HD m & f (5-8%)
	MCHC ↓	HD m (6%)
	PT ↑	HD f (9%)
	platelet ↑	HD f (19%)

* values in () reflect change from the control value as %

Up to wk 78, WBC/neutrophil count increased significantly in HDm. An increasing trend was observed in RBC count, Hb, and PCV in HD rats and sometimes MD and prothrombin time was significantly increased at end of study in HDf. Platelet count was increased in all treated m and f groups (significant only in HDf).

Blood Chemistry: a significant decrease of 33% was measured in ALP level in HDm after 11 wks. ALP and ALT (also known as SGPT) levels were significantly increased in HDm (40-45%) on wk 102. ALT level was significantly increased after wks 11 and 25 in HDm. Plasma glucose concentrations were decreased significantly in MD and HDm on wks 51 and 80 and in HDm (wk 102), and in all three f groups on wk 102, in HDf during wks 25, 51, and 80, and in MDf on wk 51. Albumin was markedly reduced in HDf throughout the study and after 102 wks, α-globulin level was reduced in all treated groups (dose-dependent and significant in males). Serum potassium concentration was significantly decreased in HDm after 11 wks, similar changes noted in other treated male groups. These changes in potassium

disappeared till wk 102 when they again were significantly less in HDm relative to the control. Also in male rats, sodium plasma levels were significantly increased on wk 78 in all three m groups. The above changes were not dose- or time-dependent, did not occur in both sexes, and showed interanimal and intragroup variation, therefore a meaningful conclusion could not be made.

Urinalysis: urine with significantly higher specific gravity and lower volumes (relative to the control group) were found in HD male and female rats on wks 24, 50, and 77. On wk 101, urine volume was significantly reduced in MD and HD males and HDf though the specific gravity was higher than that in the controls, the values did not reach statistical significance. The urine specific gravity on wk 101 was significantly reduced in LD and MDf. The higher plasma sodium levels may be partly responsible for the high urine specific gravity.

Organ Weights: the table below presents only the statistically significant changes recorded in organ wts:

Organ	absolute wt. (relative wt as % of control)
liver	↓ 19% HDm (↓ 3% LD/MD/HD m; ↑ 4% LD f)
kidney	↓ 26% HDm; ↓ 11&19% MD/Hdf (↓ 0.7% HDm)
spleen	↓ 20% HDm & f (↓ 14% LD/MD/HDm)
prostate	↓ 21&26% MD & HDm (↓ 6% MDm)
testes	↓ 12% HDm (no change)
thyroid	↓ 33% HDm* (↓ 27% HDm)
heart	no change in absolute wt (↑ 13% Hdf)
brain	no change in absolute wt (↑ 10&16% HDm & Hdf)

* SD in control was high 40±16 vs. 27±5 in control and HDm respectively.

The decrease in kidney and prostate absolute wts was dose-dependent. The decrease in relative liver and spleen wts though small, was noted in all three- dosed male groups, and only HDf showed a significant decrease in liver wt among the treated female groups. The biological significance of the increase in relative brain and heart wts is unclear.

Gross Morphology: ulcerated granuloma of the hind-limb noted in all 3-treated m and f groups and the control (higher incidence in drug-groups), thickened mucosa of the cecum in HD m and f (none in controls), tympanities in HD m and f (none in controls), some lung changes e.g. adhesion and subpleural foci, mass or nodule in the uterus in treated rats. Opacity of the eyes and sparse coat.

Histopathology: Table below summarizes non-neoplastic findings in rats that DIED OR KILLED DURING THE STUDY:

Organs/Tissue	Cont.	LD	MD	HD
Brain				
Abrostral thalamus depressed	6m/5f	7m/7f	3m/13f	5m/5f
Eyes				
stromal vascularization	3m	5m	6m	17m*
corneal granulation				
/slight	2m/2f	4m	6m/1f	10m*/2f
/moderate	-	2m	4m	8m*/1f
disruption of Bowman's membrane	-	6m	4m/1f	5m*
hyperkeratosis	1m	3m	6m	11m*
corn. polymrph. infilt.	3m	7m*	8m*/1f	20m*/2f
epith. polymorph. infilt.	-	1m	3m/1f	9m*
Heart				
chronic myocard. slight	-/4f	1f	-	6m/1f
Hind Limbs				
polymorph area	1m	-	7m*	9m*
ulcer	1m	2m/2f	13m*/4f	17m*/4f
bony proliferation	1m	1m/1f	6m	7m*/2f
underlying granulation tissue	1m	1m	4m/1f	6m/3f
mature underly.granul. tissue	-	1m/2f	6m*	6m*/2f
mature vascul.granul. tissue	-	-	3m	8m*
peripheral acanthosis	1m	2f	9m*	12m*/2f
Kidney				
slight pyelitis	2m/1f	1m	2m/1f	1m/7f*
Liver				
centriacinar lg.fatty vacullization/slight	4m/4f	2m/4f	5m/13f*	4m/7f
Lymph nodes (Cervical)				
paracortical plasma-cytosis	5m/5f	2f	1m	7m/13f*
Ovary				
follicular cyst	-	-	2f	2f

Histopathology table cont.

Organs/Tissue	Cont.	LD	MD	HD
Spleen				
extramedullary hemopoiesis	1m/5f	2m	2m/2f	9m*/8f
Stomach				
dilation of gastric gland	1m/7f	2m/2f	4m/1f	8m*/8f
Total no. of animals examined:	40/32	32/34	37/34	35/30

- no value given to a finding indicates 0 incidence.

* p<0.05 relative to the control

Table below summarizes non-neoplastic findings in rats **KILLED AT TERMINATION**:

Organ/Tissue	Cont.	LD	MD	HD
Brain				
lymph. infilt. from blood vessels next to pineal body or slight mineralization/ or inflammation of pineal meninges	-	1m/5f	3m/1f	2f
focal fiber degeneration with gliosis	-	-	-	1f
Eye				
cataract	1m	-	1m	4f
retinal atrophy/degeneration	1m	1m/2f	1m/2f	2m/9f*
corneal granulation/slight	-	2m	12m*	3m/2f
moderate	-	-	-	13m*
marked	-	-	-	3m
absence/virtual loss of nuclear layer	1m	1m/2f	1m/2f	2m/4f
disruption of Bowman's mem.	-	2m	7m*	-
polymorph. leucocy. infil./stroma	-	2m	12m*	1f
hyperkeratosis	-	-	10m	-
vascularization of stroma	-	-	10m*	-
Hind Limbs				
acanthosis	1m/1f	7m/4f	9m*/12f*	1m/4f
hyperkeratosis	1m	3m/3f	4m/9f*	1m
ulcers	3m/1f	6m/2f	6m/7f*	16m*/14f*
necrosis	1m	1f	-	13m*/9f*
polymorph. leuco. infilt.	1m	-	-	7m/8f*
bony proliferation	-	2m/2f	4m/6f*	11m*/2f
mature granulation tissue/ underlying	1m	1m	4f	11m/4f

Organ/Tissue	Cont.	LD	MD	HD
<u>Liver</u>				
fatty vacuolation/slight centriacinar	1f	2m/5f	15f*	1m/6f
periacinar eosinophilic hepatocyte hypertrophy	-	-	-	6m*/2f
hepatocyte hyperplastic nod.	-	-	-	3f
<u>Lymph Node (Cervical)</u>				
paracortical plasmacytosis	3m/14f	1m	1m	16m*/15f
<u>Pancreas</u>				
slight pancreatitis	1f	-	-	4m/5f
<u>Stomach</u>				
slight dilation of gastric glands	8m/14f	3m	2m	7m/24f*
fibrosis in lamina propria	-	-	-	4m/4f
Total no. of animals examined:	20/28	28/26	23/26	25/30

Neoplastic Lesions:

- Rats killed/died during treatment period: testes interstitial cell carcinoma found in 1/35 HDm, astrocytoma and malignant lymphoma found in 1/32 and 1/30 HDf, and granulocytic leukemia found in MDm and f and HDm (1/37, 1/34, 1/35 respectively), mammary gland carcinoma in 3/32 cont, 2/34 MD, 2/30 HD females, thyroid parafol. hyperplasia 1/40 cont m, 1/32 LDm, 6/32 cont f, 2/30 HDf, pancreatic islet hyperplasia 1/30 HDf (see attached tables).

- Rats killed at termination: mammary gland carcinoma noted in 1/23 MDm, 2/26 MDf and in 2/30 HDf; none in controls. Renal carcinoma reported in 1/26 MDf and 1/25 HDm, 2/23 MDm skin chondroma, and hemangioma of mesenteric lymph nodes in 1/26 LDf, 1/26 MDf, and 2/25 HDf, thyroid parafol. hyperplasia 9/25 HDm, 4/20 cont m, and pancreatic cell adenoma 4/30 HDf and 2/28 cont f (attached tables).

Attached tables present distribution of animals bearing 1 or more tumor types. These results show no significant difference in tumor incidences or distribution between drug groups and the corresponding controls.

Statistical Analyses Of The Lesions: see the mouse study for background information. For lesions other than skin and subcutis, only pair-wise comparison of controls and HD was done. These lesions were considered non-fatal and were analyzed by the prevalence method.

12.

Similar to the mouse study, there was no difference in mortality incidence of either sex and no inter-group differences were noted. Incidence of skin fibromas in male rats was significantly higher in HD compared with the control group ($p < 0.018$ and $p < 0.059$ for trend test test). When the incidences of fibrosarcoma and fibromyosarcoma were added to the incidence of fibromas the p values were 0.089 and 0.21 respectively (see below).

	Male				Female			
	1	2	3	4	1	2	3	4
Fibroma	2	8	4	8	-	2	1	-
Fibrosarcoma	1	2	1	-	-	1	-	1
Fibromyosarcoma	1	-	-	-	-	-	-	-

In female rats an increased incidence of pancreatic islet cell adenoma or hyperplasia with statistical significance reached in HDf ($p = 0.053$).

The sponsor indicated that these lesions occurred only in one sex and were not present in the mouse study therefore, may not be a true drug-related effect.

Statistical analyses were done on lesions and combination of lesions as follows:

- Skin and subcutis (fibroma and fibroma + fibrosarcoma + fibromyosarcoma)
- Liver (hyperplastic focus and hyperplastic focus + hepatocellular carcinoma)
- Thyroid (parafol. cell adenoma + parafol. cell carcinoma and parafol. cell adenoma + parafol. cell carcinoma + parafol. cell hyperplasia)
- Pancreas (Islet cell adenoma and islet cell adenoma + islet hyperplasia)

SUMMARY AND CONCLUSION(s):

DS 103-282 was administered to male and female rats in feed at 0, 1, 3, and 9 mg/kg/d for 104 wks. The carcinogenic potential of this drug was assessed by examining a number of parameters at specified times throughout the study duration. The drug had no effect on animal survival. A significant decrease in body weight

occurred in HD rats and persisted till study end; food consumption was decreased throughout the study but the values did not reach statistical significance. Water intake was markedly reduced in all three female drug groups but intake significantly increased in HD males during wk 55. Changes in drinking behavior in females corresponded with the reduced urine volume reported in MD and HD females during this period, but did not correlate to the reduced urine volume in male rats. Urine specific gravity was significantly increased in HD and sometimes MD rats during wks 24, 50, 77, and 101. The increase in specific gravity may have been partially caused by the marked increase in sodium plasma levels on wk 78; other explanations apply. Clinical signs included piloerection, clonic convulsions, sparse coat, ocular opacity, and hypersensitivity/hyperactivity. The drug induced hematological changes from wk 12 and up. Total WBC count increased in HD rats during wks 12 and 25, from wk 51 and up, RBC and Hb level increased in HD and sometimes MD rats in a dose-dependent fashion. On wk 102 a significant increase in prothrombin time and platelet count recorded in HD females. Blood ALP and ALT levels increased significantly in HDm at end of study; ALT levels were also markedly increased on wks 11 and 25. Plasma glucose concentration significantly decreased in MD and HD male rats on wks 25, 51, and 80, and in MDf on wk 51. The drug-induced effects on ALT and glucose are similar to those reported in the 13-wk rat toxicity study. Albumin was markedly reduced in HDf throughout the study and α -globulin was reduced in all treated groups. Absolute and/or relative weights of the liver, kidneys, spleen, prostate, and testes were significantly reduced in MD and HD (some changes were dose-dependent). The relative weights of the brain and heart were significantly increased in HD; the biological significance of this is unclear and similar findings reported in the 13-wk rat study. The main gross morphological findings were granuloma of hind limbs in all treated and control groups with higher incidence in treatment groups, ocular opacities swollen eye lids/keratitis, and hair loss in abdomen and limbs. The eye changes were confirmed in ophthalmoscopy and histology. The eyes had vascularization, corneal granulation, hyperkeratosis, cataract, retinal atrophy/degeneration, and inflammation. Hind limbs had acanthosis, ulcers, necrosis, bony proliferation, and inflammation. The liver had centriacinar fatty vacuolation (all treated f), hepatocyte hypertrophy, and hyperplastic nodule (HD m and f). Neoplastic lesions found in treated rats but not in the concurrent controls included carcinoma (mammary gland, kidney, and testes interstitial cells), astrocytoma, granulocytic leukemia, and hemangioma of mesenteric lymph nodes. A statistically significant finding was **pancreatic islet cell adenoma or hyperplasia in female rats and skin fibroma in male rats** when compared with the incidence in the control group. None of these or other neoplastic lesions showed dose-dependent relationship and the differences from the control findings though reached statistical significance in some cases, were within or slightly higher than historical control data (historical data were not available to the reviewer). Also these

lesions were detected in one sex and similar findings could not be observed in the mouse study. Therefore, it was concluded by the sponsor that tizanidine is not carcinogenic in rats.

It is concluded that 103-282 caused certain toxicities when administered in the diet to the rat for 104 wks. Most of the toxicities were evident at 9 mg/kg dose. The drug caused changes in body weight, hematology, ophthalmoscopy, gross morphology, organ weight, and histopathology. There were no dose-dependent significant differences in neoplastic lesions of treated and control animals. The only lesions that reached statistical significance are skin fibroma in males and pancreatic hyperplasia or adenoma in females. Untill the sponsor provide neoplastic historical control data and the results of the Agency's statistical analysis of the data are performed, a final conclusion can not be made at this time.

VO 1.1.1
 Re-representation of neoplastic lesions & pre-neoplasia data in Rats
 Sandz Research report May 1984 (125)

Table 1
 DS 103-282 104 weeks study in rats
 Table of tumours and hyperplasias (males)

Numbers of rats with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 3 mg/kg/day		Group 4 9 mg/kg/day	
	D	T	D	T	D	T	D	T
SKIN AND SUBCUTIS:								
-keratoacanthoma							1	
-papilloma			3	6	3			
-fibroma		2	2	4	2	2	3	5
-lipoma	1	1			1	3	2	2
-fibrosarcoma	1		1	1	1			
-fibrosarcoma	1							
-basal cell hyperplasia							1	
MAMMARY GLAND:								
-fibroepithelial tumour								
-carcinoma			1	1		1		
LIVER:								
-hepatocell. carcinoma		1						
-hyperplastic focus	3	11	4	9	3	9	2	11
KIDNEYS:								
-adenoma								
-carcinoma								1
-transitional hyperplasia	3	4	4	1	1			4
HEART:								
-mesothelioma				1				
BRAIN:								
-ependymoma	1							
-astrocytoma	1		1					
-glioma					1			
-meningioma		2		1		1		
PITUITARY:								
-adenoma	22	11	10	8	13	3*	11	7
-carcinoma			1					
-focal hyperplasia	1	2						4

D=animals died or killed in extremis T=animals killed at termination
 *significantly different from Controls. P<0.01

Table 1 cont.

DS 103-282 104 weeks study in rats

Table of tumours and hyperplasias (males)

Numbers of rats with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 3 mg/kg/day		Group 4 9 mg/kg/day	
	D	T	D	T	D	T	D	T
THYROIDS:								
-fol. cell adenoma	2				1			
-parafol. cell adenoma	5	5	2		3		4	5
-parafol. cell carcinoma	1							
-parafol. hyperplasia	1	4	1					9
ADRENALS:								
-mal. pheochromocyt.				1				
-ben. pheochromocyt.	5	2	1	1	1	2	2	2
-cortical adenoma						1		
-cortical hyperplasia	5	8	6	8		3	1	6
-medullary hyperplasia	2		3				1	1
PANCREAS:								
-exocrine cell adenoma					1			
-islet hyperplasia	5							
-exocrine hyperplasia	1							1
TESTES:								
-interstitial cell tumour	4	3			1	2	1	2
-interstitial hyperplasia	3	2						1
PROSTATE:								
-adenoma				1				
URINARY BLADDER:								
-epithelial hyperplasia	2				1			
SPLEEN:								
-liposarcoma		1						
HAEMATOPOIETIC SYSTEM:								
-histiocytic sarcoma	1							
-mal. lymphoma		1	1		1			
-granulocytic leukemia		1	1		1			

D=animals died or killed in extremis T=animals killed at termination

Table 1 cont.
 DS 103-282 104 weeks study in rats
 Table of Tumours and hyperplasia (males)

Numbers of rats with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 3 mg/kg/day		Group 4 9 mg/kg/day	
	D	T	D	T	L	T	D	T
<u>LYMPH NODES:</u> -haemangioma	1							2
-focal hyperplasia							1	
<u>STOMACH:</u> -leiomyosarcoma					1			
<u>INTESTINE:</u> -carcinoma							1	
<u>THORAX:</u> -fibroma							1	
<u>EYES:</u> -fibroma							1	
<u>EARS:</u> -chondroma						2		
<u>SALIVARY GLANDS:</u> -haemangiosarcoma -sarcoma	1		1		1			
<u>BONE:</u> -osteogenic sarcoma			1		1			
<u>HANDIBLE:</u> -squamous cell carcinoma				1				
<u>TAIL:</u> -papilloma				1				
<u>MISCELLANEOUS:</u> -rhabdomyosarcoma -sarcoma of unknown origin				1		1		
Total number of rats with tumours	31	16	20	19	25	15	21	15
Total number of rats with malignant tumours	5	3	5	4	7	1	3	1
Numbers of rats examined	40	20	32	28	37	23	35	25

D=animals died or killed in extremis T=animals killed at termination

Re-interpretation of neoplastic lesions & pre-neoplastic data for
 Sandez Research report May 1984

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Table 2
 DS 103-282 104 weeks study in rats
 Table of tumours and hyperplasias (females)

Numbers of rats with Tumours and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 3 mg/kg/day		Group 4 9 mg/kg/day	
	D	T	D	T	D	T	D	T
SKIN AND SUBCUTIS:								
-papilloma	1							
-fibroma			1	1	1			
-lipoma		1	1			2		
-fibrosarcoma			1				1	
-squamous cell carcinoma		1		1				
-basal cell tumour				1	1			
MAMMARY GLAND:								
-fibroepithelial tumour	12	18	14	18	15	17	15	14
-carcinoma	3				2	2	2	2
-hyperplastic	4		5			1		
LIVER:								
-hepatocell. carcinoma		1						
-hyperplastic focus	3	12	4	9	8	7	1	15
KIDNEYS:								
-carcinoma								
-transitional hyperplasia	1	8		1		1		3
BRAIN:								
-astrocytoma							1	
PITUITARY:								
-adenoma	17	12	19	7	21	8	17	13
-carcinoma	1		2	1				
-focal hyperplasia	2	4	2		1	2	1	2
THYROIDS:								
-foll. cell adenoma		1					1	
-parafoll. cell adenoma	4	3		2			4	6
-parafoll. hyperplasia	6	14					2	15

D=animals died or killed in extremis T=animals killed at termination

Table 2 cont.
 DS 103-282 104 weeks study in rats
 Table of Tumours and hyperplasias (Females)

Numbers of rats with Tumour and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 3 mg/kg/day		Group 4 9 mg/kg/day	
	D	T	D	T	D	T	D	T
ADRENALS:								
-ben. pheochromocyt.	1	2	1	3		1		1
-cortical hyperplasia	3	5	3	2	4	1	1	6
-medullary hyperplasia	1		1				1	
PANCREAS:								
-islet cell adenoma		2					1	4
-islet hyperplasia							1	
-exocrine hyperplasia	2							
HAEMATOPOIETIC SYSTEM:								
-alignant lymphoma			1				1	
-granulocytic leukemia					1			
-lymphoid hyperplasia						1		
LYMPE NODES:								
-haemangioma				1		1		
ABDOMEN:								
-fibrosarcoma					1			
-lipoma								1
OMENTUM:								
-mesothelioma			1					
INTESTINE:								
-submucosal lipoma							1	
EARS:								
-chondroma	1	1	1					
THYMUS:								
-sarcoma			1					
-lymphoma						1		

D=animals died or killed in extremis T=animals killed at termination

Table 2 cont.
DS 103-282 104 weeks study in rats
Table of tumours and hyperplasias (females)

Numbers of rats with Tumour and hyperplasias	Group 1 Controls		Group 2 1 mg/kg/day		Group 3 3 mg/kg/day		Group 4 9 mg/kg/day	
	D	T	D	T	D	T	D	T
<u>UTERUS:</u> -endometrial hyperplasia	1	1		2			1	
<u>UTERINE CERVIX:</u> -endometrial hyperplasia	1							
<u>MISCELLANEOUS:</u> -undifferentiated sarcoma -xiphoid cartilage lipoma			1		1			1
Total number of rats with tumours	24	24	30	20	31	21	25	23
Total number of rats with malignant tumours	3	1	7	1	5	3	4	2
Numbers of rats examined	32	28	34	26	34	26	30	30

D=animals died or killed in extremis T=animals killed at termination

TABLE 13A

Incidences of neoplastic pathology in rats
which died or were killed during the treatment period (Groups 1 and 4)

Group	:	1	2	3	4
Compound	:	Control	---	DS 103-282	---
Dosage (mg/kg/day)	:	0	1	3	9

Organ and neoplasm	Group and sex			
	1 ♂	4 ♂	1 ♀	4 ♀
Number of animals examined:	40	35	32	30
Benign skin and subcutis epithelial keratoacanthoma	0	1	0	0
Benign skin and subcutis epithelial papilloma	0	0	1	0
Mammary gland benign fibroepithelial tumour	0	0	12	15
Mammary gland carcinoma	0	0	3	2
Pancreas islet cell adenoma	0	0	0	0
Intestinal carcinoma	0	1	0	0
Pituitary adenoma	22	11	17	17
Pituitary carcinoma	0	0	1	0
Thyroids - follicular cell adenoma	2	0	0	1
Thyroid - parafollicular cell adenoma	5	4	4	4
Thyroid - parafollicular cell carcinoma	1	0	0	0
Adrenal - pheochromocytoma	5	2	1	0
Testes - interstitial cell adenoma	4	0	-	-
- interstitial cell carcinoma	0	1	-	-
Skin and subcutis, mesenchymal (benign) - fibroma	0	3	0	0
- lipoma	1	2	0	0
Skin and subcutis, mesenchymal (malignant)				
- fibrosarcoma	1	0	0	1
- fibromyosarcoma	1	0	0	0
Thorax - fibroma	0	1	0	0
Eye - fibroma	0	1	0	0
Caecum - submucosal lipoma	0	0	0	1
Histiocytic sarcoma	1	0	0	0
Haemangioma - mesenteric lymph nodes	1	0	0	0
Haemangiosarcoma - salivary gland	1	0	0	0
Ear - chondroma	0	0	1	0
Ependymoma	1	0	0	0
Astrocytoma	1	0	0	1
Malignant lymphoma	0	0	0	1
Granulocytic leukaemia	0	1	0	0

TABLE 189

Incidences of neoplastic pathology in rats
which died or were killed during the treatment period (Groups 2 and 3)

Group	:	1	2	3	4
Compound	:	Control	---	DS 103-282	---
Dosage (mg/kg/day)	:	0	1	3	9

Organ and neoplasm	Group and sex			
	2 ♂	3 ♂	2 ♀	3 ♀
Number of animals examined:	32	37	34	34
Skin and subcutis, epithelial benign papilloma	3	3	0	0
Mammary gland benign fibroepithelial tumour	1	0	14	15
Mammary gland carcinoma	0	0	0	2
Basal cell tumour	0	0	0	1
Pancreas - exocrine cell adenoma	0	1	0	0
Kidneys - renal adenoma	1	0	0	0
Kidneys - squamous cell carcinoma	0	0	2	0
Pituitary - adenoma	10	13	19	21
Pituitary - carcinoma	1	0	2	0
Thyroids - follicular cell adenoma	0	1	0	0
Thyroids - parafollicular cell adenoma	2	3	0	0
Adrenals - phaeochromocytoma	0	1	1	0
Testes - interstitial cell adenoma	0	1	-	-
Skin and subcutis, mesenchymal (benign) fibroma	2	2	1	1
- lipoma	0	1	1	0
Skin and subcutis, mesenchymal (malignant)				
fibrosarcoma	1	1	1	0
Abdominal fibrosarcoma	0	0	0	1
Salivary gland sarcoma	1	1	0	0
Thymus sarcoma	0	0	1	0
Stomach leiomyosarcoma	0	1	0	0
Omentum - papillary mesothelioma	0	0	1	0
Osteogenic sarcoma	1	1	0	0
Sarcoma of unknown origin	0	1	0	0
Undifferentiated sarcoma	0	0	1	1
Chondroma	0	0	1	0
Brain - glioma	0	1	0	0
Astrocytoma	1	0	0	0
Malignant lymphoma	1	1	1	0
Granulocytic leukaemia	0	1	0	1

TABLE 19A

Incidences of neoplastic pathology
in rats killed at termination (Groups 1 and 4)

Group	:	1	2	3	4
Compound	:	Control	---	DS 103-282	---
Dosage (mg/kg/day)	:	0	1	3	9

Organ and neoplasm	Group and sex			
	1 ♂	4 ♂	1 ♀	4 ♀
Number of animals examined:	20	25	28	30
Skin and subcutis epithelium malignant squamous cell carcinoma	0	0	1	0
Mammary gland benign fibroepithelial tumour	0	0	16	14
Mammary gland carcinoma	0	0	0	2
Pancreas - islet cell adenoma	0	0	2	4
Liver - hepatocellular carcinoma	1	0	0	0
Pancreas - exocrine adenoma	0	0	1	0
Kidneys - renal adenoma	0	1	0	0
- renal carcinoma	0	1	0	0
Pituitary - adenoma	11	7	12	13
Thyroids - follicular cell adenoma	0	0	1	0
Thyroids - parafollicular cell adenoma	5	5	3	6
Adrenals - pheochromocytoma	2	2	2	1
Testes - interstitial cell adenoma	3	2	-	-
Skin and subcutis, mesenchymal (benign) - fibroma	2	5	0	0
- lipoma	1	2	1	0
Xiphoid cartilage - lipoma	0	0	0	1
Abdominal fat pad - lipoma	0	0	0	1
Spleen - liposarcoma	1	0	0	0
Haemangioma - mesenteric lymph nodes	0	2	0	0
Chondroma (ears)	0	0	1	0
Meningioma	2	0	0	0
Malignant lymphoma	1	0	0	0

TABLE 19B

**Incidences of neoplastic pathology
in rats killed at termination (Groups 2 and 3)**

Group : 1 2 3 4
 Compound : Control --- DS 103-282 ---
 Dosage (mg/kg/day) : 0 1 3 9

Organ and neoplasm	Group and sex			
	2 ♂	3 ♂	2 ♀	3 ♀
Number of animals examined:	28	23	26	26
Skin and subcutis epithelial malignant squamous cell carcinoma	0	0	1	0
Mammary gland benign fibroepithelial tumour	1	1	18	17
Mammary gland carcinoma	0	1	0	2
Basal cell tumour	0	0	1	0
Musculature of lower jaw - squamous cell carcinoma	1	0	0	0
Tail - papilloma	1	0	0	0
Kidneys - renal carcinoma	0	0	0	1
Prostate adenoma	1	0 ^b	-	-
Pituitary - adenoma	8	3 ^b	7	8
Pituitary - carcinoma	0	0	1	0
Adrenals - cortical adenoma	0	1	0	0
Thyroids - parafollicular cell adenoma	0	0	2	0
Adrenals - benign phaeochromocytoma	1	2	3	1
Adrenals - malignant phaeochromocytoma	1	0	0	0
Testes - interstitial cell adenoma	0	2	-	-
Skin and subcutis, mesenchymal (benign) - lipoma	4	3	0	2
- fibroma	6	2	1	0
Skin and subcutis, mesenchymal (malignant) fibrosarcoma	1	0	0	0
Rhabdomyosarcoma	1	0	0	0
Benign mesothelioma	1	0	0	0
Haemangioma - mesenteric lymph nodes	0	0	1	1
Chondroma	0	2	0	0
Meningioma (epithelioid type)	1	1	0	0
Thymic benign lymphoma	0	0	0	1

b Significantly different from Controls, P < 0.01.

TABLE 20A

Incidences of rats bearing one or more tumour types
in animals which died or were killed during the treatment period

Group	:	1	2	3	4
Compound	:	Control	---	DS 103-282	---
Dosage (mg/kg/day)	:	0	1	3	9

Distribution of animals bearing various tumour types	Group and sex							
	1 ♂	2 ♂	3 ♂	4 ♂	1 ♀	2 ♀	3 ♀	4 ♀
Number of animals examined:	40	32	37	35	32	34	34	30
Animals with one tumour type	20	15	19	15	13	17	22 ^a	10
Animals with two tumour types	7	5	3	5	6	13	6	11
Animals with three tumour types	3	0	3	1	5	1	3	4
Animals with four tumour types	1	0	0	0	0	0	0	0
Total number of tumour types:	47	25	34	28	40	46	43	44

a Significantly different from Controls, $P < 0.05$.

TABLE 209

Incidences of rats bearing one or more tumour types in animals killed at termination

Group	:	1	2	3	4
Compound	:	Control	---	DS 103-282	---
Dosage (mg/kg/day)	:	0	1	3	9

Distribution of animals bearing various tumour types	Group and sex							
	1 ♂	2 ♂	3 ♂	4 ♂	1 ♀	2 ♀	3 ♀	4 ♀
Number of animals examined:	20	28	23	25	28	26	26	30
Animals with one tumour type	9	11	12	8	11	8	11	11
Animals with two tumour types	2	7	3	3	8	9	8	8
Animals with three tumour types	4	1	0	3	8	3	2	5
Animals with four tumour types	1	0	0	1	0	0	0	0
Total number of tumour types:	29	28	18 ^a	27	42	35	33	24

a Significantly different from Controls, $P < 0.05$.

TABLE 21A

Incidences of benign and malignant tumours
in rats which died or were killed during the treatment period

Group : 1 2 3 4
 Compound : Control --- DS 103-282 ---
 Dosage (mg/kg/day) : 0 1 3 9

Distribution of animals bearing various tumour types	Group and sex							
	1 ♂	2 ♂	3 ♂	4 ♂	1 ♀	2 ♀	3 ♀	4 ♀
Number of animals examined:	40	32	37	35	32	34	34	31
Number of benign tumours	42	20 ^a	27	25	36	38	37	40
Number of malignant tumours	5	5	7	3	4	8	6	4
Total number of tumours:	47	25	34	28	40	46	43	44

a Significantly different from Controls, $P < 0.05$.

TABLE 21B

Incidences of benign and malignant tumours in rats killed at termination

Group : 1 2 3 4
 Compound : Control --- NS 103-282 ---
 Dosage (mg/kg/day) : 0 1 3 9

Distribution of animals bearing various tumour types	Group and sex.							
	1 ♂	2 ♂	3 ♂	4 ♂	1 ♀	2 ♀	3 ♀	4 ♀
Number of animals examined	20	28	23	25	28	26	26	30
Number of benign tumours	26	24	17	20	41	32	30	40
Number of malignant tumours	3	4	1	1	1	3	3	2
Total number of tumours:	29	28	18 ^a	27	42	35	33	42

a Significantly different from Controls, P < 0.05.

OVERALL SUMMARY:

Mouse: Basis for dose selection for the carcinogenicity was not provided by the sponsor and there was no subchronic or chronic toxicity studies conducted in mice.

Male and female mice were administered tizanidine at 1, 4, and 16 mg/kg in the diet for 78 weeks. The drug did not cause any clinical signs or any other significant changes in the 1 and 4 mg/kg doses. It is therefore, concluded that the 4 mg/kg dose is the NOEL for general toxicity. At 16 mg/kg dose clinical signs included piloerection and self-inflicted wounds. A dose-dependent increase was found in frequency of ear necrosis and corneal opacities. Tizanidine did not affect body weight and the effect on food intake was not determined. An increase in lymphocytes produced a marked leukocytosis in 2HD (1m and 1f; in one mouse agranulocytosis), also presence of many Gumprecht's shadows (smudge cells); all other hematology and clinical changes were dose-independent and occurred in both the control and drug-treated animals. Statistical analysis of tumor data showed a positive trend in bone hyperplasia of females and a significant difference in incidence between the control and HDf. Other tumor incidence were slightly higher than the historical background (historical data were not provided) but did not reach statistical significance. These tumors included lymphoreticular, pulmonary, and liver.

Rat: Selection of the carcinogenicity doses was based on the results of a 13-wk dose-range finding study. Tizanidine was administered in the feed to male and female rats at dietary doses of 1.7, 8, and 40 mg/kg. Clinical signs noted only in MDf (piloerection and miosis) and HD rats (miosis, corneal clouding, and convulsions). Only 2 rats died, one from bleeding due to biting, and the 2nd rat cause of death was unknown. Changes in body wt, food intake, blood chemistry, urinalysis, gross morphology, histopathology, and organ wt, all noted mostly in HD animals. The microscopical changes included focal necrosis of the heart, focal and single cell necrosis of the liver, and ulcers of the eye and skin. The NOEL is 1.7 mg/kg and the LOEL is 8 mg/kg based on presence of clinical signs and blood chemistry changes (decrease in blood glucose level in MDf).

Doses selected for the carcinogenicity study were 1, 3, and 9 mg/kg of tizanidine administered in the diet to male and female rats for 104 wks. Body weight was significantly reduced in rats from wk 13 till study end. A corresponding decrease in food intake was recorded but the change was not significant from the control. Urine volume was reduced in male and female rats this effect might have been caused by the changes in drinking behavior noted in females; water intake in male rats however, was not affected. In addition to decreased urine volume, urine specific gravity was significantly increased in HD and some MD rats during wks 24, 50, 77, and 104. A contributing factor to increased urinary specific

TABLE 14
Studies Assessing the Mutagenetic Potential of Tizanidine

Assay (Reference)/ Laboratory	Species/Cell Line	Dose Levels	Control Groups	Results
<i>In Vitro</i> Ames Test (67) Sandoz, Basel	<i>Salmonella typhimurium</i> strains: TA1535, TA1538, TA98, TA100	10, 100, 1000, 10000 µg/mL (± nonactivated S-9 mix)	Positive: MNNG and 6-amino-chrysene Vehicle: A. dest.	Tizanidine negative for inducing mutations in bacteria
Ames Test (68) Sandoz, Basel	<i>Salmonella typhimurium</i> strains: TA1535, TA1537, TA1538, TA98, TA100	500, 5000, 15000, 50000 µg/mL (± S-9 mix)	Positive: 2-aminoanthracene; benzo(a)pyrene; MNNG; 9-aminoacridine 2-nitrofluorene Vehicle: DMSO	Tizanidine negative for inducing mutations in bacteria
Ames Test (69) Sandoz, Basel	<i>Salmonella typhimurium</i> strains: TA1535, TA1537, TA1538, TA98, TA100	500, 5000, 15000, 50000 µg/mL (± S-9 mix)	Positive: 2-aminoanthracene; benzo(a)pyrene; MNNG; 9-aminoacridine 2-nitrofluorene Vehicle: DMSO	Tizanidine negative for inducing mutations in bacteria
V79/HGPRT locus mutation test (70,71) Sandoz, Basel	V79 Chinese Hamster cells	0.6, 6.6, 66.6, 666, 6660 µg/mL (± S-9 mix) 0.6-10,000 µg/mL	Positive: Daunomycin; B1 Vehicle: Distilled water	Tizanidine negative for inducing gene mutations
Chromosomal Aberration Test (73) Sandoz, Basel	V79 Chinese Hamster cells	5, 25, 200 µg/mL (± activated S-9 mix)	Positive: EMS (-S-9 mix), CPA (+S-9 mix) Vehicle: DMSO	Tizanidine did not induce chromosomal aberrations.
<i>In Vivo</i> DNA Synthesis Assay (72) Sandoz, Basel	CD-1 mice	25, 50 mg/kg po (gavage)	Positive: MMS Vehicle: 2% gelatin solution	Tizanidine negative for inducing unscheduled DNA synthesis in sperm cells.
Dominant Lethal Test (74) Sandoz, Basel	CD-1 mice	40, 80 mg/kg po	Vehicle: 0.9% NaCl Positive: TEM	Tizanidine negative for inducing dominant lethal mutations.
Bone Marrow Micronucleus Test (75,76) Sandoz, Basel	CD-1 mice	12.5, 25, 50 mg/kg po for 2 days	Vehicle: Distilled Water	Tizanidine negative for inducing formation of micro-nuclei.
Bone Marrow Micronucleus & Cytogenicity Test (77,78) Sandoz, Basel	Chinese hamsters	30, 60, 120, mg/kg ip for 2 days	Vehicle: Distilled water	Tizanidine negative for inducing formation of micronuclei or chromosomal aberrations.

MNNG = N-methyl-N-nitro-N-nitrosoguanidine; EMS = ethylmethanesulfate; CPA = cyclophosphamide;
MMS = methylmethane sulfonate; TEM = triethylenemelamine

gravity is the marked increase in plasma sodium level on wk 78. Tizanidine caused changes in hematology and clinical chemistry but the changes were not dose-dependent and were not present in both sexes. Absolute and/or relative organ weights were affected in MD and HD rats and some of the changes were dose-dependent. A significant decrease was noted in liver, kidney, spleen, prostate, and testes but a significant increase in relative weight of the brain and heart occurred in HD; the biological significance of this is unclear (similar results reported in the 13-wk study). A significant finding in the rat gross morphology and histopathology was the high incidence of hind-limb granuloma, ocular opacities, swollen eye lids/keratitis, and hair loss on the abdomen and limbs. All treated f rats had centriacinar fatty vacuolation of the liver, and males and females of HD had hepatocyte hypertrophy and hyperplastic nodule. The only statistically significant neoplasm was pancreatic islet cell adenoma or hyperplasia in female rats and skin fibroma in male rats when compared with the incidence in the control group. None of these or other neoplastic lesions occurred in both sexes or showed dose-dependent relationship and the differences from the control findings though reached statistical significance in some cases, were within or slightly higher than historical control data (historical data were not available to the reviewer). Also, similar findings were not observed in the mouse study.

RECOMMENDATION:

At this time a final recommendation can not be made because:

1. Statistical analysis of tumor data has not yet been conducted by the Agency. This is because the raw data has not been sent by the sponsor.
2. Because of the quantitative differences in metabolism between humans and animals, the potential toxicity/carcinogenicity of the metabolites can not be assessed. Specifically, of the 3 major human metabolites (#3, 4, 10); see the pharmacokinetic section for detail.

It is also noted that exposure data were not available from the rat or mouse carcinogenicity studies or from the oral subchronic/chronic studies in rats and dogs. Such information would have been highly desirable in assessing toxicity and dose.

Reproductive and Developmental Studies:
vol. 1-16 and 1-17

The following studies were reviewed by Dr. Ann Wilk in 1991 (Review attached):

1. Segment I Fertility and Reproductive Performance in Male Rats. Sandoz report# 203-013 August 1978. Doses: m3, 10, 30 mg/kg.
2. Segment I Fertility and Reproductive Performance in Female Rats. Sandoz report# 203-014 August 1978. Doses: 3, 10, 30 mg/kg.
3. Segment II Teratology Study in Rats. Sandoz report# 203-006 August 1976. Doses: 1, 3, 10, 100 mg/kg and in a 2nd experiment within that study doses were: 0.3 and 1 mg/kg.
4. Segment II Teratology Study in Rabbits. Sandoz report# 203-007 August 1976. Doses: 1, 3, 30, 100 mg/kg.
5. Segment III Peri- and Post-natal Study in rats. Sandoz report# 203-017 Feb 1979. Doses: 3, 10, 30 mg/kg.

Dr. Wilk's concluded that a concern exists for the embryo/fetal loss at doses ≥ 3 mg/kg in the rat. She indicated that the effects at higher doses (30 mg/kg) may be secondary to the maternal toxicity; at lower doses the mechanism is unknown. She recommended that the Investigator's brochure clearly describes the results of the reproductive findings regarding pre- and post-natal fetal loss following tizanidine administration.

The following are studies reviewed by Dr. Atrakchi:

1. Segment II/A teratology Study in Rats/English document March 20 1985 Study conducted in Sandoz Preclinical Research Lab in Japan/Report# 203-032

Methods:

Animals/no.: 38/dose pregnant Jcl-SD rats 12 wks old.
Dose/Duration: 1, 3, 10, 30 mg/kg during gd 7-17 post coitum.
Doses were selected based on previous studies (Basel Switzerland and a pilot study with doses up to 60 mg/kg). The control group was administered 2.5% gum arabic solution/5 ml/kg in a similar regimen to the treated groups. One male paired with 2 f overnight. Two thirds of pregnant females were sacrificed on gd 21 and together with their fetuses, were examined; the remaining third delivered spontaneously. Female reproductive parameters and postnatal growth and development of pups were evaluated. Pups physical development was assessed with the following tests:

righting reflex	pp 4,5
separation of ear auricula	pp 4,5,6
appearance of hair	pp 10,11
eruption of upper incisors	pp 10,11,12,13
separation of eyelids	pp 14,15,16,17
grasping wire	pp 17,21

Behavioral and functional development were assessed as follows:

Rota rod/locomotor coordination	pp 21
Open field test	4 wks post birth
Learning ability/avoidance test	5 wks post birth

Also, the auricular reflex (startle response), pupil reflex, and pain sensation using Galton whistle at 4.5kz.

Some of the pups (1:1 sex ratio) composed F1 generation were mated at the age of 11-12 wks. Pregnant females were killed on gd 21 and subjected to complete examination as their parents (F0).

All data were statistically analyzed by Fisher's two-sided exact test and Kruskal Wallis test followed by Mann-Witney U-test.

Results:

Mortality/Clinical Signs: None of the dams aborted or died. There were no clinical signs at 1 mg/kg. At ≥ 3 mg/kg the following were observed: ataxic gait, hypomotility, flaccidity, exophthalmos, mydriasis, bradypnea, irregular respiration, piloerection, and salivation; these effects were dose-dependent. In general, the number of rats that delivered prior to gd 21 was higher among treated than the control (0 in control and 1-2/treated group).

Body Weight/Food Consumption: mean weight and weight gain in the 10 and 30 mg/kg groups were significantly reduced from gd 13 and during the whole dosing period respectively. Food intake decreased from gd 7 in the 10 and 30 mg/kg groups.

Necropsy: none that was drug-related.

Litter Data:

Findings in Dams: mean no. of corpora lutea, implantation sites, resorptions, and live/dead fetuses were comparable between treated and control groups (table 1). Placental weight was decreased dose-dependently starting at 10 mg/kg (significantly in 30 mg/kg), fetal weights were significantly and dose-dependently reduced starting at 10 mg/kg. A slight but significant increase in gestation period was found in HD females (tables 1&2). However, it was indicated by the sponsor that this change was within the normal historical data.

Maternal Data: no significant drug-related results noted in delivery rate, implantation sites, litter size, number of live/dead pups or sex ratio.

Skeletal findings in fetuses: the incidence of dumbbell shaped thoracic vertebrae was significantly increased in HD relative to

NDA-020397

FIRM: ATHENA NEUROSCIENCES

TRADE NAME: ZANAFLEX ORAL TABS.

GENERIC NAME: TIZANIDINE HCL

4MG

6 OF 7

Teratology Study in rats/Tokyo 1985
 Study 203-32

Table 2 Litter data

Dose (mg/kg)	No. of Litter	CL		IP		IP/CL		LF		LF/IP		IP		Resorptions		Post-implantation loss	Weight of fetuses	Weight of placentae	Sex Ratio M/F
		CL	IP	IP	CL	IP	CL	IP	FT	ET	FT	ET	(9)	(9)					
Control	21	17.29	14.90	86.2	13.71	92.0	0.00	0.05	1.14	1.19	5.36	0.50	0.06						
		+3.24	+1.01 (313/363)	+2.01 (200/313)				+0.22	+2.15	+2.10		+0.31	+0.05 (133/131)						
1	22	17.73	14.95	84.4	14.40	95.4	0.00	0.05	0.65	0.70	5.33	0.52	1.17						
		+3.49	+2.30 (329/399)	+2.52 (200/302)				+0.22	+0.08	+0.96		+0.36	+0.05 (135/131)						
3	22	18.23	15.00	82.3	14.10	94.9	0.05	0.00	0.70	0.75	5.43	0.52	0.97						
		+3.21	+2.64 (330/401)	+2.63 (202/307)				+0.00	+0.73	+0.79		+0.23	+0.00 (139/142)						
10	23	19.04	14.74	77.4	13.71	94.4	0.00	0.05	0.70	0.81	4.90	0.49	1.32						
		+3.52	+2.56 (339/432)	+2.03 (200/305)				+0.22	+1.10	+1.17		+0.45	+0.05 (164/124)						
30	22	18.50	15.00	81.1	14.05	94.2	0.00	0.00	0.06	0.06	4.74	0.46	0.90						
		+5.26	+2.62 (330/407)	+2.50 (295/313)				+0.00	+0.73	+0.73		+0.32	+0.05 (140/151)						

CL : corpus luteum
 LF : live fetus
 FT : fetal death
 IP : implantation site
 IF : dead fetus
 ET : embryonic death
 Mean ± S.D. * : P<0.05 ** : P<0.01

toxicology study in Rats 1985
 study # 203-032

Table 4

Maternal delivery data

Dose (mg/kg)	No. of animals	No. of pregnant animals	No. of delivered animals	Duration of gestation	Implantation site	Litter size	Live birth index	Average No. of pups		Sex ratio male/female
								male	female	
Control	14	11	11	21.2	14.5	13.5	93.1	5.0	7.7	0.75
		(78.6)	(100.0)	±0.40	±1.44	±1.21	(149/160)	±1.66	±1.68	
1	14	10	10	21.3	14.8	13.3	89.9	5.9	7.4	0.80
		(71.4)	(100.0)	±0.43	±1.93	±2.58	(133/140)	±2.18	±1.84	
3	14	12	12	21.4	15.0	13.9	93.9	6.9	7.0	0.99
		(85.7)	(100.0)	±0.51	±2.30	±2.66	(153/163)	±2.70	±1.61	
10	14	13	13	21.7	15.2	12.4	81.7	5.2	6.2	0.95
		(92.9)	(100.0)	±0.63	±1.20	±2.57	(161/197)	±2.38	±2.65	
30	14	12	12	21.8	14.7	11.6	80.6	6.4	5.2	1.23
		(85.7)	(100.0)	±0.39	±2.93	±2.60	(116/144)	±2.67	±1.69	

* : p < 0.05 ** : p < 0.01 Mean ± S.D.

- 1) : No. of pregnant animals/no. of animals
- 2) : No. of delivered animals/no. of pregnant animals
- 3) : No. of new borns/no. of implantation sites

the control. Asymmetry + hypoplasia of 5th sternebra was increased in all treated groups but significant difference found only in the 10 and 30 mg/kg (tables 3&4). Rudimentary/non-ossified and hypoplastic 5th sternebrae significantly increased in the 10 and 30 mg/kg groups relative to the control. The numbers of proximal phalanges and metatarsals of hind limbs were significantly reduced in the 10 and 30 mg/kg groups and fore limb proximal phalanx were decreased in HD (table 5). Sacral + coccygeal vertebrae were significantly reduced in the two high doses. Supplements to these tables summarize the skeletal findings and affected fetuses (table 6). A significant and dose-dependent increase in retarded fetuses is found in all treated groups (not significant in LD).

Findings in Dams during lactation: body wt gain was significantly higher in all treated groups except LD, food intake was also increased in all groups but remained within the normal range. Except for the 1 mg/kg, some pups died within the first 4 days of nursing but no relationship was found between incidence and dose. No other effects were noted in postnatal development or behavior of pups.

F1/Necropsy at 8 wks: absolute wt of the heart in F1 males was significantly increased (2-5%) in all treated groups and, in f the absolute wt of the heart increased slightly in the HD, and the absolute kidney weight was increased (4-16%) in all but the LD group. No effects on fertility parameters of F1, body wt or food intake. There was no significant drug-related findings at necropsy.

Summary/Conclusion:

Oral administration of tizanidine at 0, 1, 3, 10, 30 mg/kg to pregnant female rats during gd 7-17 (organogenesis) caused dose-dependent clinical signs in all treated dam groups except LD, with most severe findings in the 10 and 30 mg/kg. Body wt and food intake were also reduced however, in dams that were allowed to deliver, body wt recovered. Pre-natal findings included significantly reduced fetal wts at 10 and 30 mg/kg, retarded skeletal ossification, and significantly smaller placenta in the HD. There were no embryoletality or teratogenicity for up to 30 mg/kg. Post-natal findings were non-remarkable except for a longer mean gestation period in HD. Litter size, wt, physical and behavior of F1 offspring were normal. It is concluded that tizanidine at doses ≥ 3 mg/kg is toxic to the dams but not teratogenic or embryoletal for doses up to 30 mg/kg. The reproductive NOEL in this study is 1 mg/kg since clinical signs and few skeletal abnormalities were evident in the 3 mg/kg dose.

Study 203-32
 teratology study in Rat. 1985
 Table 3 Skeletal findings of fetuses
 3

Amendment 1

Dose (mg/kg)	Control	1	3	10	30
No. of litters	21	20	20	21	21
No. of fetuses	208	207	202	208	205
Vertebral bodies (except cervical V.b)					
dumbbell shaped	3 (3)	6 (6)	11 (9)	7 (6)	28(13, 14)
cleaved	2 (2)	6 (6)	2 (1)	3 (2)	5 (4)
flat	1 (1)	0	3 (3)	4 (3)	2 (2)
asymmetry	1 (1)	1 (1)	1 (1)	1 (1)	4 (4)
rudimentary or not ossified	1 (1)	0	2 (2)	2 (2)	1 (1)
hyperplasia	1 (1)	3 (3)	1 (1)	7 (5)	4 (3)
displaced	0	0	1 (1)	0	0
Vertebral arch					
displaced	7 (5)	1 (1)	2 (2)	1 (1)	1 (1)
Vertebral body & arch					
absent	0	0	0	0	1 (1)
5th sternbra					
asymmetrical	39(18)	29(14)	58(19)	68(20)	74(20)
rudimentary or not ossified	7 (5)	16 (8)	9 (8)	23(12)	33(14)
hypoplasia	2 (2)	3 (4)	4 (4)	18(11)	12(10)
cleaved + asymmetrical	1 (1)	2 (2)	2 (2)	0	1 (1)
cleaved + rudimentary	1 (1)	0	1 (1)	0	1 (1)
hypoplasia + asymmetrical	2 (2)	8 (5)	7 (4)	9 (8)	11 (13)

() : No. of litters
 V.b : Vertebral body
 * : p<0.05 ** : p<0.01

Study → 203-32
teratology study in Rat 1985

Table 5-2 Skeletal findings of fetuses

4

Amendment 1

Dose (mg/kg)	Control	1	3	10	30
No. of litters	21	20	20	21	21
No. of fetuses	288	287	282	288	295
Other than 5th sternebra					
asymmetrical	6 (3)	8 (5)	8 (5)	15 (11)	15 (11)
cleaved	0	0	0	3 (3)	0
cleaved + rudimentary	0	0	0	1 (1)	0
hypoplasia	2 (2)	2 (2)	1 (1)	9 (3)	7 (7)
hyperplasia	1 (1)	3 (3)	0	1 (1)	3 (3)
rudimentary or not ossified	0	2 (1)	1 (1)	5 (3)	1 (1)
bifurcation	0	0	0	1 (1)	0
hypoplasia + cleaved	1 (1)	0	0	1 (1)	0
hypoplasia + asymmetrical	0	0	1 (1)	2 (1)	2 (2)
cleaved + asymmetrical	0	0	0	1 (1)	0
Ribs					
undulation	3 (3)	0	0	0	0
13 rib short	0	0	0	0	1 (1)
14 rib					
short bilateral	10 (7)	4 (4)	8 (5)	4 (3)	5 (4)
unilateral	19 (9)	15 (10)	21 (10)	16 (7)	15 (6)
total	29 (13)	19 (11)	29 (11)	20 (7)	20 (7)
extra bilateral	0	2 (2)	0	2 (2)	3 (2)
unilateral	1 (1)	4 (3)	9 (6)	1 (1)	2 (1)
total	1 (1)	6 (3)	9 (6)	3 (2)	5 (2)
cervical rib	0	0	0	1 (1)	2 (2)
27 presacral vertebrae (cervical + thoracic + lumber)	2 (2)	3 (3)	2 (2)	0	1 (1)

→

() : No. of litters
* : p<0.05

study 203-32

Table 5 Ossification degree of fetal skeleton

5

Dose (mg/kg)	No. of litters	No. of fetuses	Average No. of bones				
			S + C	Fore limb		Hind limb	
				p	MC	P	MT
Control	21	288	11.0 ±0.74	3.8 ±0.17	4.0 ±0.00	2.5 ±1.07	4.8 ±0.18
1	20	286	10.9 ±0.81	3.7 ±0.41	4.0 ±0.02	2.0 ±1.21	4.7 ±0.29
3	20	282	10.9 ±0.91	3.9 ±0.17	4.0 ±0.03	2.2 ±1.23	4.8 ±0.23
10	21	288	10.3** ±0.90	3.6 ±0.83	3.9 ±0.19	1.4** ±1.12	4.6** ±0.31
30	21	295	10.1** ±0.63	3.3** ±0.45	4.0 ±0.05	0.7** ±1.10	4.4** ±0.29

S+C : Sacral + Coccygeal
 p : proximal phalanx
 MC : metacarpal bone
 MT : metatarsal bone

Mean ± S.D.

* : p<0.05 ** : p<0.01

Skeletal study in rat

Teratology study in Rats

Report # 203-032

Amendment I Supplement to Table 5-1, 5-2 table 6

Morphological findings in fetuses
:skeletal findings

A) Absolute values
(Number affected/Number examined)

	Litters containing affected fetuses		
	Retardations	Minor findings	Major findings
Control	20/21	17/21	0/21
1 mg/kg	18/20	17/20	2/20
3 mg/kg	20/20	13/20	0/20
10 mg/kg	21/21	10/21	0/21
30 mg/kg	21/21	13/21	1/21

	Affected fetuses		
	Retardations	Minor findings	Major findings
Control	81/288	37/288	0/288
1 mg/kg	72/288	33/288	2/288
3 mg/kg	87/282	37/282	0/282
10 mg/kg	144/288	33/288	0/288
30 mg/kg	183/285	34/285	1/285

B) Average number of affected fetuses per litter and S.D.

	Retardations	Minor findings	Major findings
Control	2.80 1.87	1.78 1.70	0.00 0.00
1 mg/kg	3.80 3.02	1.85 1.18	0.10 0.31
3 mg/kg	4.85** 2.78	1.85 1.87	0.00 0.00
10 mg/kg	6.88*** 3.80	1.57 2.38	0.00 0.00
30 mg/kg	8.71*** 3.48	1.82 2.31	0.05 0.22

* : Difference to control group value significant at 5% level.
** : Difference to control group value significant at 1% level.

Teratology study in Rats
203-032

table c (cont.)

C) Relative values as % of examined material

	Litters containing affected fetuses		
	Retardations	Minor findings	Major findings
Control	85.24	80.85	0.00
1 mg/kg	90.00	85.00	10.00
3 mg/kg	100.00	85.00	0.00
10 mg/kg	100.00	47.82	0.00
30 mg/kg	100.00	61.80	4.78

	Mean percentage of affected fetuses		
	Retardations	Minor findings	Major findings
Control	22.15	12.87	0.00
1 mg/kg	24.18	11.52	0.83
3 mg/kg	33.43	13.52	0.00
10 mg/kg	50.48	10.27	0.00
30 mg/kg	61.61	12.59	0.40

2. Treatment of pregnant rats shortly before and during delivery/Sandoz Switzerland 1978/Report# 203-012

Methods:

Female OFA-Sandoz rats 9-11 wks old were mated (2f with 1 m); the exact date of conception was unknown (vaginal smears were not taken). The drug was suspended in 2% gelatin solution and administered 2 to 6 days prior to delivery with last administration occurring on the day of delivery. Doses were 10 and 30 mg/kg and 6-7 pregnant rats per dose group were tested; control group was administered the vehicle. Number of live pups was recorded on day of birth (0), and pp days 4 and 21. Statistical analysis was made using U-test for comparison of litter size and Chi-square for comparison of postnatal mortality.

Results:

Mean number of live pups was significantly decreased at both doses with significant difference on pp day 21 in the 10 mg/kg dose, and on pp days 4 and 21 in the 30 mg/kg group. A significant increase in postnatal mortality occurred in HD within 4 days after birth (94% and all pups died after pp day 4 (Tables 1-3).

Summary and Conclusion:

Oral administration of tizanidine to pregnant rats at 10 and 30 mg/kg few days before delivery caused a significant increase in postnatal loss. Also the number of live pups was significantly reduced in both doses on pp day 21. At 30 mg/kg all offspring died within 4 days pp, the cause of death was unknown but the sponsor suggested a possible interference with the delivery process. The sponsor also indicated that the dams at these doses were heavily sedated for several hrs post dose which might have interfered with the maternal care during birth. It was concluded that these effects on offspring are secondary to maternal toxicity caused by the high doses of the drug.

treatment of dams 2-6 days before delivery
 study # 203-012
 Rat Segment III

4. EXPERIMENTAL DATA table 1

4.1. Mean Litter Size and Postnatal Mortality

treatment	litters	duration of treatment ¹ (days)	live offspring			postnatal loss (%) days		
			day 0	day 4	day 21	0 - 4	4 - 21	0 - 21
Controls	7	4.1	13.4	13.1	12.7	2.1	3.7	5.3
10 mg/kg/d	7	4.4	11.7	10.4	9.3 ²	11.0 ²	11.0 ²	20.7 ²
Controls	6	4.5	12.0	12.0	10.8	0	9.7	9.7
30 mg/kg/d	7	5.0	9.6	0.6 ²	0.6 ²	94.0 ²	0	94.0 ²

¹ Last treatment occurred on the day of birth (day 0 p.p.).

² p < 0.5

teratol. Seg II in Rats

Table 2

4.2. Data of Single Litters

treatment	dam no.	duration of ¹ treatment (days)	day 0 p.p.	live offspring day 4 p.p.	day 21 p.p.
gelatine	41	4	12	11	11
	44	3	12	12	12
	47	3	15	15	13
	51	6	13	12	12
	53	4	13	13	13
	57	5	13	13	12
	59	4	16	16	16
	mean		4.1	13.4	13.1
S.D.		1.1	1.5	1.0	1.6
DS 103-282 10 mg/kg/d	43	4	12	9	8
	45	3	13	12	8
	49	5	10	6	5
	52	5	11	10	10
	55	6	11	11	11
	58	3	12	12	10
	60	5	13	13	13
	mean		4.4	11.7	10.4
S.D.		1.1	1.1	2.4	2.6

¹ Last treatment occurred on the day of birth (day 0 p.p.).

teratop. Seg II in Rcds
 study # 203-012

Table 3

treatment	dam no.	duration of ¹ treatment (days)	day 0 p.p.	live offspring day 4 p.p.	day 21 p.p.
gelatine	22	5	9	9	9
	25	3	13	13	13
	28	7	14	14	13
	31	5	14	14	12
	33	4	12	12	9
	36	3	10	10	9
	mean		4.5	12.0	12.0
S.D.		1.5	2.1	2.1	2.0
DS 103-282 30 mg/kg/d	21	7	7	0	0
	23	5	12	0	0
	26	4	9	0	0
	30	4	14	0	0
	32	4	7	4	4
	34	5	4	0	0
	40	6	14	0	0
	mean		5.0	9.6	0.6
S.D.		1.2	3.9	1.5	1.5

¹ Last treatment occurred on the day of birth (day 0 p.p.).

Supplements:

The sponsor submitted on Oct. 1986, comments on the teratology results. They stated that the teratology study in rats used high doses (100 mg/kg) that invalidated the study. In a second experiment (within the same study), lower doses (0.1 and 3 mg/kg) were tested to support the results of the low doses in the first experiment. These studies were conducted in Switzerland in 1976 and met the generally accepted SOP at the time. Another teratology study in rats was carried out in Japan in 1985 according to the Japanese standards. The doses in the Japanese study were 0, 1, 3, 10, 30 mg/kg/d from gd 7-17, the doses of the first study/Switzerland were 1, 3, 10, 100 mg/kg/d from gd 6-17 (see Dr. Wilk's review). The Japanese study did not show any teratology findings up to 30 mg/kg/d however, developmental fetal retardation was evident at doses ≥ 3 mg/kg/d. This retardation was manifested as smaller fetuses and significantly retarded skeletal ossification. In the Swiss study on the other hand, fetal malformation was seen at 100 mg/kg and consisted in addition to fetal deaths of: encephalocele (6/1 litter) and microphthalmia (5/1 litter; the same litter with the encephalocele) in addition to fetal deaths. Encephalocele was also observed in 1 mg/kg (1/1 litter) and 3 mg/kg (1/1 litter). These malformations appear to occur frequently at maternally toxic doses as demonstrated in teratology studies conducted in mice, rats, hamsters and rabbits (review by Khera 1984, 1985 in: Teratology vols. 29:411 and 32:129 respectively). The sponsor therefore, did not consider the increased incidence of malformed fetuses at 100 mg/kg as evidence of teratogenic potential of tizanidine. At the 1, 3, 10 mg/kg doses, tizanidine did not induce embryoletality or teratogenicity however, developmental retardation occurred. A single major (type C) anomalies found in the 1 and 3 mg/kg occurred at an incidence of 0.33 and 0.42% per group which is similar to the spontaneous occurrence of 0.38% in prior control group. Higher incidence of minor type B anomalies observed in 3 and 10 mg/kg dose groups (incomplete rib formation and vertebrae) reflected developmental retardation rather than teratogenic effect. The renal changes noted in several fetuses in the 10 mg/kg dose were identical to those reported by Woo and Hoar (1972) as "apparent hydronephrosis" that followed retarded fetal development. The retarded skeletal ossification was explained as the result of low body weights; in addition the number of litters with the above effects was not significantly different from that of the control in any dose group.

In a supplementary study, tizanidine at 0.3 and 1 mg/kg did not produce major type C or minor type B anomalies and no maternal toxicity or embryoletality were seen. It was concluded that the fetal malformation/retarded development noted at doses ≥ 3 mg/kg in the rat are likely to be the consequence of maternal toxicity. The 3 mg/kg is 4 times the maximum clinical dose or 8 times on a mg/m² basis (clinical dose 36 mg/d).

In the same submission the rabbit teratology study was also discussed. The doses were 1, 3, 30, and 100 mg/kg on gd 6-18. Tizanidine was not teratogenic at any dose but maternal toxicity was observed at 3 mg/kg, and at 100 mg/kg all dams died. Therefore, the results at the 100 mg/kg were considered irrelevant. As in the rat study, there was no evidence of teratogenicity up to 30 mg/kg (the maximum relevant dose).

It was concluded that tizanidine in rats and rabbits impaired maternal health at doses ≥ 3 mg/kg and consequently caused developmental retardation in fetuses. These effects did not persist as demonstrated by the normal postnatal development of offsprings. At >30 mg/kg severe maternal toxicity was noted (including death), which caused marked impairment of fetal development and survival, therefore, doses >30 mg/kg were considered by the sponsor to be irrelevant for safety assessment. The maximum clinical dose is 36 mg/d which is 42 fold the maximum relevant animal dose of 30 mg/kg/d providing a reasonable margin of safety. Tizanidine therefore, is a teratogen only at excessively high doses.

Summary and Evaluation of Reproductive/Developmental Studies:

The studies conducted fulfill the recommended testing of a drug for its teratogenic, reproductive, and developmental potential. Some of these studies have been reviewed in IND 37,891 by Dr. Ann Wilk. The NOEL(s) for Segment I m and f studies are 10 and 3 mg/kg respectively, for Segment II rat is 1 mg/kg, Segment II rabbit none was established, and for Segment III rat is 3 mg/kg. Dr. Wilk's main concern was the embryo/fetal loss, but indicated that at least some of these effects could be secondary to maternal toxicity specifically at higher doses (≥ 30 mg/kg).

Tizanidine when administered to pregnant rats at 10 and 30 mg/kg few days before delivery caused a significant decrease in postnatal loss and the number of live pups was significantly reduced in both doses on ppp 21. At the HD all offspring died within 4 days pp, the cause of death was unknown but the sponsor indicated a possible interference with the delivery process. The sponsor also reported that the dams at these doses were heavily sedated for several hrs post dose which might have interfered with the maternal care during birth. It was concluded that these effects on offspring are secondary to maternal toxicity caused by the high doses of the drug.

Khera in two review articles (1984 & 1985) surveyed a large number of teratology studies conducted between 1963-1983 in mice, rats, hamsters, and rabbits. He found a strong association between maternal toxicity and fetal mortality and/or malformations in all these species. Among the malformations in the rat are encephalocele, microphthalmia, and several skeletal deformations

(vertebrae and sternebrae). It was indicated that at non-maternally toxic doses of the chemical or using antagonists, all the fetal toxicities disappeared. Therefore, fetal malformations and/or mortality maybe secondary to maternal toxicity and unrelated to direct effect of the drug. Although fetal toxicity is also found in absence of maternal toxicity and the criteria used to describe maternal toxicity varied, in general the article's arguments were adequate and therefore, it maybe concluded that tizanidine's teratogenic potential at high doses (>30 mg/kg) is secondary to maternal toxicity since no malformations per se were observed at lower doses. However, since the human teratogenic potential of tizanidine is unknown, administration of this drug to pregnant women should be based on risk/benefit assessment.

Labelling:

Category C; caused teratogenicity in rats at doses >50x the maximum human dose on a mg/kg basis or 8x on a mg/m² basis. At doses 50x the human dose on a mg/kg basis, the drug caused severe maternal toxicity including death and impaired fetal development. At lower doses (0.5-0.8x the maximum clinical dose on a mg/m² basis), both in rats and rabbits, maternal health was impaired. The teratogenic potential of tizanidine in humans during pregnancy is unknown. Since there are no data on use of tizanidine in pregnant women, administration of the drug to pregnant women must be based on risk/benefit evaluation.

Genetic Toxicology

In Vitro:

Bacterial Ames Assay

Mammalian Gene mutation

/V79-HGPRT Locus/Chinese Hamster Cells

Mammalian Chromosomal Aberration

V79 Chinese Hamster Cells

In Vivo:

Bone Marrow Micronucleus/Mouse

Bone Marrow Micronucleus & Cytogenetics/

Chinese Hamster

UDS/Mouse

Dominant Lethal/Mouse

Summary results for these studies are presented in the attached table provided by the sponsor. The studies were reviewed by Dr. Wilk (Appendix A).

TABLE 14
Studies Assessing the Mutagenetic Potential of Tizanidine

Assay (Reference)/ Laboratory	Species/Cell Line	Dose Levels	Control Groups	Results
<i>In Vitro</i> Ames Test (67) Sandoz, Basel	<i>Salmonella typhimurium</i> strains: TA1533, TA1538, TA98, TA100	10, 100, 1000, 10000 µg/mL (± nonactivated 8-9 mix)	Positive: MNNG and 6-amino-chrysene Vehicle: A. dest.	Tizanidine negative for inducing mutations in bacteria
Ames Test (68) Sandoz, Basel	<i>Salmonella typhimurium</i> strains: TA1533, TA1537, TA1538, TA98, TA100	500, 5000, 15000, 50000 µg/mL (± 8-9 mix)	Positive: 2-aminoanthracene; benzo(a)pyrene; MNNG; 9-aminoacridine 2-nitrofluorene Vehicle: DMSO	Tizanidine negative for inducing mutations in bacteria
Ames Test (69) Sandoz, Basel	<i>S. typhimurium</i> strains: TA1533, TA1537, TA1538, TA98, TA100	500, 5000, 15000, 50000 µg/mL (± 8-9 mix)	Positive: 2-aminoanthracene; benzo(a)pyrene; MNNG; 9-aminoacridine 2-nitrofluorene Vehicle: DMSO	Tizanidine negative for inducing mutations in bacteria
V79/HGPRT locus mutation test (70,71) Sandoz, Basel	V79 Chinese Hamster cells	0.6, 6.6, 66.6, 666, 6660 µg/mL (± 8-9 mix) 0.6-10,000 µg/mL	Positive: Daunomycin; B1 Vehicle: Distilled water	Tizanidine negative for inducing gene mutations
Chromosomal Aberration Test (73) Sandoz, Basel	V79 Chinese Hamster cells	5, 25, 200 µg/mL (± activated 8-9 mix)	Positive: EMS (-8-9 mix), CPA (+8-9 mix) Vehicle: DMSO	Tizanidine did not induce chromosomal aberrations.
<i>In Vitro</i> DNA Synthesis Assay (72) Sandoz, Basel	CD-1 mice	25, 50 mg/kg po (gavage)	Positive: MMS Vehicle: 2% gelatin solution	Tizanidine negative for inducing unscheduled DNA synthesis in sperm cells.
Dominant Lethal Test (74) Sandoz, Basel	CD-1 mice	40, 80 mg/kg po	Vehicle: 0.9% NaCl Positive: TEM	Tizanidine negative for inducing dominant lethal mutations.
Bone Marrow Micronucleus Test (75,76) Sandoz, Basel	CD-1 mice	12.5, 25, 50 mg/kg po for 2 days	Vehicle: Distilled Water	Tizanidine negative for inducing formation of micro-nuclei.
Bone Marrow Micronucleus & Cytogenicity Test (77,78) Sandoz, Basel	Chinese hamsters	30, 60, 120, mg/kg ip for 2 days	Vehicle: Distilled water	Tizanidine negative for inducing formation of micronuclei or chromosomal aberrations.

MNNG = N-methyl-N-nitro-N-nitrosoguanidine; EMS = ethylmethanesulfate; CPA = cyclophosphamide;

MMS = methylmethane sulfonate, TEM = triethylenemelamine

Appendix A

**Pharmacology and Toxicology Review
Original Summary**

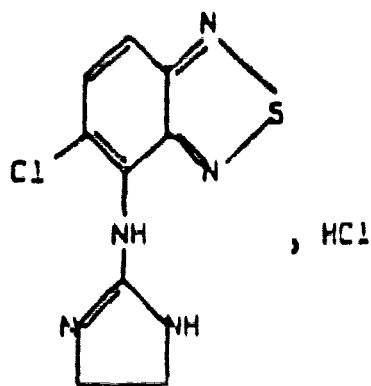
IND: 37,891

Drug: Tizanidine HCL tablets

Sponsor: Athena Neurosciences
South San Francisco, California 94080

Related IND: (Sandoz)

Chemical name and structure:



5-chloro-4-(2-imidazolyl-2-ylamino)-2,1,3-
benzothiadiazole

Tablet components:

Ingredients

Tablets

IND

2

Proposed Clinical Study (021-001):

Multicenter, double blind, placebo controlled study in 250 patients with multiple sclerosis (MS) who have muscle spasticity. Males and females (not pregnant or using a barrier contraceptive) ages 17-70 years old.

Dosage Titration Schedule

Days	Dosage of Tizanidine (mg)			No. of Tablets	Total Daily Dose (mg)
	Morning	Noon	Evening		
1	0	0	2	1 (2 mg)	2
2	0	0	4	2 (2 mg)	4
3	2	2	4	4 (2 mg)	8
4	4	4	4	3 (4 mg)	12
5	4	4	4	3 (4 mg)	12
6	4	4	4	3 (4 mg)	12
7	6	4	6	2 (2 mg)+3 (4 mg)	16
8	6	4	6	2 (2 mg)+3 (4 mg)	16
9	6	4	6	2 (2 mg)+3 (4 mg)	16
10	6	6	8	2 (2 mg)+4 (4 mg)	20
11	6	6	8	2 (2 mg)+4 (4 mg)	20
12	6	6	8	2 (2 mg)+4 (4 mg)	20
13	8	8	8	6 (4 mg)	24
14	8	8	8	6 (4 mg)	24
15	8	8	8	6 (4 mg)	24
16	10	8	10	2 (2 mg)+6 (4 mg)	28
17	10	8	10	2 (2 mg)+6 (4 mg)	28
18	10	8	10	2 (2 mg)+6 (4 mg)	28
19	10	10	12	2 (2 mg)+7 (4 mg)	32
20	10	10	12	2 (2 mg)+7 (4 mg)	32
21	12	12	12	9 (4 mg)	36

22-84 Plateau phase

(Note: Tizanidine is marketed in more than 20 countries).

Preclinical Studies:

Summary and Evaluation

(Also see Pharmacologist reviews IND)

- I. Basic Pharmacology
 - A. Myotonolytic activity

1. Central inhibition of muscle rigidity

- a) Thalamonal (2.5 mg droperidol + 0.05 mg fentanyl/ml) induced a rigor.

		ED min	ED block (mg/kg)
tizanidine	IV	0.013	0.055
	oral	0.5 (ED ₅₀)	
diazepam	IV	0.011	2.2
baclofen	IV	0.71	4.5
dantrolene	IV	0.34	7.1

- b) Intercollicular decerebration induced rigor.

		ED (block) mg/kg
tizanidine	IV	0.49 ± 0.35
diazepam	IV	3.8 ± 1.6
baclofen	IV	1.3 ± 0.69

2. Rabbit (conscious)

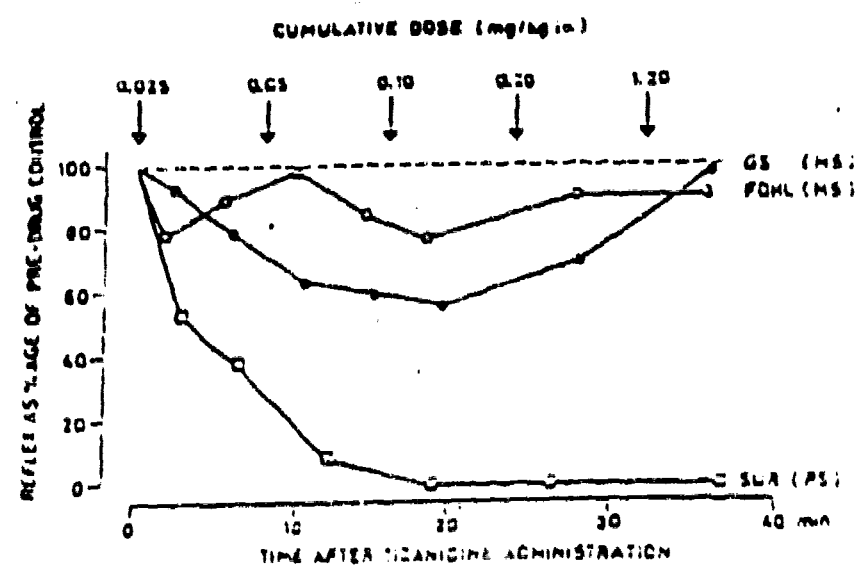
- a) Inhibition of hind limb extensor reflex activity.

		ED ₅₀ (block) mg/kg
tizanidine	IV	0.019
diazepam	IV	0.23
baclofen	IV	0.3

3. Cat

a) Inhibition of polysynaptic - evoked ventral root reflexes in the spinalized cat.

Effects of Tizanidine on Polysynaptic and Monosynaptic Reflex Activity in the Spinalized Cat (3)



FDHL: flexor digitorum hallucis longus (monosynaptic); GS: gastrocnemius/soleus (monosynaptic); SRA: sural (polysynaptic)

B. Mechanism of action

Evidence for impaired release of excitatory/amino acids from spinal interneurons (e.g. D-aspartate). This effect is mediated by the agonistic action of tizanidine at α_2 adrenergic receptors.

This mechanism supported by:

- a) Selective binding affinity of tizanidine for α_2 noradrenergic receptors ($IC_{50} = 2.1$ nM in calf cortex in vitro).
- b) Inhibition of electrically-induced release of NA from rat occipital cortex slices by tizanidine ($IC_{50} = 39$ nM) and the α_2 agonist clonidine ($IC_{50} = 15$ nM).
- c) In in vitro experiments with rat spinal cord tissue tizanidine (50 μ M) inhibited K induced release of [³H] D-aspartate which indicates that the drug may inhibit excitatory transmission via a presynaptic action on excitatory interneurons. D-aspartate release was also inhibited by NA at 200 μ M.

C. Cardiovascular Effects

a) Rat

The cardiovascular activity of tizanidine, at oral doses shown to inhibit α -rigidity, in the conscious animal appears to be mild and transient and consistent with that expected of a drug known have α_2 -agonist properties. In the conscious rat, oral doses of tizanidine (0.1 to 1.0 mg/kg) induced an initial reduction in blood pressure followed at 3-5 hours later by an increase (maximum increase of 12%). The increase in blood pressure was accompanied by a non-dose-dependent reduction in heart rate (maximum reduction of 9%). In pithed rats, blood pressure was increased, the dose causing an increase of 100 mm Hg being 0.3 mg/kg, iv. The pressor response to noradrenaline was also potentiated by tizanidine in this preparation. These actions are likely attributable to the vasoconstriction resulting from the α_2 -adrenergic effects of the drug.

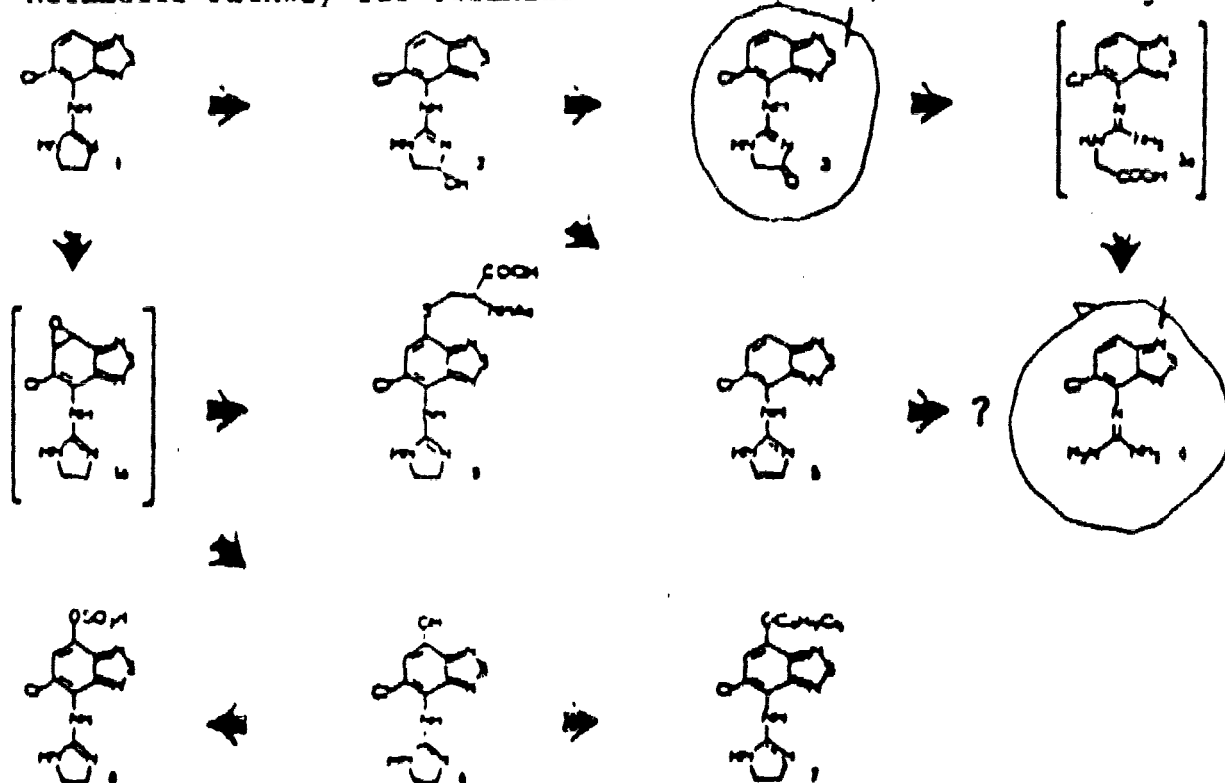
b) Dog

In the open chest dog preparation, tizanidine had no marked effect on blood pressure at doses of 4.0 to 80.0 ug/kg, iv (bolus injection), but caused a dose-dependent bradycardia (maximal reduction of 50%). The latter effect was likely of central origin, since it was abolished by vagotomy.

II. ADME

A. Metabolism [^{14} C] tizanidine

Metabolic Pathway for Tizanidine in Mouse, Rat, Rabbit and Dog



IND

¹[3,4] major metabolites in human blood and urine. No muscle relaxant activity; ex. no activity in rat a rigor test at IV doses up to 10 mg/kg.

Summary of Pharmacokinetic Parameters Following Oral Administration of Tizanidine in Mouse, Rat, Rabbit and Dog

Parameter (Reference)	Mouse (1)	Rat (2)	Rabbit (4)	Dog (5)	
Dose (mg/kg)	4	1.5	3	0.1	<i>0.04 - .4</i>
Absorption (% dose)	>70%	90%	90%	90%	<i>770%</i>
Peak Conc. (µg equiv/g blood)	0.79	0.93	0.93	0.038	
Time to Peak (hr)	0.76	0.75	1.0	2.2	<i>1-1.5</i>
Excretion (% dose)					
Urine	64%	61%*	64%	72%	<i>20%</i>
Feces	26%	1%*	22%	24%	<i>30%</i>
Bile	--	29%*	--	--	
T1/2 elimination (hr)	5	2	45	10	<i>2-30-60 (in plasma)</i>
Primary Metabolites in Plasma	9	**	7.9	3.4.8	<i>7.4</i>

* Data from bile fistula rat in which 8 mg/kg dose was given
** Single unidentified metabolite

Large first pass in all species and fraction metabolized >90%. Little or no accumulation of tizanidine was found in rats and humans after multiple dosing. (Note: in humans there is low plasma protein binding of tizanidine).

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III. Mutagenicity Studies

Assay/Test System	Species/Cell Line	Dose Range	Control Groups	Results
Ames Test (18)	<u>Salmonella typhimurium</u> strains: TA 1538, 1538 98, 100	10-10,000 ug/ml	Vehicle (A. dest.) Positive (5-amino-chrysene; MNNG)	Tizandine neg. for inducing mutations in bacteria
Ames Test (19)	<u>Salmonella typhimurium</u> strains: TA 98, 100, 1538, 1537, 1538	50-50,000 ug/ml	Vehicle (DMSO) Positive (MNNG; Benzo(a)pyrene; 2-amino-anthracene; 9-amino-acridine; 2-nitro-fluorene)	Tizandine neg. for inducing mutations in bacteria
Chinese Hamster Cell Test (20)	V79 Chinese hamster cells	1.5-1650 ug/ml (3-7 days)	Vehicle (distilled water); Positive (daunomycin; aflatoxin B1)	Tizandine neg. for inducing gene mutations
DNA Synthesis Assay (21)	CD-1 mice	25-50 mg/kg intraperitoneally	Vehicle (2% gelatin solution) Positive (methylmethane sulfonate)	Tizandine neg. for inducing unscheduled DNA synthesis in sperm cells
Bone Marrow Micronucleus & Cytogenetic Test (22)	Chinese hamsters	25-100 mg/kg i.p. for 2 days	Vehicle (distilled water)	Tizandine neg. for inducing formation of micronuclei or chromosomal aberrations
Bone Marrow Micronucleus Test (23)	CD-1 mice	10.5-50 mg/kg i.p. for 3 days	Positive (TEM)	Tizandine neg. for inducing formation of micronuclei
Dominant Lethal Test (24)	CD-1 mice	10-50 mg/kg i.p.	Vehicle (0.9% saline) Positive (TEM)	Tizandine neg. for inducing dominant lethal mutations

KEY: MNNG: N-methyl-N'-nitros-N-nitrosodimethylamine; TEM: ortho-terphenylamine; neg. = negative

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IV. Toxicology and Carcinogenicity

A. Summary of oral studies

Summary of Acute and Multiple Dose Toxicology Studies with Tizanidine

Species/ Strain	Sex	Doses (mg/kg/day)	Duration	Formulation	No./ Group (M/F)
ORAL					
OF1 Mouse	M/F	100-420	Acute	2% solution	5/5
OFA Rat	M/F	240-1000	Acute	2% solution	5/5
Silver fawn Rabbit	M/F	56-180	Acute	2% solution	3/3
OFA Rat	M/F	0, 1.7, 8, 40	13 weeks + 4-week recovery	Feed admix.	10/10 ^a
Beagle Dog	M/F	0, 0.3, 1, 3-4	13 weeks	Capsule	2/2
Beagle Dog	M/F	0, 0.15, 0.15 1.5	52 weeks + 6-week recovery	Capsule	4/4
OF1 Mouse	M/F	0, 1, 4, 16	78 weeks	Feed admix.	50/50
GD Rat	M/F	0, 1, 3, 9	104 weeks	Feed admix.	60/60

- a) 5/sex for recovery group in MD and HD.
- b) Sandoz SPF breed.

B.

LD50 Values Following Oral or Intravenous Administration of Tizanidine

Species	Route of Administration	LD50 Values (mg/kg)*	
		24-hr	7-day
Mouse	Oral	271 (229-337)	235 (201-278)
	Intravenous	52 (43-62)	48 (41-56)
Rat	Oral	859 (738-1133)	602 (494-745)
	Intravenous	48 (39-69)	46 (33-62)
Rabbit	Oral	122 (74-372)	98 (66-154)
	Intravenous	23 (20-25)	23 (20-25)

LD50 values calculated using probit analysis based on 24-hr or 7-day post-dose observation period.

* LD50 Value (95% confidence limits)

Most deaths occurred within 24 hours Signs were sedation, salivation, dyspnea, piloerection, convulsions. Corneal abrasions in rats at end of observation period—a result of decreased blinking.

C. Multiple dose studies

1. Rat

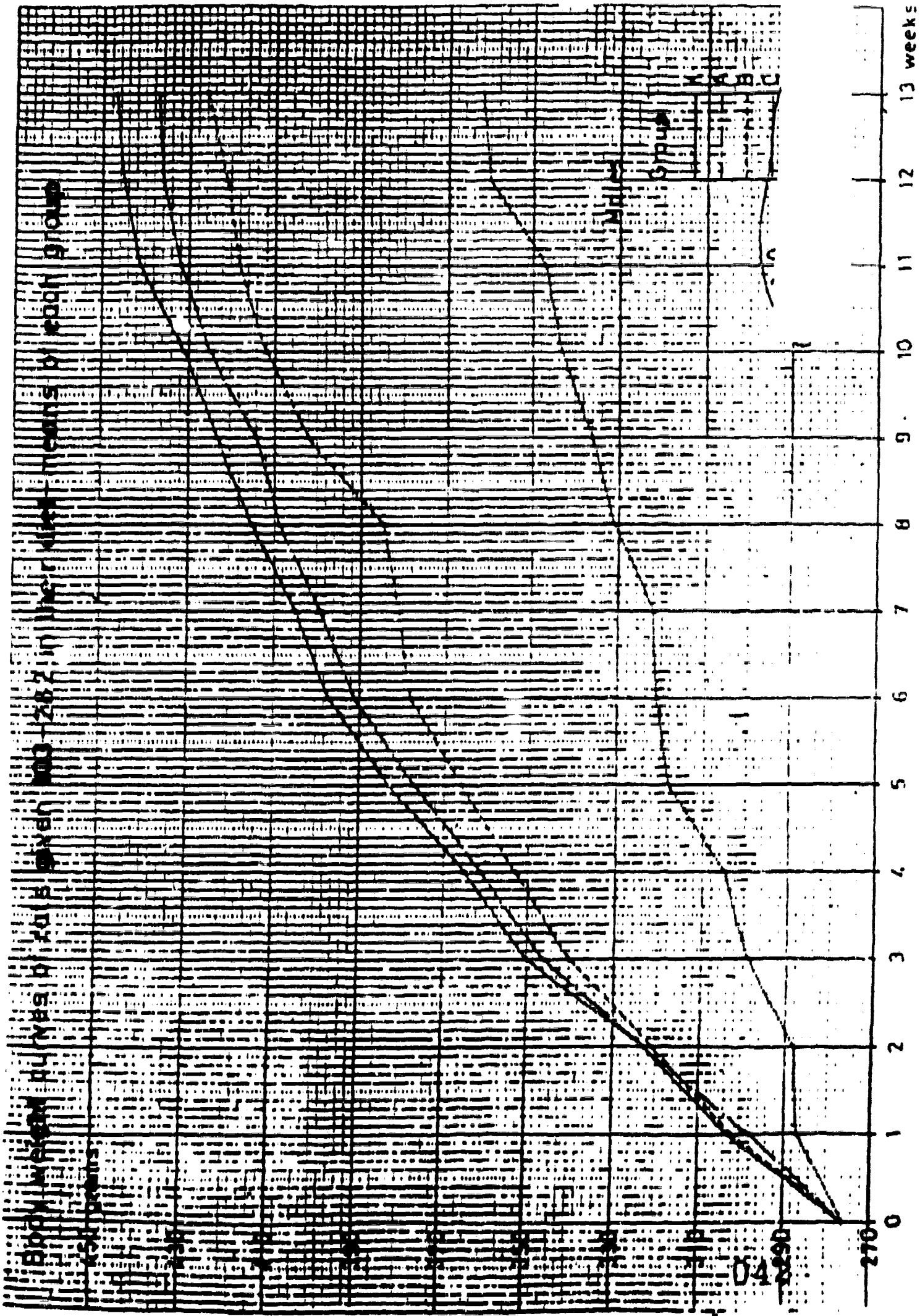
	13 Week	104 Weeks
Strain	OFA (SPF, Sandoz) 10/sex/group 5/sex MD+HD recovery	(carcinogenicity/toxicity) SD CD 60/sex/group
Doses	0, 1.7, 8, 40 mg/kg (diet)	0, 1, 3, 9 mg/kg in the diet
Signs	<u>Daily</u> MDF: slight piloerection and miosis. HD: Miosis, perianal wetting, piloerection, sensitivity to touch, dermatitis, bleeding injuries due to scratching, corneal clouding, convulsions (in F).	<u>Daily</u> HD: Hyperactivity, piloerection, convulsions (from week 23). Granuloma like lesion in hind limbs of most rats in all groups from week 55 on. Hair loss MD+HD.
Mortality	2 HD; 1 bleeding from biting, scratching, 1 unknown in week 12.	<u>Table 1</u> No dose response.
Weight gain/food consumption	Fig 1+2: Sign. decrease in MD and HD. Corresponding decrease in food consumption.	<u>Figures 4 and 5</u> HD: -10 to -15% from control.
Hematology	<u>6+13 weeks</u>	<u>11, 25, 50, 78, 104 weeks</u> Hb, RBC increased dose related at and after 50 weeks.

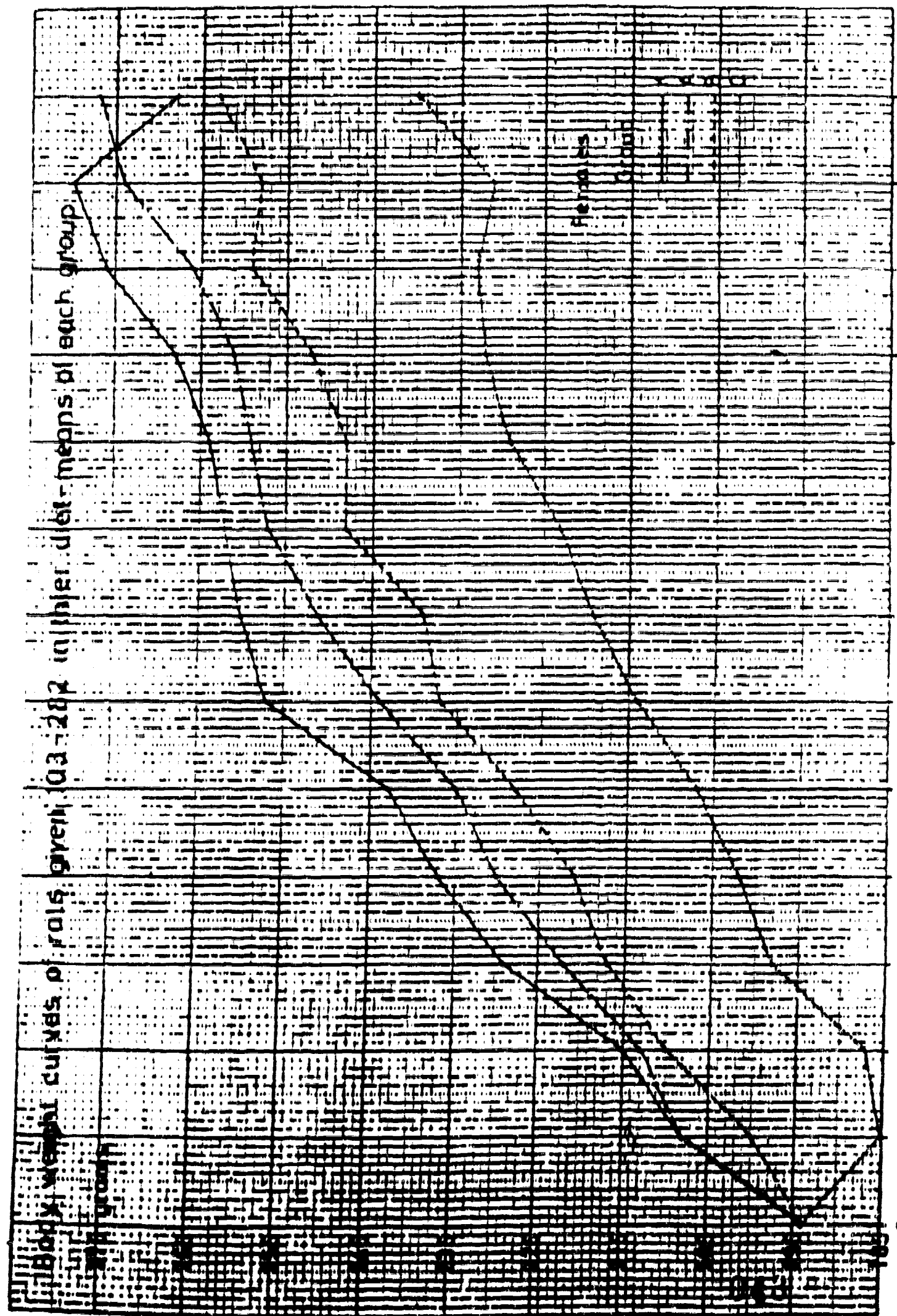
	13 Week	104 Weeks
Blood Chemistry	Slight dec. glucose at 6+13 weeks in <u>MDF</u> . Sign. decrease in glucose at 6+13 weeks in <u>HD</u> . Increase in SGPT at 6 weeks in M and 6+13 weeks in M+F <u>HD</u> .	
Urinalysis	6+13 weeks	No clear effects
Gross Pathology	<u>HD</u> : skin lesions, ulcers.	Pallor, opacity of eyes, granuloma in plantar surface of hind limbs, sparse coat all dose-related.
Organ Weights	Decrease mean absolute and relative liver weights. Increase in mean relative heart and adrenal weight in <u>HD</u> .	Decrease in mean absolute and relative liver, spleen, kidney, and thyroid weight in <u>HD</u> at term.
Microscopy	<u>HD: Heart</u> : slight increase in focal necrosis. <u>Liver</u> : focal & single cell necrosis. <u>Eye</u> : Corneal ulcers. <u>Skin</u> : ulcers	<u>Eye</u> : Cortical ulcers, degeneration (dose related) in MD and HD. <u>Liver</u> : eosinophilic hypertrophy in HDM. <u>Hind limbs</u> : Dose related increase in granulation tissue all doses. No drug related neoplasms.
NOEL Min. EL	1.7 mg/kg 8 mg/kg Dec. weight gain (-10%) pilcerrection.	1 mg/kg: Hind limb granulomas at term. Slight corneal changes (opacity).

thy SA.
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	13 Week	104 Weeks
RL	40 mg/kg convulsions Vasoconstriction Elevated SGPT Organ changes Liver necrosis (focal+single cell) Heart (single cell necrosis) (All Reversible)	9 mg/kg: convulsion Liver hypertrophy. 1 and 9 mg/kg: Dose related corneal changes, hair loss.





13 weeks

TABLE 1

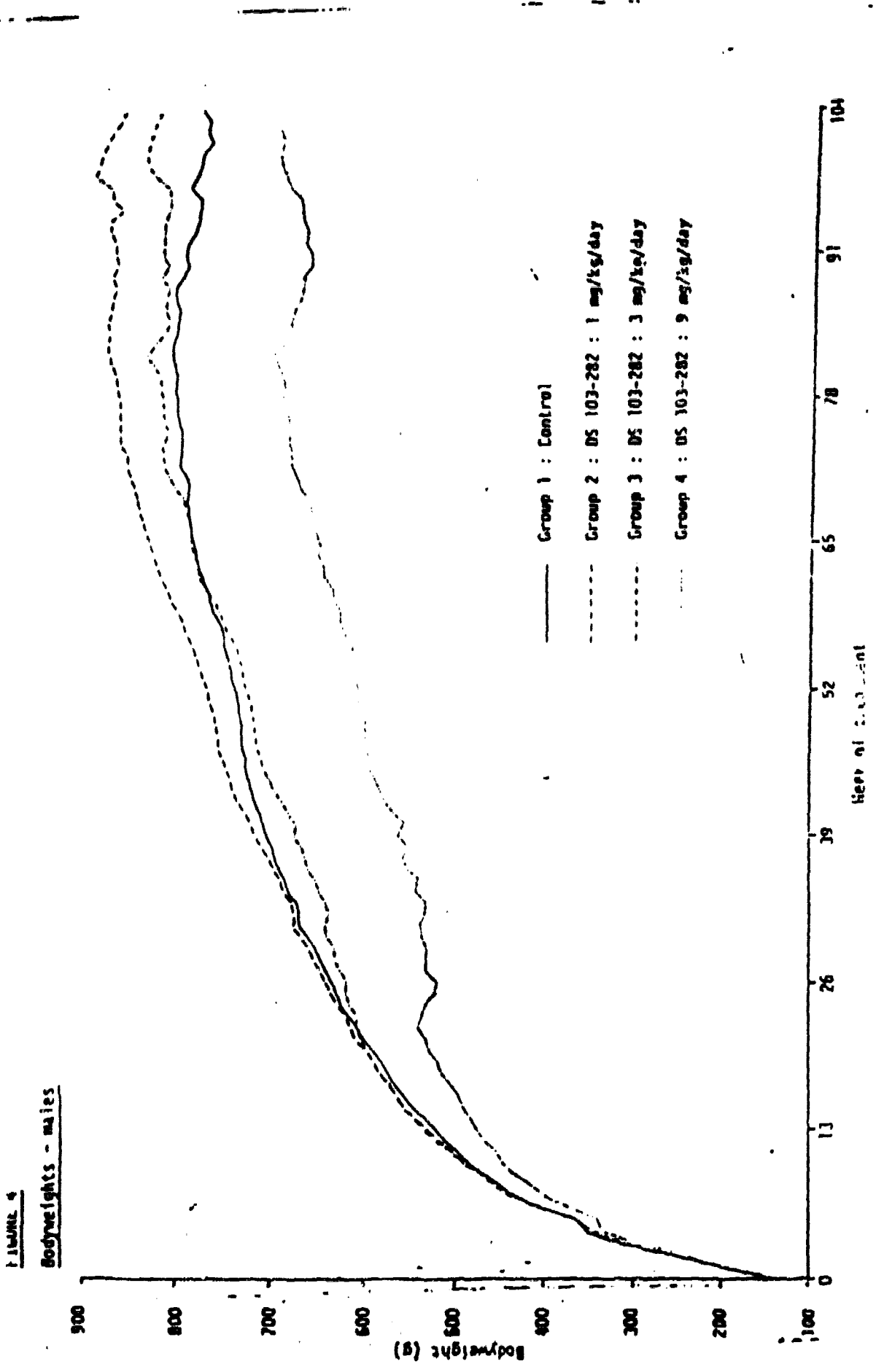
Mortality distribution

Group : 1 2 3 4
 Compound : Control --- DS 103-202 ---
 Dosage (mg/kg/day) : 0 1 3 9

Group & sex	Week of treatment									Total Weeks 1-107
	1-13	14-26	27-39	40-52	53-65	66-78	79-91	92-104	105-107 [†]	
1 ♂	0	1	0	0	1	6	12	18	2	40
2 ♂	1	1	0	2	1	3	10	13	1	32
3 ♂	0	0	2	1	1	4	14	12	3	37
4 ♂	0	2	1	3	1	4	12	12	0	35(3)
1 ♀	2	2	1	2	1	4	10	9	1	32(3)
2 ♀	0	0	2	1	3	6	9	13	0	34
3 ♀	0	0	0	2	1	6	12	13	0	34
4 ♀	0	0	1	0	4	3	5	16	1	30

Figures in parentheses indicate numbers of animals that died as a result of routine blood sampling procedures.

† Died while awaiting terminal sacrifice.



2. Dog

	13 Weeks	52 Weeks
Strain	beagle	beagle
	2/sex/group	4/sex/group* (* 1/sex/group 6 week recovery)
Dose	0, 0.3, 1, 3-4 mg/kg (capsule) (4 mg/kg from weeks 11-13).	0, 0.15, 0.45, 1.5 mg/kg (capsule).
Signs	<u>Daily</u> Dose related sedation at MD and HD. Emesis balance problems in HD Slight reduction in body temperature in MD and HD normalized by 24 hours.	Slight sedation, balance problem, emesis, salivation in HD.
Clinical Chemistry	<u>predose, 6 and 13 weeks</u> SGPT upper limits of normal 2/4 HD dogs at week 13. 1 HD dog slightly increased SAP. <u>Note:</u> BSP retention at week 9 was normal.	<u>predose, 7, 13, 26, 51 weeks</u> Slightly higher SGPT 2/8 MD at 3 weeks. Sporadic increases in SGPT in HD.
EKG	Slowing of HR (dose related) in MD and HD <u>(not bradycardia)</u> associated with slightly prolonged QRS and QT intervals.	Bradycardia (-40%) in 4/8 HD in 2 hour EKG. Longer QT interval in 5/8 dogs. Reversible in recovery dogs. (EKG taken pretest, 13, 26, 52 weeks).
Histopathology	<u>Liver:</u> 2/4 MD and 3/4 dogs had slight to moderate polymorphonuclear cell infiltrates.	No drug effects

	13 Weeks	52 Weeks
NOEL	0.3 mg/kg	0.45 mg/kg (see table 2)
EL	1 mg/kg sedation, balance problems. Slowing of HR (not bradycardia). Liver: slight polymorph cell infiltrates.	1.5 mg/kg sedation, balance problems. Bradycardia (-40%). Some elevation of SGPT.

Table 2

Mean SGPT values after treatment with DS 103-282

CONTROL		A		B		C		DOSE WEEK
♂	♀	♂	♀	♂	♀	♂	♀	
19.6 + 3.6	25.0 + 7.0	21.1 + 3.0	20.8 + 6.9	21.3 + 2.6	24.4 + 2.9	18.2 + 2.2	20.2 + 2.0	0
21.7 + 6.0	16.5 + 2.9	20.8 + 4.6	17.6 + 2.1	26.2 ¹ + 8.3	41.6 ⁴ + 37.1	28.9 ³ + 11.6	21.7 ⁴ + 10.5	3
20.8 + 5.9	21.0 + 1.8	22.0 + 2.5	20.8 + 2.6	23.3 + 5.7	18.1 + 3.9	23.4 + 3.0	21.1 + 6.4	6
19.9 + .5	22.0 + 3.6	24.6 + 2.4	21.5 + 3.6	25.5 + 5.5	22.2 + 2.7	35.5 ⁵ + 3.5	46.0 ⁶ + 33.4	13
21.7 + 6.4	19.7 + 1.3	13.9 + 2.7	13.0 + 3.9	21.3 + 5.3	21.4 + 6.7	21.7 + 4.9	35.1 ⁷ + 23.5	25
14.5 + .0	15.0 + .9	15.9 + 2.8	14.7 + .3	15.4 + 2.3	14.7 + .5	17.1 + 3.0	13.6 + 8.5	39
24.1 + 7.2	13.8 + 2.1	17.6 + 4.2	17.5 + 3.0	21.5 + 2.3	16.3 + 2.1	35.3 ⁸ + 4.9	35.4 ⁹ + 24.5	51

♀ ♀ 2 p < 0.01 nonparametric * 2 p < 0.01 parametric test VS Controls

1. (S19) 37 2. (B21) 96 3. (C25) 41, (C27) 35
 4. (C31) 36 5. (C25) 34, (C26) 33, (C27) 35, (C28) 41
 6. (C29) 34, (C30) 95, (C31) 35 7. (C30) 77
 8. (C25) 33, (C26) 42, (C27) 40, (C28) 32 9. (C29) 70

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V. Reproduction Studies

A. Fertility study in male rats

Male rats (OFA-Sandoz) 10 weeks old at 0 (2% gelatine solution), 3, 10 and 30 mg/kg by gavage (5 mg/kg) at 70 days pre-mating and during mating for 4 weeks. The HD group was remated after end of the original experiment.

Results:

Dosage	No. of males	Mor-tality	Weight gain in % pretreatment	Number of females	
				mated	pregnant
Controls	15	0	41	25/30	18/25
3 mg/kg	15	0	42	25/30	24/25
10 mg/kg	15	0	37*	27/30	23/27
30 mg/kg	15	0	19*	23/30	11/23

Prenatal Part (Day 13 p.c.)

Dosage	Litters	Weight gain, days %	Corpora lutea	Implan-tations	Litter size	Pre-Implant. loss	Post-Implant. loss	Abnormal embryos
Controls	10	21	15.0	20.1	13.9	20.0	2.3	0/109
3 mg/kg	13	21	15.0	20.7	13.0	3.3	4.9	0/135
10 mg/kg	12	21	14.2	20.7	12.7	10.6	7.9	0/140
30 mg/kg	7	21	12.5	19.1	9.9	12.3	2.3	0/51

Postnatal Part (Day 21 p.p.)

Dosage	Litters	Weight gain of dams in % pregnancy	of dams in % lactation	Implantations	Litter size
Controls	8	53	5	12.4	12.4
3 mg/kg	12	61	2	12.0	12.4
10 mg/kg	11	60	4	12.7	12.0
30 mg/kg	4	51	2	3.3	12.0 ¹

Dosage	Pre- and post-natal loss of pups %	Postnatal loss of pups %	Postnatal weight gain of pups	Abnormal pups
Controls	9.0	4.4	567.7	0/91
3 mg/kg	4.5	6.0	524.1	0/135
10 mg/kg	5.3	4.9	533.0	0/140
30 mg/kg	8.1	8.3	600.9	0/51

¹ one dam killed on day 21 p.c. excluded
* p < 0.05

Recovery

Dosage	No. of males	Mortality	Weight gain % recovery	Number of females	
				mated	pregnant
Controls	15	0	3.1	13/15	8/13
30 mg/kg	15	0	11.1 ^b	11/15	8/11

Prenatal Part (Day 13 p.c.)

Dosage	Litters	Weight gain days %	Corpora lutea	Implan- tations	Litter size	Pre- Post-		Abnormal embryos
						implant. %	loss %	
Controls	8	23	14.8	12.9	12.3	12.7	4.9	0/98
30 mg/kg	8	22	12.4	11.1	10.4	10.1	6.7	0/83

^b $P < 0.05$

(Tokyo) March 1985

- B. Fertility study in female rats 30F (OFA-Sandoz) 10 weeks old were treated with 0 (2% gelatine), 3, 10, 30 mg/kg 2 weeks before mating and continuing to sacrifice.

Results:

Pretreatment and Mating

Dosage	No. of females	Mortality	Weight gain in % pretreatment	Number of females	
				mated	pregnant
Controls	30	0	8	23/30	23/23
3 mg/kg	30	0	7	26/30	22/26
10 mg/kg	30	0	4	21/30	21/21
30 mg/kg	30	0	-5	20/30	17/20

Prenatal Part (Day 13 p.c.)

Dosage	Litters	Weight gain day 1	Corpora lutea	Implantations	Litter size	Pre- / Post-implant. loss		Abnormal embryos
						1	2	
Controls	11	19	13.3	12.9	12.2	2.7	5.6	0/134
3 mg/kg	10	19	14.1	12.5	11.3	11.3	9.6	0/113
10 mg/kg	10	18	15.0	14.1	13.0	5.0	6.4	0/130
30 mg/kg	6	17	12.3	11.5	9.3	6.8	18.8*	0/56

Postnatal Part (Day 21 p.p.)

Dosage	Litters	Weight gain of dams in %		Implantations	Litter size
		pregnancy	Lactation		
Controls	11	61	7	14.4	13.5
3 mg/kg	11	56	6	12.5	11.9
10 mg/kg	10	44	5	13.5	11.5
30 mg/kg	10	41	-	11.9	8.0*

Dosage	Pre- and perinatal loss of pups %	Postnatal loss of pups %	Postnatal gain change of pups %	Abnormal pups
Controls	5.8	12.1	695	3/150
3 mg/kg	8.0	34.1*	647	1/116
10 mg/kg	14.1*	30.0*	593	0/99
30 mg/kg	32.7*	100 *	-	1/31

* significant difference to the controls (p<0.05)

C. Teratology study in rats

Mated female rats (OFA) were treated by gavage from day 6 to 15 p.c.

- Type A - Anomalies developing during the late fetal phase of maturation (e.g. inhibition or retardation of skeletal ossification etc.). All minor variations in skeletal development fall into this group.
- Type B - Anomalies occurring during the early fetal phase of organ differentiation and fetal growth, comprising minor anomalies such as abnormal flexure of carpal joints, bipartite or bifurcated sternbrae etc.
- Type C - Anomalies developing during the organogenetic phase. This type comprises genetically determined variations as well as major abnormalities.

EXPERIMENT I

A) DAMS	♀ mated	Litters	Mortality	Abortions	Pregnancy rate %	Body weight change %
Controls	30	24	0/30	0	80.0	+16.4
1 mg/kg	30	26	0/30	0	86.7	+14.7
3 mg/kg	30	25	0/30	0	83.3	+13.5*
10 mg/kg	30	24	0/30	0	80.0	+12.1*
100 mg/kg	30	23	3/30	0	86.7	-11.7*

B) LITTERS (means)	Corpora lutea	Implantations	Pre-implan- ¹ tations loss %	Litter size	Post-implan- ² tation loss %
Controls	13.8	11.6	15.5	11.3	2.9
1 mg/kg	13.2	9.9	25.2*	9.0	8.6*
3 mg/kg	15.3	12.6	17.5	12.0	5.4
10 mg/kg	14.7	12.2	16.9	11.6	4.1
100 mg/kg	13.8	11.4	17.0	4.5*	60.8*

C) FETUSES	Body weight g	Placental weight g	Sex ♂/♀	Fetuses showing Anomalies		
				Type A	Type B	Type C
Controls	5.25	0.86	1.101	42/271	3/271	0
1 mg/kg	5.30	0.92*	1.003	40/235	3/235	1/235
3 mg/kg	4.93*	0.87	1.157	60/299	5/299	2/299
10 mg/kg	4.71*	0.78*	0.972	55/282	13/282*	0
100 mg/kg	3.45*	0.73*	1.229	79/103*	2/103	11/103*

* significant difference to the control value

1 % of corpora lutea

2 % of implantations

EXPERIMENT II

A) DAMS	♀ mated	Litters	Mortality	Abortions	Pregnancy rate %	Body weight change %
Controls	30	20	0	0	66.7	+ 15.2
0.3 mg/kg	30	20	0	0	66.7	+ 14.5
1 mg/kg	30	21	0	0	70.0	+ 16.1

B) LITTERS (means)	Corpora lutea	Implan- tations	Pre-implan- ¹ tations loss %	Litter size	Post-implan- ² tation loss %
Controls	13.2	10.5	20.7	9.75	7.14
0.3 mg/kg	13.6	9.6	28.8*	9.25	4.15
1 mg/kg	14.4	11.0	23.4	10.3	6.47

C) FETUSES	Body weight g	Placental weight g	Sex ♂ / ♀	Anomalies		
				Type A	Type B	Type C
Controls	5.24	0.94	0.930	61/180	2/180	0
0.3 mg/kg	5.18	0.91	0.947	31/177	0	0
1 mg/kg	5.17	0.94	0.955	57/207	0	0

* significant difference to the control value

¹ % of corpora lutea

² % of implantations

D. Teratology study in rabbits

Inseminated rabbits (yellow-silver strain) were dosed by gavage from day 6-18 p.c.

Results:

A) DAMS	♀ mated	Litters	Mortality	Abortions	Pregnancy rate %	Body weight change %
Controls	16	11	0/16	0	68.8	+7.61
1 mg/kg	15	10	0/15	1	73.3	+5.38
3 mg/kg	16	10	1/16	1	75.0	+3.08*
30 mg/kg	16	10	3/16	1	87.5	+1.45*
100 mg/kg	5	0	5/5	-	80.0	-

LD5 = 5 mg/kg } Dam
LD50 = 50 mg/kg }

B) LITTERS (means)	Corpora lutea	Implantations	Pre-implantation loss %	Litter size	Post-implantation loss %
Controls	7.00	4.52	34.2	4.54	3.5
1 mg/kg	7.00	5.20	25.7	4.00	23.2*
3 mg/kg	5.40	3.90	27.8	3.00	23.1*
30 mg/kg	5.50	4.40	21.4	3.70	15.5*
100 mg/kg	-	-	-	-	-

C) FETUSES	Body weight g	Placental weight g	Sex ♂/♀	Anomalies ³			Fetal loss %
				Type A	Type B	Type C	
Controls	34.4	5.21	1.313	13/51	3/51	1/51	3.9
1 mg/kg	34.7	6.00*	0.533	15/40	3/40	1/40	15.0
3 mg/kg	36.0	6.03*	0.579	7/30	1/30	1/30	0.0
30 mg/kg	34.9	5.53	1.457	6/37*	1/37	0	6.1
100 mg/kg	-	-	-	-	-	-	-

* significant difference to the control value

1. % of corpora lutea

2. % of implantations

E. Segment III study in rats.

Female rats were orally treated from day 15 p.c. until day 21 p.p.

Findings in dams

Dosage	No. of females			Pregnancy length (days)	Weight gain %	
	mated	died	pregnant		pregnancy	lactation
Controls	30	0	28	22.1	28	9
3 mg/kg	30	0	26	22.3	27	6
10 mg/kg	30	0	29	22.5	19	7
30 mg/kg	30	0	25	22.9	3	-

Litter Data

Dosage	Litters	Implantations	Litter size (day 0 p.p.) ²	Pre- and peri-natal loss of pups %	
				Pre- and peri-natal loss of pups %	Postnatal loss of pups % (days 0-21 p.p.)
Controls	27	13.0	10.4	13.0	5.3
3 mg/kg	26	13.0	11.7	9.5	4.5
10 mg/kg	29	13.1	10.5	19.5 ¹	42.3 ¹
30 mg/kg	24	13.6	4.3 ¹	63.8 ¹	100 ¹

Dosage	Postnatal weight gain of pups ¹ (day 0-21 p.p.)	Morphological changes pups affected %	Behavior pups affected %
Controls	761	1.1	25.1
3 mg/kg	725	1.0	10.8
10 mg/kg	572	7.4	72.5
30 mg/kg	-	19.4	-

Fertility of F₁-pups

Dosage	No. of mated males and females	Females		Pre- and peri-natal loss of pups %	Postnatal loss of pups %	Morphological changes pups affected %
		inseminated	pregnant			
Controls	46/45	80	94	6.9	23.5	0
3 mg/kg	48/48	90	81	9.1	25.4	0
10 mg/kg	24/24	96	83	10.1	13.1	0
30 mg/kg	-	-	-	-	-	-

1 p < 0.05

2 before standardization of litter size

Comments and Evaluation

These preclinical studies have been previously reviewed in IND 14,424. Additional comments are given here. The sponsor has submitted a 3 month rat toxicity study and a 2 year rat toxicity/carcinogenicity study. It is considered that the latter study satisfies our guideline for a 1 year toxicity study in a rodent species even though an interim sacrifice at 52 weeks was not performed. The reasoning is that clinical signs, hematology, clinical chemistry and ophthalmoscopic examination were conducted at 25, 50, and 78 weeks and clearly a maximally tolerated dose of 9 mg/kg was used since this dose resulted in convulsions (at week 23) sufficient decreases in weight gain and significant hind limb lesions during the study. These two studies adequately characterize the toxicity of this drug in the rat.

2. Reproduction Studies

The concern is embryo/fetal loss after tizanidine administration. Some effect at high dosage (30 mg/kg) may be related to maternal toxicity; at lower dosages the mechanism is not apparent.

Study	NOEL (mg/kg)	EL (mg/kg)
Rat M Segment I	10	30 [decrease fertility (11/23) reversible]
Rat F Segment I	3	10, 30 [14 and 33% pre- perinatal loss vs 6% in C.]
		3, 10, 30 [34, 30, 100% postnatal loss vs 18% in C.]
Rat Segment II	10	100 [60% postimplantation loss vs 3% in control]

Study	NOEL (mg/kg)	EL (mg/kg)
Rabbit Segment II	none	1, 3, 30 [postimplantation loss 16-23% vs 4% in C. Note: No dose response and rate within range of historical laboratory control]
Rat Segment III	3	10, 30 [pre and perinatal loss 20 and 70% vs 13% in C] [postnatal loss 42 and 100% vs 5% in control]

Recommendation:

1. No objections to the proposed clinical study.
2. The investigator brochure should more adequately describe the results of the preclinical reproduction studies concerning pre-perinatal and postnatal fetal loss after drug administration.

Ann L. Wilk
 Ann L. Wilk, Ph.D.
 Pharmacologist

cc: IND
 HFD-120
 HFD-120/GFitzgerald 99* 12/4/91
 /AWilk/11/29/91
 ft/ejs/12/2/91

05ANU02
SUBSTANCE NH: 103-202
SPECIES : RAT

4.22. 5.7J.10.02.02

TABLE 6: ANOMALIES IN FETUSES

A) ABSOLUTE VALUES

	EVALUATED LITTERS	LITTERS CONT. ABNORMAL FETUSES		
		TYPE A	TYPE B	TYPE C
CONTROLS	24	10	3	0
1.00 MG/KG	26	16	3	1
3.00 MG/KG	25	21	2	
10.00 MG/KG	24	14	5	0
100.00 MG/KG	23	10	1	12

	FETUSES SHOWING ANOMALIES >)		
	TYPE A	TYPE B	TYPE C
CONTROLS	40/271	3/271	0/271
1.00 MG/KG	40/235	3/235	1/235
3.00 MG/KG	60/299	5/299	2/299
10.00 MG/KG	55/282	13/282*	0/282
100.00 MG/KG	79/103*	2/103	11/103*

* P<.05 • P<.005

>) X/Y, WHERE X = NUMBER OF POSITIVES.
Y = NUMBER OF EXAMINED (VIABLE FETUSES, DEAD FETUSES AND FETAL RESORPTIONS)

TYPE DESCRIPTION: SEE METHODS

5. APPENDICES

5.1. Appendix I - Description of Anomalies

5.1.1. First Experiment

5.1.1.1. Type A Anomalies

	Controls	1 mg/kg	3 mg/kg	10 mg/kg	100 mg/kg
<u>Sternbrae:</u>					
1. deformed					1
dumbbell-shaped					4
cleft					4
retard. ossification					4
2. dumbbell-shaped	2	2	9	4	.21
cleft					3
retard. ossification	4	2	4	5	-15
not ossified					2
3. dumbbell-shaped	2	1	6	1	18
cleft					4
retard. ossification					3
4. dumbbell-shaped	9	1	12	5	20
cleft					1
retard. ossification					5
5. deformed	2	2			
dumbbell-shaped	25	14	29	23	32
retard. ossification	8	8	9	10	21
not ossified			1		9
6. deformed	7	9	6	6	
dumbbell-shaped					1
retard. ossification			1	3	25
not ossified					7
<u>Vertebral Bodies:</u>					
10. thoracic vertebral body dumbbell-shaped	2	1	2	1	2
11. thoracic vertebral body dumbbell-shaped	2	2	3	4	5
cleft					1
12. thoracic vertebral body dumbbell-shaped			1	1	1
cleft		1			
13. thoracic vertebral body dumbbell-shaped					1
<u>Phalanges (forelimbs)</u>					
retard. ossification	1	1	1	1	25
not ossified					1

Type A Anomalies (continued)

	Controls	1 mg/kg	3 mg/kg	10 mg/kg	100 mg/kg
<u>Phalanges (hindlimbs):</u>					
retard. ossification	7	13	21	24	59
not ossified	1	1			1
Total incidence of Type A anomalies	72	50	105	88	296
Fetuses with Type A anomalies	48	40	60	55	79

5.1.1.2. Type B Anomalies

Controls

Litter 3, LF No. 8 ♀ 4.1 g 5th sternebra assymetric cleft
 Litter 20, LF No. 7 ♂ 5.4 g 3rd sternebra assymetric cleft
 Litter 23, LF No.10 ♂ 4.8 g Hydronephrosis, right

1 mg/kg:

Litter 105, LF No. 8 ♂ 5.0 g 5th sternebra assymetric cleft
 Litter 119, LF No. 5 ♂ 5.5 g hydroureter, left
 Litter 126, LF No. 8 ♂ 5.0 g renal papilla not present, right

3 mg/kg:

Litter 204, LF No. 1 ♀ 1.7 g all ribs undulated; all vertebral arches of lumbar region wide open
 LF No. 4 ♀ 1.6 g all ribs undulated; all vertebral arches of lumbar region dorsal wide open
 LF No. 5 ♂ 1.7 g all ribs undulated; all vertebral arches of lumbar region dorsal wide open
 LF No. 8 ♂ 1.8 g all ribs undulated; all vertebral arches of lumbar region wide open
 Litter 225, LF No. 5 ♂ 5.7 g 5th sternebra assymetric cleft

10 mg/kg:

Litter 414, LF No. 1 ♀ 4.7 g renal papilla not present, right
 Litter 416, LF No. 1 ♀ 4.9 g renal papilla not present, left
 LF No. 5 ♀ 5.0 g renal papilla not present, right
 LF No. 9 ♀ 4.8 g renal papilla not present, bilateral
 Litter 418, LF No. 3 ♀ 4.9 g renal papilla not present, right
 LF No. 5 ♀ 4.4 g renal papilla not present, bilateral
 LF No. 6 ♂ 4.9 g renal papilla not present, bilateral
 LF No. 8 ♂ 5.0 g renal papilla not present, bilateral
 LF No.12 ♂ 4.5 g renal papilla not present, right
 Litter 421, LF No. 1 ♀ 4.5 g renal papilla not present, bilateral
 Litter 429, LF No. 9 ♂ 4.6 g hydroureter bilateral
 LF No.10 ♂ 4.7 g hydroureter left
 LF No.12 ♂ 4.7 g hydroureter left

Type B Anomalies (continued)

100 mg/kg:

Litter 610, LP No. 3 ♀	2.0 g	2nd sternebra assymmetric cleft and fused with 1st sternebra
LP No.10 ♀	2.6 g	3rd and 4th sternebrae assymmetric cleft

5.1.1.3. Type C Anomalies

Controls:

None

1 mg/kg:

Litter 115, LF No. 2 ♀ 3.6 g encephalocele

3 mg/kg:

Litter 204, LF No. 5 ♂ 1.7 g whole skeleton retarded;
all ribs undulated; all vertebral arches in the lumbar region dorsal wide open; 6th thoracic vertebral body fused with 7th thoracic vertebral body.

LF No. 8 ♂ 1.8 g encephalocele

10 mg/kg:

None

100 mg/kg

Litter 610, LF No. 2 ♂ 2.5 g encephalocele

LF No. 3 ♂ 2.0 g "

LF No. 6 ♂ 2.6 g "

LF No. 8 ♂ 2.5 g "

LF No.10 ♀ 2.6 g "

Litter 619, LF No. 3 ♀ 3.7 g microphthalmia right

LF No.11 ♂ 4.0 g "

Litter 623, LF No. 8 ♂ 2.2 g microphthalmia left

LF No.11 ♂ 2.9 g " right

Litter 627, LF No. 4 ♂ 2.5 g microphthalmia left

LF No. 6 ♀ 2.0 g encephalocele, microphthalmia prolapse of tongue

LF = Live fetus

Historical Control-56 Data

5.4. APPENDIX IV - CONTROL DATA (1969-1971)

Results from the Control Groups of 30 Teratological Studies in OFA, IFFA-CREDO, SPF-Rats, performed in Sandoz Ltd., Basel, between 1969 and 1971.

Summary

	Total	Range ¹
No. of control groups	30	
No. of animals mated	912	
No. of animals pregnant	741 81.3%	51.5% - 90.0%
No. of abortions	0	
No. of litters assessable	734	
No. of litters with total resorptions	7 0.96%	0.0% - 8.33%
Weight gain of dams between day 6 and 15 p.c.	12.7%	9.8% - 16.4%

Litters

	Total	Mean per litter ²	% ²	Range per litter ¹	% ²
No. of corpora lutea	10738	14.7	121.3	13.4-16.2	109.7-137.6
No. of implantations	8854	12.1	100.0	10.1-13.7	-
No. of live fetuses (litter size)	8472	11.6	95.7	9.6-13.5	86.5- 98.7
No. of resorptions	382	0.52	4.3	0.16-1.50	1.34-13.5
- embryonic	375	0.51			
- fetal	3				
- dead fetuses	4				
Pre-implantation loss	1884		17.5 ³		8.8 -27.3 ³

- 1 range for all groups
- 2 % of implantations
- 3 % of corpora lutea

Fetuses

	Total	Mean		Range ¹	
		per litter	%	per litter	%
No. of live fetuses	8472	11.6	95.7 ²	9.6 - 13.5	86.5 - 98.7 ²
- ♂	4182				
- ♀	4290				
Sex ratio (♂ : ♀)		0.97		0.80 - 1.30	
Fetal weight (g)		5.11 ³		4.83 - 5.27 ³	
No. of live fetuses examined for anomalies	8410				
No. of fetuses with					
- Type A anomalies	1669	2.29	19.8 ⁴	0.95 - 5.72	7.9 - 48.6 ⁴
- Type B anomalies	55	0.08	0.65 ⁴	0 - 0.18	0 - 1.73 ⁴
- Type C anomalies	6	0.01	0.07 ⁴	0 - 0.09	0 - 0.34 ⁴
No. of litters examined for anomalies	728				
No. of litters with fetuses showing					
- Type A anomalies	565		77.6 ⁵		47.6 - 96.3 ⁵
- Type B anomalies	48		6.6 ⁵		0 - 14.8 ⁵
- Type C anomalies	6		0.8 ⁵		0 - 8.7 ⁵

- 1 range for all groups
- 2 % of implantations
- 3 mean per fetus
- 4 % of examined fetuses
- 5 % of examined litters

Abnormalities

	Total	Mean		Range ¹	
		per litter	%	per litter	%
Litters examined	747				
Litters with fetuses showing					
- Type A anomalies	431	-	57.7 ²	-	30.8-91.3 ²
- Type B anomalies	21	-	2.81 ²	-	0-12.5 ²
- Type C anomalies	7	-	0.94 ²	-	0-4.76 ²
Fetuses examined	8731				
Fetuses showing					
- Type A anomalies	1088	1.46	12.5 ³	0.44-4.28	3.33-38.2 ³
- Type B anomalies	21	0.03	0.24 ³	0-0.13	0- 1.11 ³
- Type C anomalies	7	0.01	0.08 ³	0-0.05	0- 0.45 ³

1 range of individual groups
 2 in % of litters examined
 3 in % of fetuses examined

Type A anomalies - Number and percentage

	Number	%
Fetuses examined	8410	
Fetuses with Type A anomalies	1669	19.85
Sternebra 1 dumbbell-shaped	25	0.30
cleaved	3	0.04
Sternebra 2 not ossified	1	0.01
rudimentary	23	0.27
dumbbell-shaped	308	3.66
cleaved	5	0.06
Sternebra 3 rudimentary	1	0.01
dumbbell-shaped	312	3.71
cleaved	4	0.05
Sternebra 4 rudimentary	1	0.01
dumbbell-shaped	662	7.87
cleaved	2	0.02
Sternebra 5 not ossified	7	0.08
rudimentary	55	0.65
dumbbell-shaped	1345	15.99
cleaved	17	0.20
Sternebra 6 not ossified	1	0.01
rudimentary	2	0.02
dumbbell-shaped	22	0.26
Vertebral bodies		
not ossified	2	0.02
rudimentary	2	0.02
dumbbell-shaped	208	2.47
cleaved	14	0.17
Vertebral arches		
rudimentary	1	0.01
Metatarsalia incomplete ossification	6	0.07

Type B anomalies - Number and percentage

	Number	%
Fetuses examined	8410	
Fetuses with Type B anomalies	55	0.65
Externally detectable anomalies:		
- Runt	1	0.01
- Oedema (subcutaneous)	2	0.02
- Hydrops fetus	5	0.06
Skeletal anomalies:		
- Sternebrae asymmetrical	43	0.51
- Sternebrae fused	4	0.05
- vertebral bodies displaced laterally	3	0.04
- vertebral arches fused	1	0.01
- flying ribs	2	0.02
- ribs undulating	2	0.02
thickened	3	0.04
bifurcated	2	0.02

Type C anomalies - Number and percentage

	Number	%
Fetuses examined	8410	
Fetuses with Type C anomalies	6	0.07
Externally detectable anomalies:		
- Exencephaly	1	0.01
- Anury	2	0.02
- Polydactyly	1	0.01
Skeletal anomalies:		
- Sternum shapeless	1	0.01
- vertebrae fused	1	0.01
- Fusions of vertebrae and ribs	2	0.02
- Aplasia of vertebrae and ribs	1	0.01
- Aplasia of all lumbar, sacral and caudal vertebrae	2	0.02
- Dysplasia of pelvic bones	2	0.02
- Hypoplasia of long bones	1	0.01

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APPENDIX V - CONTROL DATA (1972-1975)

Results from the control groups of 30 teratological studies in OFA-SANDOZ, SPF-Rats, performed in Sandoz Ltd., Basle between 1972 and 1975.

Findings in the Dams

	Total	%	Range % ¹
Number of control groups	30		
Number of animals mated	904		
Pregnant animals	747	82.6	65.7 - 100
Abortions	0		
Assessable litters	747		
Litters without live fetuses	3	0.4	0 - 4.0
Weight gain between day 6 and 15 p.c.		16.4	11.1 - 21.6

Litter Data

	Total	Mean		Range ¹	
		per litter	% ²	per litter	% ²
Corpora lutea	10844	14.5	120.3	11.4-15.5	105.9-136.0
Implantation sites	9016	12.1	100	10.6-13.7	-
Live fetuses	8725	11.7	96.8	10.2-13.3	91.2- 98.8
Pre-implantation loss	1828	-	16.9	-	5.61- 26.4
Post-implantation loss (prenatal mortality)	291	0.38	3.22	0.14-1.08	1.2 - 8.8
- embryonic resorptions	283	0.37	3.1	0.14-1.08	-
- fetal resorptions	6	0.01	0.1	0-0.08	-
- dead fetuses	2	0.003	-	0-0.04	-
Sex ratio (male : female)	$\frac{4250}{4474}$		0.94		0.62-1.12
Fetal weight g			5.21		4.92-5.39
Placental weight g			0.90		0.84-0.96

- 1 range of individual groups
 2 in % of implantation sites
 3 in % of corpora lutea
 4 in % of live fetuses at delivery
 5 mean per fetus

Type A anomalies - number and incidence

	Number	Incidence ²
Fetuses examined ¹	8731	
Fetuses with type A anomalies	1088	12.5 (38.2)
Fetuses showing retarded ossification of		
Sternebrae No. 1	10	0.11 (0.41)
No. 2	81	0.93 (3.91)
No. 3	57	0.65 (3.06)
No. 4	134	1.53 (4.42)
No. 5	533	6.10 (16.0)
No. 6	56	0.64 (2.73)
Vertebrae No. 7	1	0.01 (0.38)
(cervical) all	2	0.02 (0.45)
(thoracic) No. 2	1	0.01 (0.38)
No. 3	2	0.02 (0.38)
No. 4	3	0.03 (0.40)
No. 6	2	0.02 (0.50)
No. 7	3	0.03 (0.40)
No. 8	2	0.02 (0.80)
No. 9	10	0.11 (1.20)
No.10	30	0.34 (1.78)
No.11	73	0.84 (3.20)
No.12	32	0.37 (1.42)
No.13	10	0.11 (0.68)
(lumbar) No. 1	1	0.01 (0.30)
No. 2	2	0.02 (0.30)
No. 3	2	0.02 (0.80)
(sacral) all	1	0.01 (0.29)
Phalanges (forelimbs)	97	1.11 (10.0)
(hindlimbs)	505	5.78 (31.0)
Metacarpalia	10	0.11 (2.33)
Metatarsalia	36	0.41 (10.9)
Skull	2	0.02 (0.33)
Whole skeleton	1	0.01 (0.33)

¹ excluding embryonic and fetal resorptions

² in % of the fetuses examined; in brackets; highest incidence observed in the individual control groups.

Type B anomalies - number and incidence

	Number	Incidence ¹	
Fetuses examined	8731		
Fetuses with type B anomalies	21	0.24	(1.11)
Externally detectable			
- Runt	2	0.02	(0.39)
- Umbilical hernia	2	0.02	(0.39)
- Hydrops fetus	4	0.05	(0.34)
- Prolapse of tongue	1	0.01	(0.29)
- Bent tail	1	0.01	(0.29)
Anomalies detected at necropsy:			
- Hydroureter	1	0.01	(0.35)
- Kidney, enlarged pelvis	2	0.02	(0.37)
- Cystic cavity mid-brain	1	0.01	(0.30)
Skeletal anomalies			
- Sternebrae asymmetrical and/or fused	9	0.10	(0.74)
- Hypertrophic vertebral bodies	1	0.01	(0.40)

¹ in % of the fetuses examined; in brackets: highest incidence observed in the individual control groups

Type C anomalies

	Number	Incidence ¹
Fetuses examined	8731	
Fetuses with type C anomalies	7	0.08 (0.45)
Externally detectable anomalies:		
- Microphthalmia and open eye	1	0.01 (0.45)
- Anophthalmia	2	0.02 (0.30)
- Encephalocele	1	0.01 (0.38)
- Exencephaly	1	0.01 (0.30)
- Cleft lip and cleft palate	1	0.01 (0.30)
- Phalanges shortened	1	0.01 (0.29)
Anomalies detected at necropsy:		
- Multiple heart defect: septal defect, common origin of aorta and pulmonary artery; ventricles and main vessels dilated	1	0.01 (0.34)
Skeletal anomalies:		
- Multiple vertebral defect: vertebrae missing, rudimentary and dysplastic	1	0.01 (0.38)
- All caudal vertebrae missing	1	0.01 (0.38)

¹ in % of the fetuses examined; in brackets: highest incidence observed in the individual control group.

Amendment

6-Month dietary rat toxicity study with tizanidine HCl

NDA# 20-397

Drug: tizanidine HCl/Zanaflex

Sponsor: Athena Neuroscience, Inc.
S. San Francisco, CA

Date Submitted: Feb 3rd 1995

Date Received: Feb 7th 1995

Reviewer: Aisar H. Atrakchi 478

Supervisor: Glenna Fitzgerald

Rev Date: Mar 2nd. 1995

This study was conducted under GLP by

/Study# 3344.2

Tizanidine HCl was obtained from Sandoz Pharma Ltd. through Athena/Batch#92010-02/SLS assigned batch# S94.002.3344. The drug as powder, was mixed with purina chow at the specified amount; the test diet was prepared weekly.

Male and female Sprague-Dawley rats were housed in plastic shoe-box cages with Alpha-Dri bedding to prevent foot lesions noted in the 2-yr rat carcinogenicity study when wire mesh cages were used. Apparently, cages were placed on the top shelf of the cage rack that caused a great deal of exposure to high light intensity and consequent retinal pathology (degeneration). In order to avoid exposure to this continuous high light intensity, the cage racks were placed in a different location on day 73 of the study and the cages were covered with paper. The study design was as follows (table from the sponsor):

The study group design and dosage levels tested were as follows:

Group	No. of Animals ^a				Test Material	Tizanidine HCl Dosage Level (mg/kg/day)	Tizanidine base Dosage Level (mg/kg/day)
	Main Study		Satellites ^b				
	Male	Female	Male	Female			
Control	20	20	10	10	Vehicle	0.0	0.0
Low-Dose	20	20	10	10	Tizanidine.HCl	2.0	1.8
Mid-Dose	20	20	10	10	Tizanidine.HCl	6.0	7.0
High Dose	20	20	10	10	Tizanidine.HCl	24.0	21.0

^aAn additional 10 animals/sex/group were used as sentinel animals.

^bSatellite animals were used in the plasma drug level determination phase of this study.

At study initiation, rats were 6wks of age and the males weighed 182-242g and females weighed 162-203g.

Blood from the 10/sex sentinel animals was used to measure hematology and clinical chemistry parameters prior to- and during wk27 and study end. Plasma drug and metabolite (3&4) levels were assessed from 5/sex/group in the stellite group at 3months and from 5/sex/group of the surviving rats at 6months. Blood was collected from the orbital sinus of lightly anesthetized animals. Drug analysis was carried out by a validated LC/MS/MS. The sponsor indicated that "due to protocol ambiguity" at 3months, animals were fasted overnight prior to blood sampling and measurable amounts of parent or metabolites could not be obtained. For the 6month blood collection, maximum food consumption was determined and blood sampling was adjusted consequently (see results for details). All surviving animals were necropsied and examined for gross morphological changes. Histopathology was done on control and HD rats only and animals that died during the study as well as the following organs/tissues from LD and MD: lungs, kidneys, liver, heart, prostate, eyes, mammary glands, thyroid, adrenals, salivary glands, stomach, and gross lesions. Ocular tissues were examined by a pathology peer review, Richard H. Burner from Pathology Associates, Inc. (see discussion for detail).

Results:

Mortality: one HDm was found dead on day171 and a 2nd HDm from the satellite group died accidentally. The former rat prior to its death was cool to touch, showed hypoactivity, labored breathing, pale extremities, and partially closed eyelids. There were no other deaths. The HDm (#4040) was examined macro- and microscopically (see below for detail).

Clinical Signs: no difference in incidence between LD and control rats. Clinical signs in MDf included low incidence of salivation, hypersensitivity to touch, and high incidence of dark material around the nose. Males in MD and males and females of HD showed piloerection, vocalization, overt aggressiveness, hypersensitivity to touch, rough coat, and increased incidence of dark material around the nose. In 1HDm and 4HDf there was what the sponsor described as bulging enlargement of the hindpaws.

Body wt and food intake: mean wt was significantly reduced in HD males and females and MDf from wk2 till study end. The wt loss ranged between 5-23% in HDm, 8-17% in HDf and 7-12% in MDf. Body wt of MD males was significantly reduced only on wks 12 and 13 (5%). Mean wt was also reduced in LDf reaching statistical significance on wks 7,8,10,12-14, and 17-27 (4-8%). The decrease in wt and wt gain was dose-dependent. Together with wt loss, food intake was significantly reduced in MD and HD rats and LDf (this was significant only at specific wks not throughout the study as seen in MD&HD). It is noted that food intake in the control rats and LDm did not increase over time yet animals were gaining wt (SD was taken into account; control males and females gained 418 and 214g between wk 1 and 27 but their food intake was increased only by 2-4g/day).

Hematology: the following parameters differed significantly between treated and control animals:

RBCs ↓ MDm/HDm wk27 (2%)
MCH ↑ LDm/MDm/HDm wk13&27 (2-7%)
MCHC ↑ LDm/MDm/HDm wk13 (3%)

Female treated rats showed no significant changes in any hematology parameters.

Clinical Chemistry: the following parameters showed statistical significance from the control values:

AST ↑ HDm wk13&27 (26-67%)
T.protein ↓ HDm wk13&27 (14%)
Alb ↓ HDm wk13&27 (5%)
Glob. ↓ HDm wk13&27 (13-16%)
BUN ↑ HDm wk27 (34%); HDf wk27 (50%)
glucose ↓ MDm wk27 (21%) & HDm wk13&27 (32%); all 3 female groups wks 13&27 (14-39%) the decrease was dose-dependent.
K ↓ MD&HDm wk27 (9%)
Ca ↓ HDm wk13&27 (5-6%)

Urinalysis: no significant drug-related findings were observed in any group.

Ophthalmology: included biomicroscopic examination and indirect examination, both involves dialating the eye. Eyes were examined prior to initiation and on wks 13&26 of the study. There were no drug-related findings in any group.

Organ wt: the table below presents all changes that showed statistical significance unless noted otherwise.

Organ/absolute wt:

kidney ↓ MD&HDm (9&25% respectively); MD&HDf (9&11%)
thymus gland ↓ all 3 male groups and dose-dependently (33-43%); all 3 female groups (15-27%)
heart ↓ HDm (35%)
spleen ↓ HDm (30%); MDf (15%), HDf (18%)
prostate ↓ HDm (37%)
thyroid/
parathyroid ↓ HDm & MDm (not sig. in MDm) (14-27%)
liver ↓ MD&HDm (14-28%); MDf (10%)
eyes ↓ HDm (5%) and HDf (9%)

Organ/relative to Body. wt:

brain ↑ HDm (1.3x); HDf (1.2x)
adrenal glands ↑ HDm (1.3x)
eyes ↑ HDm (1.2x)
testes ↑ HDm 1.2x)
thymus gland ↓ MDm (30%), HDm (23%)
spleen ↓ HDm (10%)*
prostate ↓ HDm (16%)
liver ↓ all 3 male groups (7-9%); ↑ HDf (1.1x)
heart ↑ all 3 female groups (1-1.2x; dose-dependently)

Organ wts were also analyzed relative to brain wt: in males, wt of the kidney was dose-dependently and significantly reduced in MD&HDM, thymus wt reduced dose-dependently, and wts of the heart, spleen, prostate, thyroid/parathyroid, and liver were reduced in HDM. In females, the wt of the thymus and spleen were significantly reduced in HDF.

Gross and Histopathology: there were no drug-related gross morphological findings except as noted (see histopathology below). Microscopical examination was done on all control and HD rats and only the following organs/tissues were examined in LD&MD rats: adrenals, all gross lesions, eyes, heart, kidneys, liver, lungs with bronchi, mammary glands, prostate, stomach, submaxillary salivary glands, and thyroid. The following stains were used: H&E, PAS of alcohol fixed liver, and an oil red O (ORO) stained frozen section of formalin-fixed liver.

Below is excerpted from the sponsor's report on the increased incidence and severity of retinal degeneration found in HDM and all 3 treated female rats.

An increased incidence and severity of retinal degeneration in male rats from the 24.0 mg/kg/day group and in female rats from the 2.0, 8.0 and 24.0 mg/kg/day groups was considered to be test article related. Incidence of retinal degeneration, of any degree of severity, was 2, 1, 4 and 12 in males from the 0.0, 2.0, 8.0 and 24.0 mg/kg/day groups, respectively, and 4, 10, 8 and 13 in females from the same groups. Severity of the lesion also had a positive dose response relationship in affected groups.

This lesion was characterized by reduction and loss of the outer layers of the retina - the photoreceptor layer, the outer nuclear layer and the outer plexiform layer. The most prominent change was a reduction in thickness of the outer nuclear layer from the normal nine or ten nuclei in thickness to three, two, one or no nuclei in thickness. The photoreceptor layer and the outer plexiform layers were also reduced in thickness or completely absent. In the most severely affected eyes, the overall thickness of the retina appeared to have been reduced by about half by the reduction of these layers. This lesion appears to be the same as that described in light induced retinal degeneration in rats.

Incidence of retinal degeneration in rats of both sexes in the untreated control group appeared to be greater than is usually seen in rats of this age and strain. It would appear that the test article exacerbated an underlying tendency toward retinal degeneration the animals used in this study.

Other histopathological findings are listed below including some malignant and benign neoplasms; when controls are not mentioned it means the occurrence is 0:

Organ	diagnosis/occurrence	Incidence
adrenal	hypertrophy/zona glomerulosa/ minimal-mild	8/20MDm, 14/20HDm, 6/20MDf, 15/20HDF
kidney	mineralization/minimal- mild	9/20 LD&MDf, 11/20HDF, 2/20HDm, 4/20cont.females
liver	cholangiofibrosis	2/20cont rats, 5/20LDf, 7/20MDf, 8/20HDm.
	ORO +ve cytoplasm/ minimal-moderate	8/20cont.males, 5/20cont.females, 12/20MDm, 18/20HDm, 17/20HDF.
pancreatic lymph node	hemolymphoreticular neoplasm/malignant lymphoma	1/20HDm
	hemolymphoreticular neoplasm/malignant lymphoma*	1/20HDm
mammary gland.	adenocarcinoma**	1/20MDf
	galactoceles/moderate**	1/20 each LDf&MDf
spleen	hemolymphoreticular neoplasm/malignant lymphoma	1/20HDm
vagina	malignant lymphoma	1/20HDF

* the liver and pancreatic lymphoma were seen in the same animal (HDm#4040) this animal was found dead.

** both seen in the same MDf (#4125); microscopical exam confirmed the gross morphological findings. This is true for the other malignancies (i.e. macroscopic observation confirmed by histology).

It is noted that the HDf with vaginal malignant lymphoma reported by the sponsor could not be identified in the individual animal data.

Plasma Levels: drug plasma levels were analyzed by Drug Studies Unit Lab S. San Francisco, CA for Athena Inc. (report# 94-A022). A satellite group of 10/sex/dose was used for plasma drug measurements. Five of the 10 rats were sacrificed after 3 months and the other 5 rats were sacrificed at the end of the 6 months of the study. The 3 month animals were fasted overnight prior to blood sampling whereas those sacrificed at study end were allowed to eat ad libitum till blood collection. A validated LC/MS/MS was used for measurement of the parent and metabolites 3&4 in plasma with quantification limit of 0.500ng/ml.

TABLE 1**Tizanidine:
Plasma Concentrations in the Rat (ng/mL) After Dosing in Food**

Dose [mg/kg/day]	Predicted			Measured		
	C _{ssmax}	C _{ssave}	C _{ssmin}	Mean	SD	N
1	2.1	2.0	1.8			
2	4.3	4.0	3.6	3.5	2.4	10
3	6.4	6.0	5.4			
8	17.1	15.9	14.4	11.6	6.0	10
9	19.2	17.9	16.2			
24	51.2	47.7	43.3	61.3	28.3	9

Predictions based on experimental data from Report 303-028

C_{ssave} - calculated using formula $C_{ssave} = AUC(t_n \rightarrow t_{n+1}) / \text{dosing interval}$

Actual measured data are from a Six Month Oral (Dietary) Toxicity Study in Rats (SLS Study No. 3344.2); male and female data were combined since there were no significant differences in plasma concentrations between the two groups, as verified by ANOVA.

TABLE 2

Tizanidine Metabolite 3:

Plasma Concentrations in the Rat (ng/mL) After Dosing in Food

Dose [mg/kg/day]	Predicted			Measured		
	C _{ssmax}	C _{ssave}	C _{ssmin}	Mean	SD	N
1	0.8	0.8	0.7			
2	1.7	1.6	1.4	1.3	0.5	10
3	2.5	2.3	2.1			
8	6.7	6.3	5.7	5.1	2.2	10
9	7.6	7.0	6.4			
24	20.2	18.8	17.1	22.1	10.7	9

Predictions based on experimental data from Report 303-028

C_{ssave} - calculated using formula $C_{ssave} = AUC(t_n \rightarrow t_{n+1}) / \text{dosing interval}$

Actual measured data are from a Six Month Oral (dietary) Toxicity Study in Rats (SLS Study No. 3344.2); male and female data were combined since there were no significant differences in plasma concentrations between the two groups, as verified by ANOVA.

TABLE 3

**Tizanidine Metabolite 4:
Plasma Concentrations in the Rat (ng/mL) After Dosing in Food**

Dose [mg/kg/day]	Predicted			Measured		
	C _{max}	C _{ave}	C _{min}	Mean	SD	N
1	0.03	0.03	0.03			
2	0.07	0.06	0.06			
3	0.10	0.10	0.09			
8	0.28	0.26	0.23			
9	0.31	0.29	0.26			
24	0.83	0.78	0.70	1.00	1.04	9

Predictions based on experimental data from Report 303-028

C_{ave} - calculated using formula $C_{ave} = AUC(t_n \rightarrow t_{n+1}) / \text{dosing interval}$

Actual measured data are from a Six Month Oral (dietary) Toxicity Study in Rats (SLS Study No. 3344.2); male and female data were combined since there were no significant differences in plasma concentrations between the two groups, as verified by ANOVA.

FIGURE 1

Predicted Plasma Concentrations in the Rat After Dosing in Food
(Tizanidine)

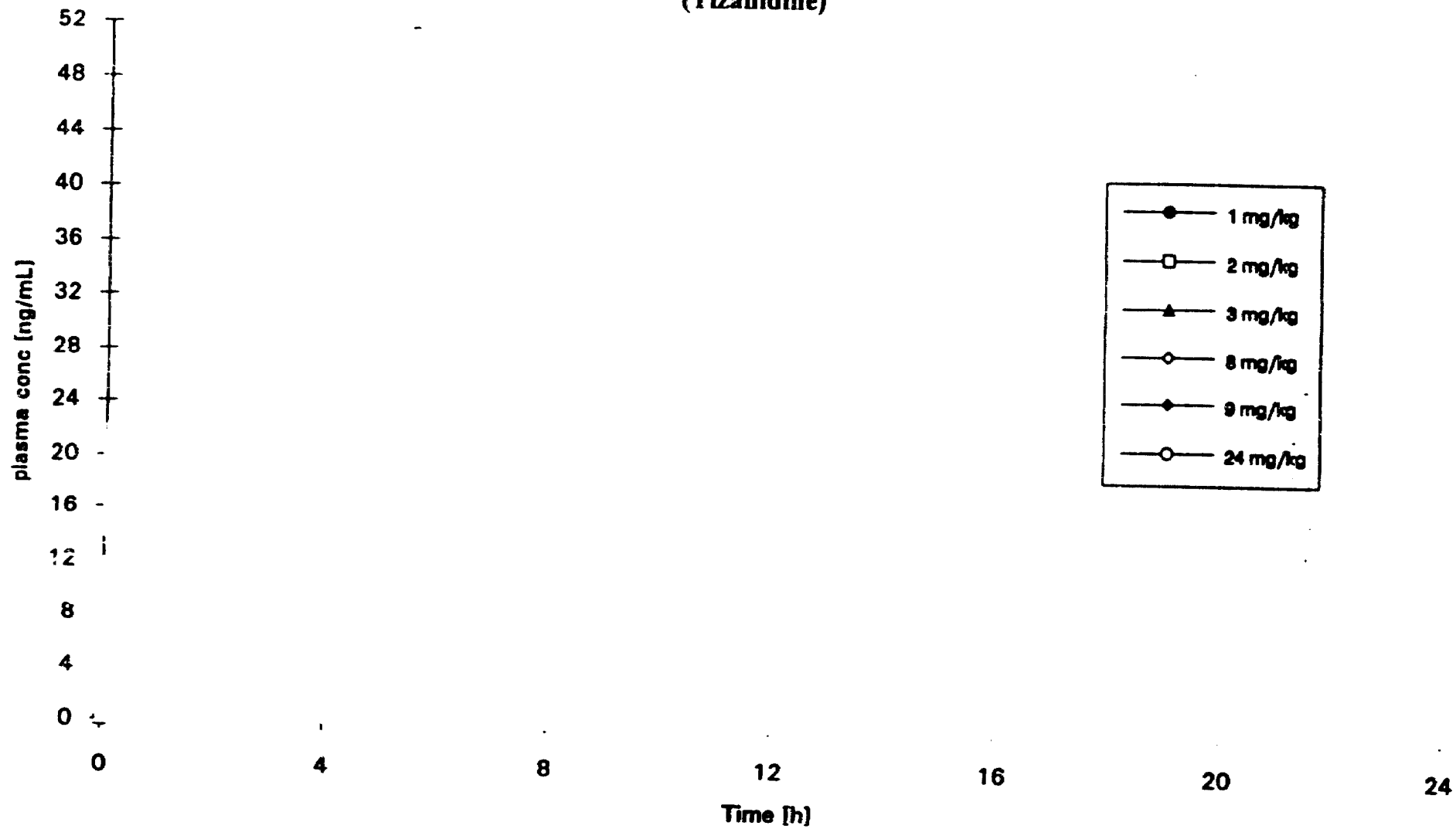


FIGURE 2

**Predicted Plasma Concentrations in the Rat After Dosing in Food
(Metabolite 3)**

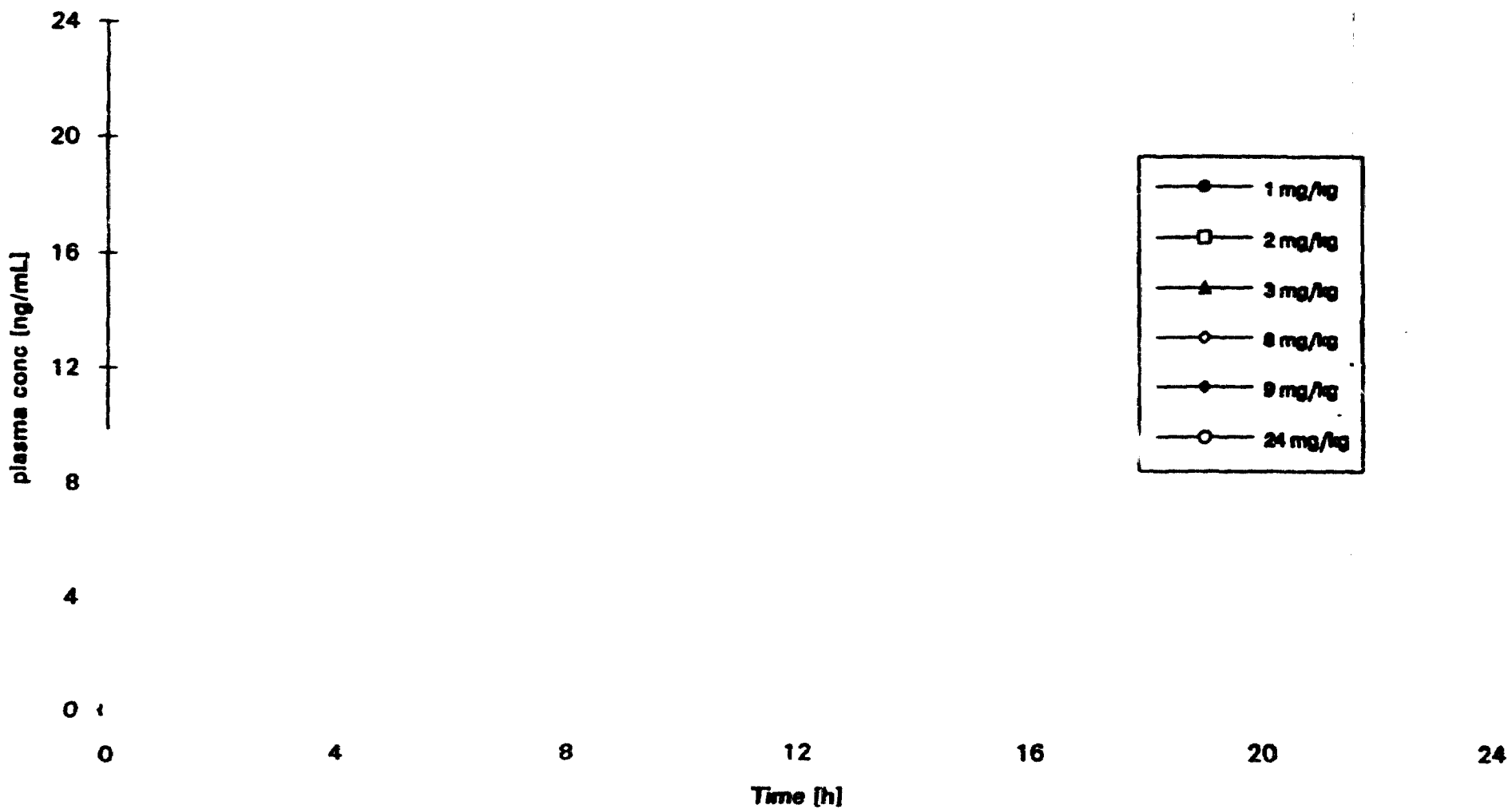
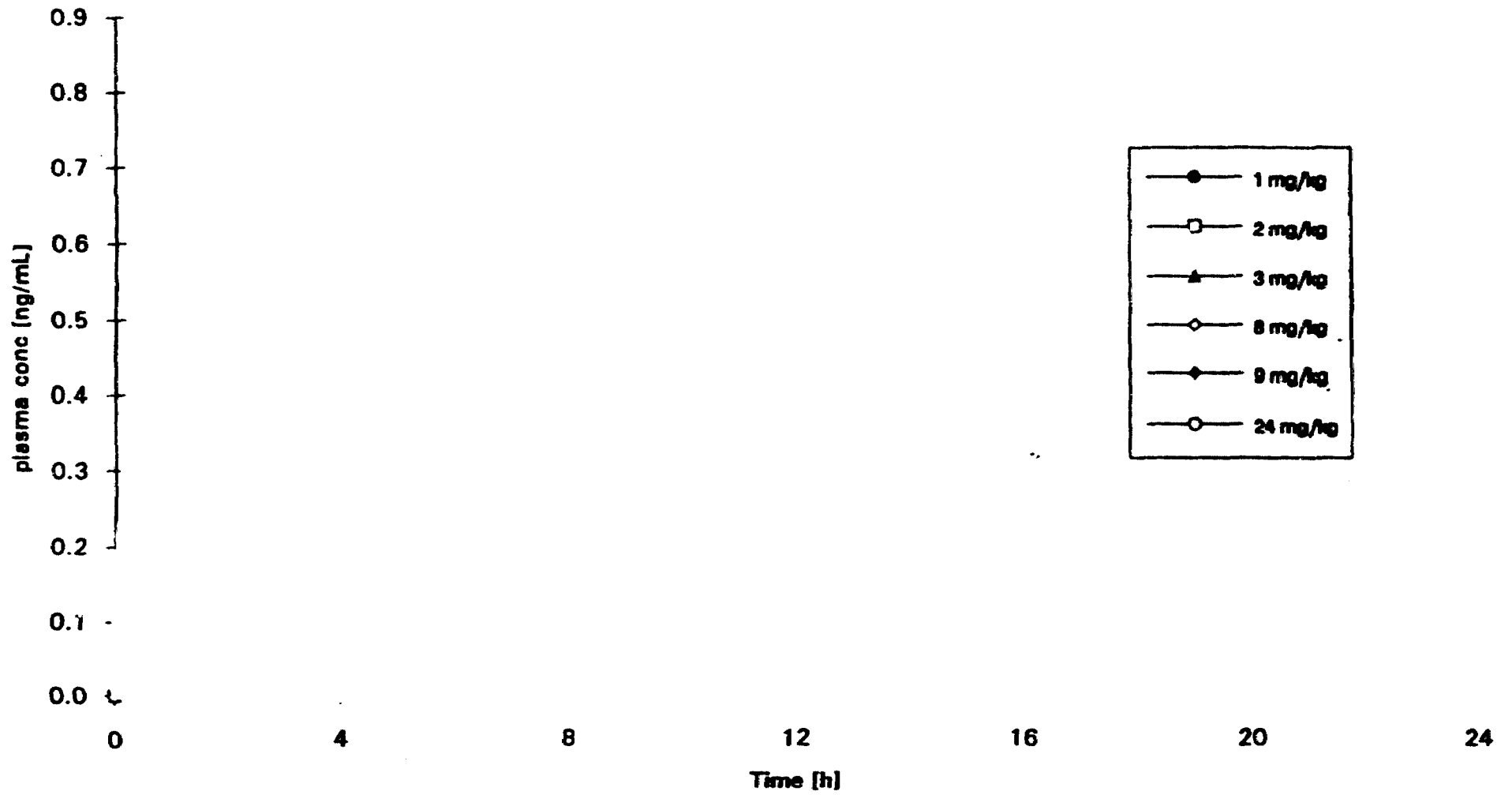


FIGURE 3

**Predicted Plasma Concentrations in the Rat After Dosing in Food
(Metabolite 4)**



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Discussion and Summary:

Tizanidine was admixed in the diet of male and female Sprague-Dawley rats at doses equivalent to 2, 8, and 24mg/kg/day for 6 months. The animals were observed for clinical signs, behavior, mortality and the following parameters were evaluated: body wt, food intake, hematology, clinical chemistry, urinalysis, ophthalmology, organ wt, gross examination and histopathology. Blood levels of tizanidine and metabolites 3&4 were determined at 3 and 6 months. A single drug-related mortality occurred in one HDm. Clinical signs were not observed in LD but seen in mid and high dosed rats and included aggressiveness, vocalization, piloerection, and hypersensitivity to touch. There was a significant and dose-dependent decrease in body wt and wt gain that correlated with decreased food intake in all drug groups except, LDm group had similar wts to the corresponding control wts. The decrease in wt was between 5-23% in HDm, 8-17% in HDf, 7-12% in MDf, and 4-8% in LDf. There was no significant drug related changes in urinalysis, hematology, or ophthalmology. The latter is important since ocular opacity seen in the life-time assay was absent in this study. Some statistically significant findings were recorded in clinical pathology and included upto 67% increase in AST level of HDm measured at mid study and at the end, increase in BUN at study end of HDm (34%) and HDf (50%), total proteins and globulins were decreased mid and end of study in HD rats (34-50%), and a significant decrease in blood glucose noted in all treated female groups (dose-dependent) and MD&HDm during mid and end of study (14-39%). Plasma calcium and potassium levels were slightly but significantly reduced in HDm and/or MDm. These clinical chemistry findings were reported by the sponsor to be small and within the range of normal biological variability (historical data or normal variation were not provided). Tizanidine and metabolites 3&4 blood levels were measured at 3 and 6 months. However at 3 months, measurable concentrations for tizanidine could be obtained only from 2HD rats (0.6 and 1.4ng/ml) and for metabolite 3 it was quantified from only one HDf sample (0.6ng/ml); metabolite 4 could not be quantified in any animal at the 3 month sacrifice. The sponsor contributed this failure or difficulty in measuring plasma levels, to fasting of the animals over night and the short half life of tizanidine and its metabolites. However, in the 6 month blood sampling, the blood collection time was adjusted close to the expected Tmax. Tizanidine and metabolite 3 were quantified from all rats but again, metabolite 4 was quantified only from few samples. Plasma levels for tizanidine ranged between 1-9ng/ml in LD, 4-20ng/ml in MD, and 28-96ng/ml in HD, those for metabolite 3 were 0.7-2ng/ml in LD, 2.5-9ng/ml in MD, and 10-41ng/ml in HD; metabolite 4 was detectable in 5 of 9 samples of HD rats with values between 1-2ng/ml. There was no gender differences and drug concentration increased with dose but the increase was non-linear. The liver seems to be the target organ for toxicity since enzyme changes, wt change (absolute and relative to body- and brain- wt), gross, and histopathology were observed. Changes in organ wts in addition to the liver included a decrease in absolute and relative wts (both relative to body-

and brain wts) of the spleen, thymus, and prostate in HD males. In males, wt of the kidney was dose-dependently and significantly reduced in MD&HD determined relative to the brain wt. Histopathology was not seen for the thymus, spleen, prostate or kidneys. A small but significant increase in relative wt of the adrenals was seen in HDm which was accompanied by increased incidence of hypertrophy of the zona glomerulosa in all 3 treated groups vs. the control. Some gastric lesions (erosion and discoloration) were related to stress in HD and the less intake of food in these animals. Some malignancies were recorded in HD animals, although the incidence was low such neoplasms were absent in the control group. There was a dose-dependent increase in severity and incidence of retinal degeneration. This degeneration involved the outer layers of the retina (photoreceptor layer), the outer nuclear layer, and the outer plexiform layer. In the most severely affected eyes, the overall thickness of the retina seemed to be reduced by one half (the eye wt was significantly reduced). The sponsor goes into a great detail of presenting published articles and consultant review to dismiss the association of the retinal degeneration as a drug effect. The sponsor contributes this lesion to the exposure of the cages to continuous light of high intensity. This was supported by the fact that most of the degeneration was in the central segments of the retina where light rays are focused as opposed to chemically-induced retinopathies which are expected to affect the entire retina. The sponsor also indicated that the animals in this study seemed to have been more sensitive to retinal degeneration as seen from the high incidence in the control animals. A consult review of this pathology is attached that made the same conclusions i.e. the retinal degeneration was not drug-related but induced by light. It can be concluded that the NOEL in this study is 2mg/kg/day.

Evaluation and Recommendation:

This study adequately described the toxicity of tizanidine during 6-month oral dosing to the rat. However, it did not measure plasma metabolite 10 which was requested from the sponsor in fax and/or letters from the Agency on July, Aug, and Sep of 1994. In these memos, we have requested that the sponsor measure plasma metabolites 3, 4, and 10. The sponsor in this study adequately assessed metabolites 3 and 4 but did not measure 10. The sponsor had indicated that attempts by their chemists and outside consultants had failed to synthesize metabolite 10. Synthesis of metabolite 10 is necessary for the analytical method used for detection and identification. It is the opinion of our Chemist Dr. M.E. Guzewska that metabolite 10 can be synthesized as found in 2 published articles Koch et al., 1989 and 1990. Therefore, it is concluded that this study failed to measure metabolite 10 which is 1 of 3 major human metabolites. See additional information in the next page.

cc.

/Orig NDA# 20-397

/G. Fitzgerald/A. Atrakchi/D. Grilley

In a meeting with Athena on July the 27th 1995, the issue of metabolite 10 synthesis was discussed. Our chemist Dr. Maria Guzewska on Dec 27 1994 had issued a memo regarding the synthesis of metabolite 10 (included in the carcinogenicity section of this package) and referenced the 2 published articles on the synthesis of this metabolite. However, during the meeting with Athena on July 27th, after discussing this issue, Dr. Guzewska reconsidered her opinion and agreed with the sponsor that synthesis of metabolite 10 is not possible. Consequently, we no longer requested measurement of metabolite 10 in the rat TK studies and accepted the data submitted for metabolites 3 and 4.

Pharmacology Reviewer
Aisar Atrakchi, Ph.D.

Statistical Review and Evaluation

DATE:

NDA#: 20-397

APPLICANT: Sandoz Ltd.

NAME OF DRUG: Zanaflex (tizanidine Hcl)

DOCUMENTS REVIEWED: Four Undated Desk Copies of Volumes Containing the Sponsor's Results of Two Carcinogenicity Studies, One in Mice and One in Rats, and One Volume Dated Oct 13, 1994, with Data Listings, Tumor Listings and a Diskette.

I. Background

Dr. Aisar Atrakchi (HFD-120) is the reviewing pharmacologist. Dr. Glenna Fitzgerald, supervisory pharmacologist (HFD-120), requested the Division of Biometrics for an oral report of findings by 1/20/95. At an in-house meeting (1/24/95) it was decided that all reviews needed to be completed by 2/3/95.

II. The Rat Study

II.a. Design

The product was studied for 104 weeks in male and female CD rats. The study was conducted between November 1977 and November 1979. Sixty animals per sex and treatment group were assigned to either control, 1, 3, or 9 mg/kg/day of the compound in the feed. Findings of mortality, food consumption, water consumption, bodyweight gain, tumor incidence rates, and other clinical findings were recorded. Statistical analyses included Student's t-test, Chi-square test, and Fisher's Exact test.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis: The sponsor presented survival curves for male and female rats and concluded that there was no indication that the compound influenced mortality.

Tumor Data Analysis: The sponsor listed tumor frequencies for various comparisons of the control and treated groups in many tables. They concluded that the incidence and variety of spontaneously occurring tumors were "undisturbed".

II.c. Reviewer's Analyses

This reviewer used the data submitted on diskette for her analyses.

Survival Analysis: The mortality experience of the male and the

female rats was analyzed using a program developed by Thomas, Breslow, and Gart: Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381 (1977). The program tests the data for a linear trend in mortality with dose, as well as general heterogeneity of the mortality distributions and tests all pairwise comparisons of control and treated groups with Cox's and the Generalized Kruskal/Wallis analyses. None of these analyses indicated any statistically significant relationship between the mortality experience of the various treated groups (including control) and the exposed dose. These findings held for the male and for the female animals. The mortality experience is summarized in Table 1 and Graphs 1 and 2.

Tumor Data Analysis: The Division of Biometrics applies the following methodology to carcinogenicity studies: Tumors with less than 1.00 of occurrence in the control group are considered rare and a positive linear trend test is statistically significant when it reaches a p-value of $\leq .05$ (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive linear trend is statistically significant when its p-value is less than .01 (one-sided). Incidence rates of tumors and other lesions as recorded by the sponsor with possible positive linear trends with increasing dose are analyzed by an exact permutation trend test (an approximate permutation trend test is used when fatal and incidental tumors of the same kind are combined and have overlapping intervals). All tests are survival adjusted. Treatment groups are weighted by the actual dose levels.

Applying this methodology there were no tumor types whose incidence rates resulted in a statistically significant positive linear dose response relationship in either male or female rats.

As there were no statistically significant tumor findings, this reviewer investigated the validity of the study:

This study was conducted between the end of 1977 and 1979 and the standards were not as rigorous then. However, it appears that no randomization to treatment groups was performed, rather that animals were assigned to treatment groups and switched until each treatment group had a body weight range of 135-136 g for males and 121-123 g for females.

The number of animals per treatment group (60) is acceptable as is the number surviving to terminal sacrifice (over 40 % per treatment group).

In terms of reduction in body weight gain of the high dose group versus the control group, it was found that the male rats had a 13 % lower body weight gain at the end of the

study when compared to their controls. The corresponding figure among female rats was 6 %.

Analyses of the mortality and body weight gain data showed that the tested animals had received an adequate drug exposure and a reasonable tumor challenge. However, other information such as clinical signs or severe histopathologic toxic effects that can be attributed to the drug should also be considered in the final evaluation of the validity of the study.

III. The Mouse Study

III.a. Design

This was a 78 week long study which was conducted between July '76 and January '78. Two hundred Sandoz SPF bred mice of each sex were randomly assigned to control and treated groups. The doses were 1, 4, and 16 mg/kg/day of Zanaflex in feed. In life and post mortem signs were observed and recorded. "Results" were subjected to parametric or non-parametric statistical analyses, in particular tests of homogeneity of variances, one-way ANOVA, multiple comparison and chi-square tests.

III.b. Sponsor's Analyses of Mouse Study

Survival Analysis: The sponsor presented a mortality table in intervals of 10 weeks and cumulative mortality curves for the male and female animals. It was concluded that there was no drug dependent influence on the mortality rates.

Tumor Data Analysis: The sponsor provided tumor frequency tables and concluded that there was no evidence that tumors occurred more frequently, earlier, or were of a different type in the treated groups than in the control groups.

III.c. Reviewer's Analyses

Again, the data on the diskette were used for analysis. Some animals had an unexplainable code of "mode and week of death an" for the death status variable. The problem could not be clarified by the sponsor by 1/26/95. This reviewer classified these animals as "terminal sacrifice" because of the late week of death attributed to them.

Survival Analysis: The same statistical methods were applied to the data as have been outlined for the rat study. For neither the male nor the female mice was there a dose related increase in mortality (Table 2 and Graphs 3 and 4).

Tumor Data Analysis: Applying the same methodologies appropriate for tumor data as were mentioned for the rat study, no

statistically significant positive linear dose response was observed for any set of tumor incidence rates.

As there were no statistically significant findings in tumor rates an evaluation of the validity of the study is appropriate:

Again, it is an old study and is being held up to current standards. However, it appears unusually short, 78 weeks, which was not necessitated by an undue number of early deaths. In fact, over 46 % of the animals in any treatment group were still alive at terminal sacrifice. It is therefore possible that there was not sufficient time for late developing tumors to occur.

The body weight data were only presented in graphs, not as actual data. Therefore, any difference in body weight gain between the high dosed animals and their respective controls cannot be calculated. The graphs indicated a reduced weight gain of the high dosed males versus their controls and to a lesser degree also for the female mice. However, the precision of this finding depends on the viewer's eye.

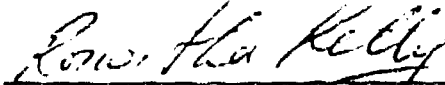
As mentioned for the rat study, the information on clinical signs and severe histopathologic toxic effects caused by the drug need to be also considered in the evaluation of the validity of this study.

IV. Summary and Conclusions

Both studies are over ten years old and suffer from less rigorous standards. However, the rat study was two years long and showed no dose related increase in either mortality or tumor incidence rates. Reduced body weight gain of high dose versus control animals by itself lends support to the validity of the study. However, other toxic effects and clinical signs need to be considered.

The mouse study was only 78 weeks long and late developing tumors may not have had time to develop. Taking the data as is, there were also no dose related effects on mortality or tumor incidence rates in this study. Body weight data were not submitted and reduced body weight gains can only be read from a graph submitted by the sponsor. Again, a total evaluation of the validity of the study needs to take clinical signs and severe histopathologic

toxic effects into account. These measures are not recorded as part of the data on diskette and have not been submitted to any statistical evaluation.



Roswitha E. Kelly
Mathematical Statistician

Concur:



Karl K. Lin, Ph. D.
Group III Leader

cc:HFD-120/Original NDA 20-397

✓HFD-120/Dr. G. Fitzgerald

HFD-120/Dr. A. Atrakchi

HFD-710/Chron.

HFD-715/Dr. K. Lin

HFD-715/Ms. Kelly

HFD-715/DRU 2.1.1 Zanaflex, carcinogenicity, Sandoz
(Attachment)

HFD-715/RKELLY/02/02/95/wp-zanaflex.rev

Table 1
INTERCURRENT MORTALITY RATES

Time (wks.)	FEMALE RATS			
	Control 0	1	3 mg/kg/day	9
0 - 52	7/61 (11%)	3/58 (5%)	2/60 (3%)	1/59 (2%)
53 - 78	5/54 (20%)	9/55 (21%)	7/58 (15%)	7/58 (14%)
79 - 91	10/49 (36%)	9/46 (36%)	12/51 (35%)	5/51 (22%)
92 -103	10/39 (52%)	10/37 (53%)	13/39 (57%)	15/46 (47%)
Term. Sac.	29/61 (48%)	27/58 (47%)	26/60 (43%)	31/59 (53%)

Time (wks.)	MALE RATS			
	Control 0	1	3 mg/kg/day	9
0 - 52	2/62 (3%)	3/59 (5%)	3/60 (5%)	6/60 (10%)
53 - 78	7/60 (15%)	5/56 (14%)	5/57 (13%)	5/54 (18%)
79 - 91	12/53 (34%)	10/51 (31%)	14/52 (37%)	12/49 (38%)
92 -103	16/41 (60%)	15/41 (56%)	12/38 (57%)	11/37 (57%)
Term. Sac.	25/62 (40%)	26/59 (44%)	26/60 (43%)	26/60 (43%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 2

INTERCURRENT MORTALITY RATES

Time (wks.)	Control 0	FEMALE MICE		
		1	mg/kg/day	
			4	16
0 - 52	6/51 (12%)	8/50 (16%)	5/51 (10%)	4/50 (8%)
53 - 77	17/45 (45%)	19/42 (54%)	16/46 (41%)	18/46 (44%)
Term. Sac.	28/51 (55%)	23/50 (46%)	30/51 (59%)	28/50 (56%)

Time (wks.)	Control 0	MALE MICE		
		1	mg/kg/day	
			4	16
0 - 52	3/50 (6%)	6/50 (12%)	6/48 (13%)	6/48 (13%)
53 - 77	17/47 (40%)	18/44 (48%)	9/42 (31%)	11/42 (35%)
Term. Sac.	30/50 (60%)	26/50 (52%)	33/48 (69%)	31/48 (65%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

2
ATTACHMENT-3

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 24, 1994

FROM: Glenna G. Fitzgerald, Ph.D.
Supervisory Pharmacologist, HFD-120

Aisar H. Atrakchi, Ph.D.
Pharmacology Reviewer, HFD-120

SUBJECT: Meeting 9:00 - 10:00 am, July 13, 1994
Parklawn Building, Room 13B-39

TO: Members of Carcinogenicity
Issues Committee

This meeting has been called to discuss the general issue of how to deal with carcinogenicity studies for drugs when the metabolism in humans differs significantly from that in rodent species, resulting in a different exposure pattern in animals than in humans. The need for such a meeting was prompted by a drug in HFD-120. A brief summary of the PK data for that drug is attached and serves as an example of a drug for which the exposure in humans is not similar to exposure in either mouse or rat.

Some of the questions we would like to have addressed are listed below. We would appreciate it if each of you would bring other relevant questions and ideas to the meeting.

1. How closely should the metabolite pattern in humans match that in carcinogenicity studies in rodents? If the metabolic pathway is similar across human and animal species, but the plasma levels of parent and/or metabolites are very different, would we be more lenient than in the case where the metabolic pathways are qualitatively different? For example, if the major metabolites formed in humans are found only in urine and/or bile but none in plasma of rats and mice, can these data replace the plasma exposure data?
2. If plasma data are to be used, is it necessary that the relative amounts of parent and metabolites in plasma be more or less the same in humans and animals? How closely should they match?

3. What should plasma levels be based on - Cmax, AUC, or should we consider tissue levels of target organs? What other factors should be considered to determine relative exposures?
4. If the drug is extensively metabolized, is it necessary that all human metabolites be present in animals? Only pharmacologically active metabolites? Only metabolites that are present at "high" levels, and what are "high" levels? In both species of rodent?
5. If a drug were just being developed, and the metabolic profile in humans was very different from that in rodents, what would you ask the sponsor to do?
 - a) Would you ask the sponsor to examine the metabolic profiles in other rat/mouse strains or hamsters to select the best matches? A different route of administration?
 - b) If no good match is found, would you ask the sponsor to dose with an appropriate mix of parent and metabolite(s) in the strain (rat) used in toxicology studies, or in the "best match" strain of rat and mouse?
6. If you received old carcinogenicity studies, such as the attached example from our new NDA, for which there is very poor concordance between animals and humans, what would you do?
 - a) Ask for a comprehensive genetic toxicology battery of parent and all metabolites and base a decision on that?
 - b) Ask for carcinogenicity studies which are more representative of human exposure (more appropriate strain/species, different route of administration, dosing with metabolites)?
 - c) When would these studies be required - pre-approval or phase IV?
 - d) What would provide a justification for approving a drug such as the one we have with either no additional requirements or some phase IV requirements?

A working example that is presently in our division is NDA 20-397. This drug has been under development for over a decade and many of the pivotal studies were conducted in the late 1970s and early 1980s, including the carcinogenicity bioassays in mouse and rats, the reproductive studies, and almost all of the pharmacokinetic studies. Recently we discovered quantitative differences in the major human plasma metabolites and those in rodents (see table). The drug in all animal species studied and in humans is extensively metabolized and the parent compound is non-detectable in plasma, except in mouse and dog. There are 4 major metabolites formed in human plasma: #3 (16.7%), #4 (14.7%), #9 (6.4%) and #10 (12.5%) based on administered radioactive doses. The major plasma metabolite in the rat is #10 (>98%); however, #3, 4 and 9 appear in urine and bile. In the mouse, #9 (64%) and #4 (4.8%), plus parent (13.4%) appear in plasma. Bile and urine were not analyzed. The metabolic pathways for this drug are presented in the attached diagram. Three pathways are identified, all involving oxidation: one pathway is the oxidation of the aromatic ring and production of metabolites 6, 7, 8, and 9, the second pathway is the oxidation of the imidazoline moiety producing metabolites 2, 3, 4 and 5, and the 3rd is oxidation of the sulfur atom, producing metabolite #10 (the major product in rat plasma and urine).

The rodent carcinogenicity studies have been conducted with the parent drug administered in the diet (doses in mice: 1, 4, 16 mg/kg/d and doses in rats: 1, 3, 9 mg/kg/d). Exposure data were not measured in these studies or in the subchronic 13-week rat and dog toxicity studies or the 52-week dog toxicity study (there was no subchronic mouse toxicity study). Based on this information, are the carcinogenicity studies appropriate to predict human risk or to provide informative labeling?

cc: A. Taylor, HFD-102
R. Temple, HFD-100
J. Bilstad, HFD-500
P. Leber, HFD-120
J. Contrera, HFD-401
Supervisory Pharmacologists, ODEI and II
R. Katz, HFD-120
J. Rouzer, HFD-120
J. Collins, HFD-400
R. Baweja, HFD-426
M. Hossain, HFD-426
V. Tammara, HFD-426
V. Hale, HFD-126
A. Atrakchi, HFD-120

Major Metabolites		Man	Rat	Mouse	Dog^a	Rabbit^a
3	Plasma	16.7	ND	ND	11	3.5
	Urine	5.5	3	*	5.4	ND
	Bile	*	7.4	*	*	*
4	Plasma	14.7	ND	4.8	23.3	1.0
	Urine	11.4	23.2	*	31.7	ND
	Bile	*	5.4	*	*	*
10	Plasma	12.5	>98	ND	3	10.7
	Urine	11.6	37.4	*	ND	ND
	Bile	*	7	*	*	*
9	Plasma	6.4	ND	64.3	4.2	26.1
	Urine	4.5	10.5	*	5.1	20
	Bile	*	7	*	*	*

^a other major plasma metabolite in the dog is #8 (33.2%) and in the rabbit is #7 (37%).

ND not detectable at analytical assay's detection limit (NR).

The above values are percent of metabolites in plasma at C_{max} and 0-24 hr pooled urine.

TABLE 17

**Inter-Species Comparison of the Biotransformation of Tizanidine
(% total radioactivity)**

Tizanidine Metabolite	Species (Reference)				
	Mouse (94)	Rat (95)	Rabbit (96)	Dog (97)	Man (100)
Plasma (at Cmax)					
1 <i>Parent</i>	13.4	ND or trace	ND or trace	11.5	ND or trace
2	ND	ND	ND	ND	0-2.7
3	ND	ND	3.5	11.0	17
4	4.8	ND	1.0	23.3	14.7
5 ^a	ND	ND	ND	ND	ND
6 ^b	ND	ND	ND	ND	ND
7	0-6.1	ND	37	4.0	1.3
8	2.4	ND	2.1	33.2	2.7
9	64.3	ND	26.1	4.2	6.4
10	ND	>98	10.7	3.0	12.5
Urine (0-25 hr pool)					
1 <i>Parent</i>	NA	ND or trace	ND or trace	2.9	ND or trace
2	NA	6.8	ND	2.7	ND
3	NA	2.9	ND	5.4	5.5
4	NA	23.2 ^c	ND	31.7 ^c	11.4
5 ^a	NA	c	ND	c	ND
6 ^b	NA	ND	ND	ND	ND
7	NA	1.4	37.2	3.7	6.6
8	NA	ND	ND	ND	ND
9	NA	10.5	19.8	5.1	4.5
10	NA	37.4	ND	ND	11.6

The numbers are taken from original reports rather than from the summary report: Reference 15

NA = not analyzed

ND = not detectable

^a This metabolite was found in rat and dog urine but not in plasma. It can be formed from metabolite of 2 as an artifact of isolation procedure and might not be a true metabolite.

^b Metabolite 6 was not detected in any of the investigated species, but it is believed to be formed, as judged by the presence of its conjugates, metabolites 7 and 8

^c Sum of metabolites 4 and 5

TABLE 16
(Continued)

Metabolic patterns following oral dose

Species		Mouse	Rat	Rat	Rabbit	Rabbit	Dog	Dog
(Reference)		(94)	(95)	(95)	(96)	(96)	(97)	(97)
Sex		Male	Male	Male	Male	Male	NS ¹	NS ¹
Dose	[mg/kg]	4	5	330	4	50	4.5	3
Parameter	Unit							
Plasma Tizanidine	[% total radioactivity] (time)	16-9% (0.25-1.5 h)	ND ²		ND ²		11.5% (1-3 h pool)	
Primary Metabolite		<u>2</u> 74-55% (0.25-1.5 h)	<u>10</u> 98% (1 h)		<u>7</u> 37% (0.5 h)		<u>8</u> 33% (1-3 h pool)	
Secondary Metabolite					<u>2</u> 26% (0.5 h)		<u>4</u> 23% (1-3 h pool)	
Urine Tizanidine	[% total radioactivity] (collect time)			ND ²	ND ²			3% (0-24 h)
Primary Metabolite				<u>7</u> 37% (0-24 h)		<u>7</u> 37% (0-24 h)		<u>4 + 2</u> 32% (0-24 h)
Secondary Metabolite				<u>4 + 2</u> 23% (0-24 h)		<u>2</u> 20% (0-24 h)		

Metabolite number underlined; See Figure 7 for structures

¹NS = Not specified

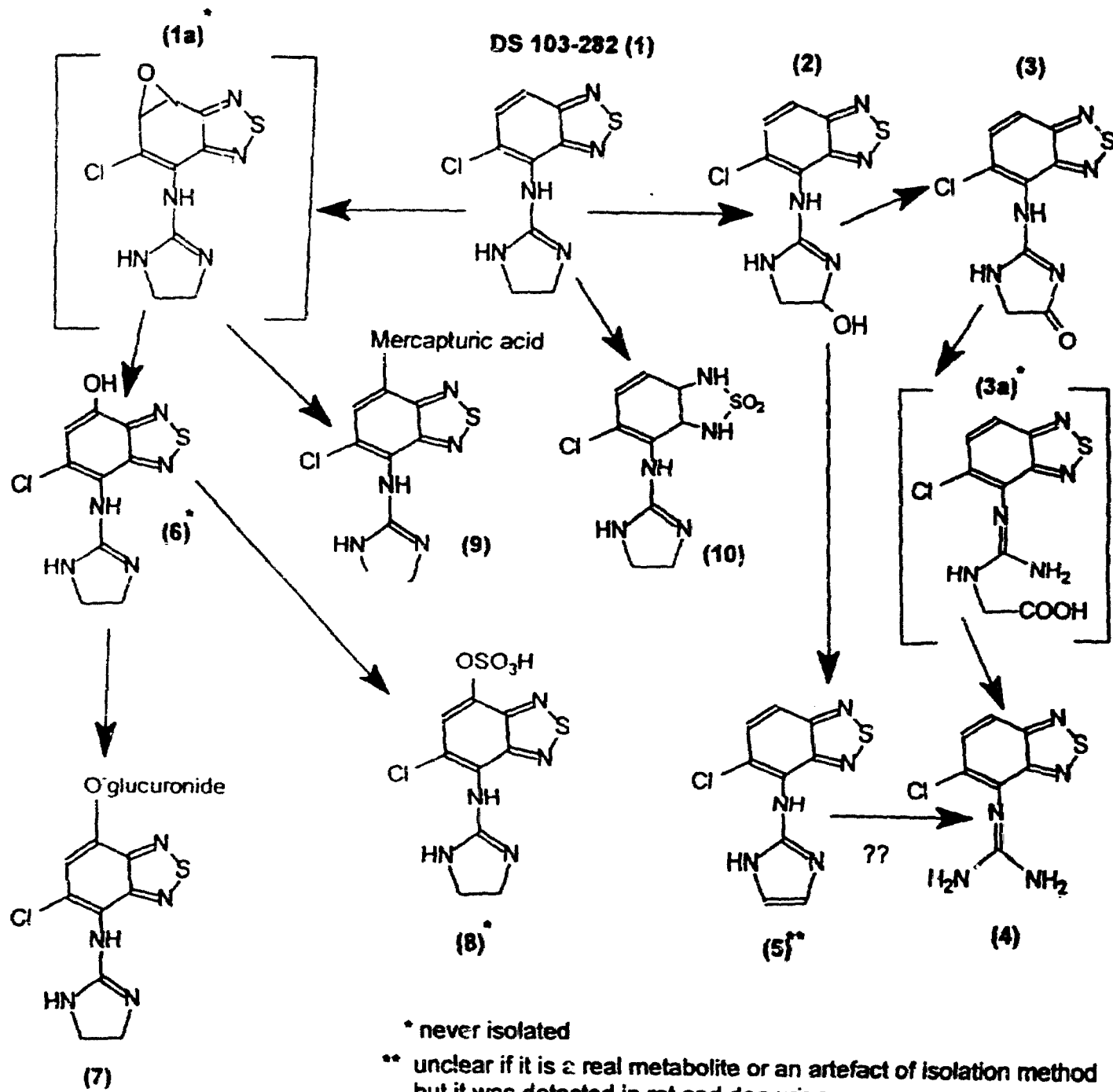
²ND = Not Detectable

Table 1: Summary of disposition parameters of DS 103-282

Parameter (oral dose)	Man	Rat	Mouse	Dog	Rabbit
<u>Absorption:</u> amount absorbed (% dose) rate of absorption	> 70 fast	90 fast	> 70 fast	90 fast	90 fast
<u>Plasma levels of radioactivity:</u> C _{max} [F-value] time to peak level (h)	0.805 1.0	0.750 0.75	0.197 0.75	0.375 2.2	0.335 1
<u>Distribution:</u> t _{1/2} α-phase (h) highest radioactivity levels in plasma protein binding (%)	2.5 30	short K,L 23	short K,L	short	2.5
<u>Biotransformation:</u> fraction metabolized first-pass effect main metabolites in plasma % of parent drug at or near peak time	> 90% 50 to 80% <u>4, 2, 10</u> 6.0 *	> 90% <u>10</u> 0.0	> 90% <u>2</u> 13.1	> 90% <u>2, 2, 2</u> 11.5	> 90% <u>2, 2</u> 0.0
<u>Elimination:</u> excretion { urinary (% dose) faecal (% dose) biliary (% dose) t _{1/2} β-phase (h) t _{1/2} parent drug (h)	= 70 20-30 22 (61) 3-5	61 1 29 2	64 26 5	72 24 10	64 22 45

* 0-24 h plasma pool

K = kidney
L = liver



ATTACHMENT 4

Carcinogenicity Issues Committee Final Report

Meeting Date: July 13, 1994

Chairperson: Taylor *NSJ* 9/1/94

Voting members present:

Resnick, DeFelice, Fitzgerald, DeGeorge, Bailey, Choudary, Osterberg, Alam, Farrelly, Chen, Contrera

Other participants:

Temple, Katz, Atrakchi, Freed, Tammara, Hale

Subject:

Policy regarding the need for qualitative and quantitative similarity in metabolism of pharmaceuticals between the test species/strain and humans with respect to acceptability of carcinogenicity studies. An example from HFD-120 (NDA 20-397) provided the impetus for discussion. (TIZANIDINE).

Major issues and recommendations are given below.

Concerning the need for exposure to human metabolites in the animal model:
A majority of the Committee (11/12) agreed that while it is desirable for there to be qualitatively similar metabolic profiles in humans and the test strains/species to insure that the carcinogenic potential of human metabolites is tested in animals, it is not reasonable to expect that quantitatively similar exposure to metabolites can be achieved. This reaffirms the position taken previously by the Committee with regard to the use of a pharmacokinetic endpoint for high dose selection in carcinogenicity studies, where it has been considered that qualitatively similar metabolic profiles are required to use this alternative to the MTD. It is not necessary to demonstrate that the relative amounts of parent and metabolites in plasma are similar across species.

Concerning the use of metabolic profiles derived from measurements of urine or bile rather than plasma:

There was a general consensus that plasma metabolite profiles are highly desirable and provide the most definitive comparator. However, the presence of metabolites in urine or bile may provide evidence for similarity in metabolic pathways and in the absence of plasma data may be supportive of an argument that animals have been exposed to relevant human metabolites. It was agreed that appearance in the bile does not guarantee that plasma/systemic exposure occurred.

The committee also discussed the use of in vitro metabolism data (e.g. liver slices or microsomes) to support similarity of metabolism across species.

Concerning the appropriate pharmacokinetic parameter for comparing systemic exposure:

Committee reaffirmed its previous recommendation that AUC is the appropriate parameter for comparison because it considers concentration and duration of exposure.

Concerning the necessity to insure that all human metabolites are tested, especially for extensively metabolized drugs:

The Committee acknowledged that it might not be feasible to insure that all human metabolites are tested in the animal studies. However, it is considered important to demonstrate that metabolic pathways in humans and rodent are similar. Where it is known prospectively that rodents are not exposed to a major human metabolite, consideration may be given to dosing with metabolite(s) rather than, or in addition to parent, when the numbers of metabolites in question makes this feasible. If alternative species/strains or routes of drug administration produce a metabolic pattern more similar to humans, use of these should be considered.

Concerning the need for additional testing when data indicate that human metabolites were not tested in the rodent carcinogenicity studies:

The Committee suggested that the approach taken would depend on the level of concern for carcinogenic potential. Scientific rationale would be needed to justify requesting a repeat carcinogenicity study to test metabolites when a carcinogenicity study of the parent drug using the traditional MTD paradigm has been conducted and was negative. Structural characterization (SAR) of metabolites and/or testing of isolated metabolites in a genotoxicity screen could provide information important for assessing the need for additional testing. Use of alternative test models to get data on carcinogenic potential of metabolites could also be considered (e.g. neonatal mouse model).

Concerning the example from HFD-120:

A majority of the committee recommended that the studies performed were acceptable for the following reasons: Not all human metabolites were seen in rats and mice. However, based on review of the metabolic pathways and metabolites reported in all analytes (plasma, urine, bile), it appeared that human metabolites were tested in either rats or mice. As noted above, a majority believed that demonstrating the presence of metabolites in the test animals was sufficient, even if levels of exposure were not similar across species.

C:
DA 20-397
FD-120/Leber
/Fitzgerald
FD-100/Temple
FD-502/CAC file

Chemist Review

Zanaflex[®]
(Tizanidine HCl) Tablets

NDA 20-397

Chemistry

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-397

CHEM. REVIEW # 4

REVIEW DATE

05-NOV-96

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

ORIGINAL
AMENDMENT .N(BC)
AMENDMENT .N(AZ)
AMENDMENT .N(BC)

06-DEC-93
20-JAN-95
08-SEP-95
12-SEP-96

07-DEC-93
23-JAN-95
11-SEP-95
13-SEP-96

16-SEP-96

NAME AND ADDRESS OF APPLICANT

ATHENA Neurosciences
800F Gateway Blvd.,
South San Francisco, CA 94080

DRUG PRODUCT NAME

Proprietary:

ZANAFLEX™

Nonproprietary (USAN):

PIRIDALUD®, TERNELIN® - Sandoz, Ltd. ex - U.S.)

Code Name/Number:

Prizanidine Hydrochloride

Chem. Type/Ther. Class

AN 021A (Athena), DS 103-282 (Sandoz)

PHARMACOLOGICAL CATEGORY/INDICATION

Treatment of spasticity of spinal cord origin

DOSAGE FORM

Tablets

STRENGTHS

4 mg

ROUTE OF ADMINISTRATION

Oral

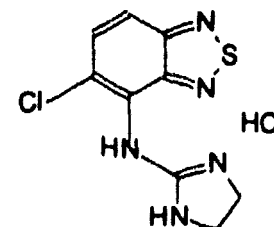
DISPENSED

XXX RX

— OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

5-Chloro-4-(2-imidazolylamino)-2,1,3-benzothiadiazole hydrochloride



C₉H₈ClN₃S · HCl

Mol. Wt. 290.2 (HCl salt), 253.74 (base)

CAS Registry #:

064461-82-1 (HCl salt), 51322-75-9 (base)

SUPPORTING DOCUMENTS: IND

(Type II) (both from _____ .D.S.)

CONSULTS: The CGMP Compliance Status of the manufacturing facilities was ACCEPTABLE as of 16-OCT-95. **FUR** was requested on 21-OCT-96 (copy attached). EA is complete & acceptable. The proposed trademark "ZANAFLEX" is acceptable by the CDER Labeling and Nomenclature Committee. The MV package is in preparation.

REMARKS/COMMENTS: Revised bottle labels for both the trade product and the professional samples are provided. The two modifications are: 1) a change in the font and color for the Zanaflex tradename (from plain all blue to stylized blue and gold), and 2) an increase in the tablet count (from 100 to 150 tablets/bottle). Shorter trays, which allow the bottle labels to be visible, will now be used for shrink-wrapping sets of six bottles. The trays will no longer carry labeling information with the exception of lot number and expiration date which will be printed on the tray. The trade bottle count will increase from 100 to 150 tablets/bottle, using the same commercial container/closure system (HDPE bottle with 33/400 Argus Loc closure and P/RVTLF liner) and packaging conditions (same equipment, SOPs, controls and manufacturing processes) as those described in the NDA. The first three lots of commercial product (150 tablets/bottle in this commercial container/closure system) have been placed on stability according to the stability protocol in the NDA. The stability data and the updated batch records will be submitted in the first annual report. In addition, the size of the trade bottles (same commercial container/closure system) has been increased from 60 cc to 75 cc. This change will also be described in the first annual report. An updated table of specifications and testing procedures that includes the previously missing test method numbers is attached (this information was received by facsimile on 31-OCT-96 in response to reviewer's request).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-397, as amended, APPROVABLE, subject to a satisfactory evaluation of the manufacturing facilities. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-397
HFD-120
HFD-120/MGuzewska
HF-120/KHiggins/CSO
HFD-120/SBlum
R/D Init by: SWB

AMB
11/22/96

M. Guzewska
M. Guzewska, Ph.D., Chemist

Filename: n20397.004

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-397 CHEM. REVIEW #3 REVIEW DATE 05-OCT-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	06-DEC-93	07-DEC-93	
AMENDMENT (BC)	20-JAN-95	23-JAN-95	
AMENDMENT (AZ)	08-SEP-95	11-SEP-95	13-SEP-95

NAME AND ADDRESS OF APPLICANT

ATHENA Neurosciences, Inc.
800F Gateway Blvd., South San Francisco, CA 94080

DRUG PRODUCT NAME

Proprietary:

ZANAFLEX™

Nonproprietary/USAN:

(SIRDALUD®, TERNELIN® - Sandoz, Ltd. ex - U.S.)

Code Name/Number:

Tizanidine Hydrochloride

Chem.Type/Ther.Class:

AN 021A (Athena), DS 103-282 (Sandoz)

PHARMACOLOGICAL CATEGORY / INDICATION

Treatment of spasticity of spinal cord origin

DOSAGE FORM

Tablets

STRENGTHS

4 mg

ROUTE OF ADMINISTRATION

Oral

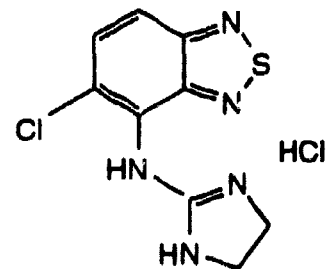
DISPENSED

~~XXX~~ RX ~~OTC~~

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

5-Chloro-4-(2-imidazolylamino)-2,1,3-benzothiazole hydrochloride

C₉H₈ClN₅S • HCl



Mol. Weight: 290.2 (HCl salt), 253.74 (base)

CAS Registry No. 064461-82-1 (HCl salt), 51322-75-9 (base)

SUPPORTING DOCUMENTS: see Review No. 1

CONSULTS: The EER (FUR) was sent on 05-OCT-95 (The CGMP Compliance Status of Sandoz' facility in Basle, Switzerland was UNACCEPTABLE as of 13-FEB-95). The EA review is pending. The MV package needs to be revised to include the new methodology for the testing of Zanaflex Tablets.

REMARKS / COMMENTS: The amendment provides for responses to the NOT APPROVABLE letter dated March 6, 1995. All CM&C deficiencies identified in the original NDA submission were addressed earlier, in the Amendment of 20-JAN-95. The responses were satisfactory (see Review #2). In the current submission, Athena refers to the August 29, 1995 tel. con with Dr. Blum and amends it's commitment regarding testing for degradation products. In the January 20, 1995 response to the deficiency #4c, Athena committed to quantification of ethylenediamine in three commercial lots of Zanaflex Tablets. The testing was to be discontinued, if the data supported Sandoz' results (NOTE: testing for ethylenediamine and p-TsOH is included in Sandoz' release testing of the NDS). Since compounds 504-78 (p-TsOH) and 503-78 (ethylenediamine) are drug substance by-products and cannot increase with time, Athena does not want to quantify them in the drug product or track them on stability.

The following dissolution methodology and specification for Zanaflex 4 mg Tablet are adopted

CONCLUSIONS & RECOMMENDATIONS: The CM&C Section of the NDA 20-397 is satisfactory, except for the methods validation and the evaluation of the CGMP Compliance status of facilities in Basel, Switzerland. Recommend NDA 20-397, as amended, APPROVABLE subject to satisfactory evaluation of Sandoz' facilities in Basel. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods. In addition, the testing of ZANAFLEX Tablets for impurities and degradation products should be performed as committed to in the 20-JAN-95 submission.

cc: Orig. NDA 20-397

HFD-120

HFD-120/MGuzowska *10.5.95*

HFD-120/DGrillley

HFD-120/SBlum

R/D Init by: SWB/ *AMB 10/12/95*

M. E. Guzowska

Maria E. Guzowska, Ph.D. Chemist

Filename: N020397.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-397 **CHEM. REVIEW #2** **REVIEW DATE** **31-JAN-95**

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**
ORIGINAL 06-DEC-93 07-DEC-93
AMENDMENT 20-JAN-95 23-JAN-95 24-JAN-95

NAME AND ADDRESS OF APPLICANT

ATHENA Neurosciences, Inc.
800F Gateway Blvd.
South San Francisco, CA 94080

DRUG PRODUCT NAME

Proprietary:

ZANAFLEX™

(SIRDALUD®, TERNELIN® - Sandoz, Ltd. ex - U.S.)

Nonproprietary/USAN:

Tizanidine Hydrochloride

Code Name/Number:

AN 021A (Athena), DS 103-282 (Sandoz)

Chem.Type/Ther.Class:

PHARMACOLOGICAL CATEGORY / INDICATION

Treatment of spasticity of spinal cord origin

DOSAGE FORM

Tablets

STRENGTHS

4 mg

ROUTE OF ADMINISTRATION

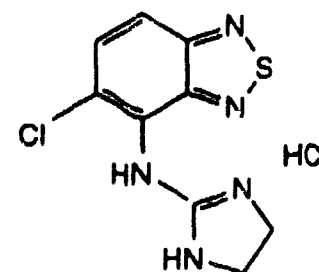
Oral

DISPENSED

~~XXX~~ RX OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

5-Chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole hydrochloride



C₉H₈ClN₅S • HCl

Mol. Weight: 290.2 (HCl salt), 253.74 (base)

CAS Registry No. 064461-82-1 (HCl salt), 51322-75-9 (base)

SUPPORTING DOCUMENTS: see Review No. 1

CONSULTS: The EER was sent on 15-AUG-94 (the inspection report for Sandoz, Basle is currently under review in the HFD-324 Division). The EA review is pending. The Methods Validation package needs to be revised to include the new methodology for the testing of Zanaflex Tablets.

REMARKS / COMMENTS: The amendment provides for responses to the CM&C deficiencies identified in the original NDA submission. Analytical methods for the drug product have been revised to include methods for the detection and quantitation of impurities in Zanaflex

Tablets. Validation results for the new methods are provided. A revised version of Specifications and Tests for the drug product, to include the new analytical methods, is given. The results of analytical testing for several batches of Zanaflex tablets are provided. DMF

It has been amended on 16-JAN-95 in response to the FDA comments and request letter dated 24-AUG-94.

CONCLUSIONS & RECOMMENDATIONS: Chemistry, manufacturing and controls information is satisfactory, except for the methods validation and the evaluation of the CGMP Compliance status of facilities in Basel, Switzerland. Recommend NDA 20-397, as amended, **APPROVABLE** subject to satisfactory evaluation of Sandoz facilities in Basel, Switzerland. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-397

HFD-120

HFD-120/MGuzewska/mg 1.31.95

HFD-120/KHiggins

HFD-120/SBlum

R/D Init by: SWB/

SWB 2/4/95

Maria E. Guzewska

Maria E. Guzewska, Ph.D. Chemist

Filename: N020397.002

AUG 22 1994

11

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

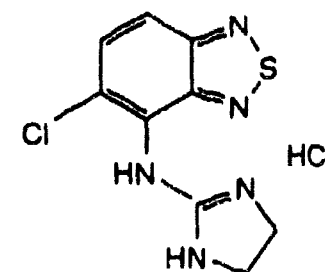
NDA 20-397	CHEM. REVIEW #1	REVIEW DATE	14-AUG-94
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	06-DEC-93	07-DEC-93	04-JAN-94

NAME AND ADDRESS OF APPLICANT ATHENA Neurosciences, Inc.
 800F Gateway Blvd.
 South San Francisco, CA 94080

DRUG PRODUCT NAME	ZANAFLEX™
Proprietary:	(SIRDALUD®, TERNELIN® - Sandoz, Ltd. ex - U.S.)
Nonproprietary/USAN:	Tizanidine Hydrochloride
Code Name/Number:	AN 021A (Athena), DS 103-282 (Sandoz)
Chem. Type/Ther. Class:	

PHARMACOLOGICAL CATEGORY / INDICATION	Treatment of spasticity of spinal cord origin
DOSAGE FORM	Tablets
STRENGTHS	4 mg
ROUTE OF ADMINISTRATION	Oral
DISPENSED	~~XXX~~ RX ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
 5-Chloro-4-(2-imidazolylamino)-2,1,3-benzothiadiazole hydrochloride



C₉H₈ClN₅S • HCl

Mol. Weight: 290.2 (HCl salt), 253.74 (base), [HCl salt/base = 1.144]
 CAS Registry No. 064461-82-1 (HCl salt), 51322-75-8 (base)

SUPPORTING DOCUMENTS: IND
 DMFs

CONSULTS: Establishment inspections will be requested on 15-AUG-94 (copy attached). The EA review is pending. The MV request will be prepared after deficiencies identified in analytical methodology for the drug product are corrected.

REMARKS / COMMENTS: The CM&C information on Tizanidine HCl drug substance is provided in DMFs. Comments and requests regarding the manufacturing and controls for the drug substance will be communicated directly to Sandoz. The information provided for the drug product is deficient for batch records, in-process sampling, reprocessing procedures, analytical methodology, information on stability batches and testing

CONCLUSIONS & RECOMMENDATIONS: Chemistry, Manufacturing and Controls information is NOT APPROVABLE now. The DRAFT DEFICIENCY LETTER is attached. Satisfactory correction of all deficiencies is required

cc: Orig. NDA 20-397

HFD-120

HFD-120/MGuzewska/mg 8.14.94

HFD-120/DGrilley

HFD-120/SBlum

HFD-100/CKumkumian

R/D Init by: SWB/

AMB 5/22/94

M. Guzewska

 Maria E. Guzewska, Ph.D. Chemist

Filename: N020397.000

NDA-020397

FIRM: ATHENA NEUROSCIENCES

7 OF 7

TRADE NAME: ZANAFLEX ORAL TABS. 4MG

GENERIC NAME: TIZANIDINE HCL

RETURN

MAR 05 1990

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-397

ZANAFLEX®

(tizanidine HCL)

Oral Tablets (4 mg)

**Division of Neuropharmacological Drug Products
HFD-120**

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DETERM
MAR 05 1996

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-397

ZANAFLEX®

(tizanidine HCL)

Oral Tablets (4 mg)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for ZANAFLEX®, Athena Neuroscience, Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Tizanidine HCL is a chemically synthesized drug which is administered as a 4 mg oral tablet in the treatment of spasticity of spinal cord origin and has been shown to be effective in reducing spasticity in patients with multiple sclerosis and spinal cord trauma. The drug substance (tizanidine) and drug product (ZANAFLEX® tablets) are manufactured at Sandoz, Basel, Switzerland. The bulk drug product is shipped to
for final filling and packaging. ZANAFLEX® is expected to used throughout the United States.

Drug substance that is introduced into the patient will be excreted up to 4.9% intact in urine and feces combined and distributed into wastewater treatment systems throughout the United States. Chemical and physical test results indicate that tizanidine will most likely be restricted to the aquatic environment and will not bioconcentrate. Tizanidine does not significantly biodegrade. Tizanidine rapidly photodegrades and may be an important mechanism of degradation.

As tizanidine may persist in the aquatic environment for some time, the most toxic effects to organisms in the environment were observed in *Scenedesmus subspicatus* (algae) having a No Observed Effect Concentration (NOEC) of 3 ppm and a E_0C_{50} (0-72 hr) of 6.9 ppm. The maximum expected environmental concentration is several orders of magnitude lower than the

reported toxicity results.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed treatment facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. For manufacture of the drug substance and drug product, the firm has provided a letter from the Swiss authorities that they are in compliance with the laws of Switzerland. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

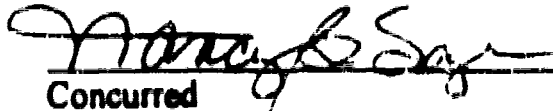
FEB 28 1996

DATE



Approved
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

3/1/96
DATE



Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

ENVIRONMENTAL ASSESSMENT

FOR

ZANAFLEX[®] (tizanidine HCl)

September 1995

Volume 1 of 2

INTRODUCTION

Athena Neurosciences, Inc. (Athena) is the sponsor of NDA # 20-397 for Zanaflex® (tizanidine HCl) 4 mg oral tablets indicated for the treatment of spasticity of spinal origin. Zanaflex has been shown to be effective in reducing spasticity in patients with multiple sclerosis and spinal cord trauma. It is particularly useful for reduction of pathologic muscle tone, painful spasms and clonus associated with spinal cord lesions without reducing muscle strength. Tizanidine hydrochloride (tizanidine) has been approved for use and is marketed in Europe under the trade name Sirdalud® and in Japan under the trade name Ternelin®. The maximum recommended daily dose of tizanidine is 36 mg.

Zanaflex tablets are manufactured for Athena by Sandoz Pharma Ltd. (Sandoz), Basel, Switzerland in compliance with applicable occupational health and environmental laws and regulations. Final filling and packaging operations for Zanaflex are performed in the in compliance with applicable environmental and public health statutes and regulations. These manufacturing operations are not anticipated to adversely affect the quality of the human environment or to alter the sponsor's ability to comply with current host country or U.S. federal, state or local emissions standards.

The chemical entity that is the focus of this EA is the active ingredient of Zanaflex, tizanidine hydrochloride. The additives of Zanaflex are common materials encountered in everyday life that will not adversely effect the environment (refer to Section 5.3). Unless otherwise stated, tizanidine hydrochloride will be referred to as tizanidine. Other nomenclature for tizanidine are as follows: tizanidine HCl, tizanidin hydrochloride.

This Environmental Assessment has been prepared according to 21 CFR 25.31(a) as required by 21 CFR 314.50(d)(iii) and 21 CFR 25.22(a)(14).

The data in this Environmental Assessment indicate that the proposed action is not expected to significantly affect the quality of the human environment according to the criteria under 40 CFR 1508.14 and 1508.27 nor is the proposed action expected to produce significant environmental effects.

The information provided in Appendices C, D, E and F are considered confidential and are protected from public disclosure by 18 U.S.C. 1905 and 21 U.S.C. 31(j).

1. DATE

September 7, 1995

2. NAME

Athena Neurosciences, Inc. (Athena)

3. ADDRESS

800 Gateway Boulevard
South San Francisco, California 94080

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Requested Approval

The proposed action is the approval of Zanaflex® (tizanidine HCl) 4 mg oral tablets. The active ingredient of Zanaflex is tizanidine hydrochloride.

This Environmental Assessment (EA) is part of the New Drug Application for the drug product named above. The format is arranged according to 21 CFR 25.31(a).

4.2 Need for the Action

Zanaflex is indicated for treatment of spasticity of spinal cord origin and has been shown to be effective in reducing spasticity in patients with multiple sclerosis and spinal cord trauma. Zanaflex is particularly useful for reduction of pathologic muscle tone, painful spasms and clonus associated with spinal cord lesions without reducing muscle strength.

Tizanidine drug product has been approved for use and is marketed in Europe under the trade name Sirdalud and in Japan under the trade name Temelin. The maximum recommended daily dose of tizanidine is 36 mg.

4.3 Locations of Manufacture

The drug substance (tizanidine) and drug product (Zanaflex tablets) are manufactured at Sandoz, Basel, Switzerland. The bulk drug product is shipped to

4.4 Locations of Use and Disposal

Zanaflex is expected to be used throughout the United States. Rejected, returned or expired tablets are currently delivered to
and disposed by the licensed treatment facility
in compliance with State of
standards.

No protected or sensitive environments, endangered or exotic species, or historic archeological areas are considered to be impacted by the manufacture, use or disposal of Zanaflex.

4.5 Environmental Settings of Facilities

The facilities of Sandoz are located in the northwestern part of the city of Basel, Switzerland along the Rhine River at the border with France.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

The composition of Zanaflex is provided in Appendix C (confidential). The inactive ingredients are common materials encountered in everyday life and will not adversely effect the environment. The active ingredient of Zanaflex, tizanidine, is described below. The Material Safety Data Sheet (MSDS) for tizanidine is provided on page 8.

5.1 Nomenclature

Chemical name: 5-chloro-4,2-(imidazolin-2-ylamino)-2,1,3,-benzothiazole hydrochloride

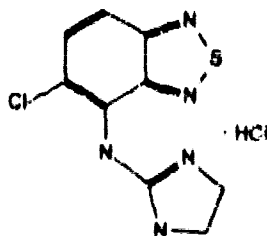
Established names: tizanidine hydrochloride (USAN)
tizanidine (INN rec, BAN)

Code names: AN021, DS 103-282, tizanidine HCl

CAS registry number: 64461-82-1

Molecular weight: 290.2 (hydrochloride)
253.7 (free base)

Structural formula:



5.2 Physical Description

In appearance, tizanidine is a white to off-white crystalline powder that is odorless or has a weak characteristic odor. The chemical and physical properties of tizanidine are listed in Table 1.

Tizanidine was discovered and developed by Sandoz. The manufacture of the drug substance and the drug product is proprietary to Sandoz.

TABLE 1: CHEMICAL AND PHYSICAL CHARACTERISTICS OF TIZANIDINE

Solubility: (25°C ± 0.03°C)	water	5.5%	IPA	0.1%
	acetonitrile	0.03%	benzene	< 0.01%
	acetone	< 0.01%	chloroform	0.01%
	ethanol	1.0%	ethyl acetate	< 0.01%
Dissolution rate: (37 ± 2°C)	gastric fluid	t _{50%} 1'24"	t _{90%} 4'44"	solubility > 2%
	intestinal fluid	1'47"	6'36"	0.05%
Melting point:	288 - 290°C			
Stereochemistry:	No asymmetric carbon			
Particle size:	< 90µ (air jet-sieve method; 99% of particles)			
Hygroscopicity:	Does not absorb water after 2 weeks at 92% relative humidity or after 5 years at 30°C/75% RH.			
Crystal properties:	Polymorphism has not been observed			
pK _{a1} value:	7.46 ± 0.05 (pK _{a2} > 10)			

Chemical Characteristics:

Tizanidine can be titrated with HClO₄ in a mixture of acetic acid/acetic anhydride in a ratio of 1:3.

Tizanidine forms ion pairs with picric acid, and is extractable with organic solvents.

As a hydrochloride, tizanidine is colorless. As a free base it has a yellow color.

Tizanidine hydrochloride reacts with the following reagents on thin layer chromatography plates:

Reagent	Color	Detection Limit (µg)
Dragendorff/H ₂ O ₂ (3%)	brown	0.1
Folin Ciocalteu/NH ₃	blue	0.1

5.3 Additives

The following is a list of additives contained in Zanaflex. These inactive ingredients are common materials encountered in everyday life and will not adversely effect the environment. The composition of Zanaflex is provided in Appendix C (confidential).

5.4 Impurities

Five possible impurities (three degradation products and two synthetic manufacturing impurities) have been identified and are listed below. No single impurity is present in the finished product at a concentration of more than 0.3%. These impurities are not discussed individually in the EA because they are either not expected to be harmful to the environment at the anticipated environmental concentrations or their structural similarity to tizanidine will direct them to a similar environmental fate.

Degradation Products:

Manufacturing Impurities:

Safety Data Sheet

 **SANDOZ**

Corresponding to EC Directive 81/185/EEC

Page: 1 / 6

XXXXXXXXXX

Date of issue: 03.12.1992
Replaces version of: 23.11.1992

Tradename: TIZANIDINE HYDROCHLORIDE

Prod.nr: 3142023

1. Identification of the product and of the company

1.1 Product name:
TIZANIDINE HYDROCHLORIDE

1.2 Company name:
SANDOZ PHARMA LTD
CH 4002 BASEL
PHONE : CH-061 324 11 11

1.3 Emergency phone number:
CH-061 324 33 33

2. Composition / information on ingredients

3. Hazards identification

Harmful by inhalation, in contact with skin and if swallowed.

4. First aid measures

- 4.1 After contact with the eyes:
Immediately rinse eyes with running water and seek medical advice.
- 4.2 After contact with the skin:
After contact with skin, wash immediately with plenty of water and soap.
- 4.3 After inhalation:
Take patient immediately to factory medical centre or call for an ambulance.
- 4.4 After ingestion or accident:
If swallowed, wash mouth with plenty of water. Take patient to physician/factory medical centre or call for an ambulance.
Change contaminated clothes immediately. Rinse, and wash as usual.
- 4.5 Symptoms:
- 4.6 Notes to physician:

5. Fire fighting measures

5.1 Extinguishing media:
Suitable:
all

Not to be used:
no restrictions

Safety Data Sheet

 **SANDOZ**

Corresponding to EC Directive 91/155/EEC

Page: 2 / 4

XXXXXXXXXX

Date of issue: 09.12.1992
Replaces version of: 23.11.1992

Tradename: TIZANIDINE HYDROCHLORIDE

Prod.nr: 3142023

5.2 Special advice in case of fire:
Cool container and metallic parts with a water spray jet

Hazardous combustion gases:
carbon oxides
hydrogen chloride
sulfur oxides
nitrogen oxides

6. Accidental release measures

6.1 After spillage, leakage, gas leakage:
Large amounts:
Must not be released into sewers, drains or walls.
Wear heavy protective equipment.
Take up as such.

Small amounts:
Take up by mechanical means and dispose.

6.2 Cleaning of equipment:
Wash with plenty of water.

7. Handling and storage

7.1 Handling:
Measures to prevent fire and explosion:
Keep away from sources of ignition - No smoking.
Avoid formation of dust.
Observe the usual precautionary measures required for chemicals with dust explosive properties (Observe national regulations).

7.2 Storage:
Technical protective measures:
Maximum storage temperature: ≤ 50 °C

Keep container tightly closed.
Keep dry.
Ensure efficient exhaust ventilation when using this product

Materials to avoid:
conc. bases

8. Exposure controls and personal protection

8.1 Exposure controls:

8.2 Industrial hygiene:

8.3 Personal protective equipments:
Respiratory protection: mask, dust filter
Eye protection: safety glasses
Hand protection: yes
Others: protective suit

Safety Data Sheet



Corresponding to EC Directive 91/155/EEC

Page: 3 / 4

XXXXXXXXXX

Date of issue: 03.12.1992
Replaces version of: 23.11.1992

Trade name: TIZANIDINE HYDROCHLORIDE

Prod.nr: 3142023

9. Physical and chemical properties

9.1 Form: powder

9.2 Colour: white yellowish

9.3 Odour: none

9.4 Change in physical state:

Melting point (°C): 288.0 - 290.0
Boiling point: not applicable

9.5 Flash point: not applicable

9.6 Ignition temperature: No reaction up to 360 C
Method: Sandoz Ignition Test of Deposited Dust

9.7 Explosion limits:

9.8 Density: not applicable
Bulk density (kg/m³): 300

9.9 Vapour pressure: not applicable

9.10 Viscosity: not applicable

9.11 pH value: not applicable

9.12 Solubility in:

water	:	55	g/l at	25°C
octanol tech.	:	0.3	g/l at	20°C
acetone	:	< 0.1	g/l at	25°C
methanol	:	CA 51	g/l at	25°C

9.13 Partition coefficient n-octanol/water:

10. Stability and reactivity

Thermal decomposition:

Stable up to: 240 °C (Isoperibol, Air open cup)

Reaction autocatalytic

Dangerous reactions:

Dust explosions are possible

11. Toxicological information

LD50 acute oral: 602 - 889 mg/kg (rat)
LD50 acute oral: 235 mg/kg (mouse)

Safety Data Sheet

 **SANDOZ**

Corresponding to EC Directive 91/155/EEC

Page: 6 / 6

Revisions:

Date of issue: 03.12.1992
Replaces version of: 23.11.1992

Trade name: TIZANIDINE HYDROCHLORIDE

Prod.nr: 3142023

12. Ecological information

Fish toxicity:
LC50 (96 h): > 100 µg/l
(rainbow trout (*salmo gairdneri*, *oncorhynchus mykiss*))
Method: OECD 203 * 1984 acute tox.

Daphnia toxicity:
EC50 (48 h): 75.6 - 139.4 µg/l
(daphnia magna (water flea))
Method: OECD 202 * 1984 acute tox.

Bacterial toxicity:
Respiration inhibition:
EC50 (3 h): > 100 µg/l
(activated sludge)
Method: OECD 209 * 1984 activated sludge. Respir. Inhib.

13. Disposal considerations

Local regulations should be adhered to.
Incineration in controlled furnace.

14. Transport information

Regulations	Class	UN-Nr.	PG.
RID/ADR:	Not classified		
ICAO/IATA-DGR:	Not classified		
GGVSee/IMDG-Code:	Not classified		

15. Regulatory information

Labelling according to EC directives:

Xn	Harmful
R20/21/22	Harmful by inhalation, in contact with skin and if swallowed.
S22	Do not breathe dust.
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection.

16. Other information

Main use: PHARMA ACTIVE SUBSTANCE

Product should be stored, handled and used in accordance with good industrial hygiene practices and in conformity with legal regulations. The information contained herein is based on the present state of our knowledge and is intended to describe our products from the point of view of safety requirements. It should therefore not be construed as guaranteeing specific properties.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Substances Emitted, Controls Exercised and Compliance with Emissions Requirements

The drug substance and drug product are manufactured at Sandoz using conventional biochemical and pharmaceutical technologies. Bulk Zanaflex tablets are packaged into fiber drums lined with low density polyethylene bags and transported from Sandoz to the contract packaging facility,

Upon receipt, the Zanaflex tablets are packaged into high density polyethylene bottles.

The manufacture of Zanaflex is not expected to alter the sponsor's ability or the ability of its contractors to comply with emission standards at sites of production.

6.1.1 Synthesis of the Drug Substance and Drug Product

The manufacture of the drug substance and drug product is proprietary to Sandoz, therefore, Athena does not have access to information regarding substances emitted during the manufacturing process. However, the complete manufacturing process has been reviewed by the Canton Basel-Stadt government for compliance with pertinent safety, environmental protection and working condition regulations and a certificate of compliance (*Environmental Protection Certificate*) has been issued. A copy of the certificate is provided on page 17. The Certificate applies to the following:

- Control of Potential Chemical Hazards
- Process Waste Treatment
- Air Emissions
- Waste Water Emissions
- Hazardous Chemical Waste
- Occupational Health and Employee Safety
- Solid Waste

In addition, an Outline for Adherence to Laws Relating to Air, Water and Wastes from Sandoz is provided on page 18. This outline states Sandoz' commitment to abide by all environmental protection laws including the Preservation of Clean Air Law and the Ordinance for Strengthening of Emission Limits. The outline generally describes treatment, control and disposal of air emissions, waste water and solid hazardous and nonhazardous waste. All procedures are in compliance with current environmental protection laws and regulations.

The tizanidine drug products marketed in Europe and Japan (Sirdalud and Temelin, respectively) are currently manufactured at the Sandoz facility in Basel. Therefore,

the production of Zanaflex for Athena will not significantly impact the overall production volume of tizanidine drug substance or drug product, nor will it adversely affect Sandoz' ability to comply with current emissions standards.

6.1.2 Filling and Packaging of the Drug Product

Final filling and packaging operations for Zanaflex will be performed in the United States in compliance with applicable environmental and public health statutes and regulations (EPA ID #PA0987389376). A flow chart showing the flow of materials used in the packaging operations for Zanaflex is provided in Figure 1 on the following page.

A transcript of the EA prepared by [redacted] for their packaging operations is included on page 24. [redacted] EA contains statements declaring that [redacted] is, and will continue to be, in compliance with all local, state and federal environmental laws, and that approval of the proposed action will not adversely affect their ability to comply with current emissions standards. The EA is signed by a responsible [redacted] official. Due to poor copy quality, the original copy of the [redacted] is barely legible. Therefore, a transcript has been provided for ease of review, and the original copy is provided in Appendix B.

It is expected that during the final fill and finishing operations [redacted] minimal materials including no hazardous materials are expected to enter the environment. It is anticipated that at maximum production, typical volumes of nonhazardous packaging and administrative wastes will be generated and disposed as general trash in a solid waste landfill. These manufacturing operations are not anticipated to adversely affect the quality of the human environment or to alter the ability of [redacted] to comply with federal, state or local emissions standards.

6.2 Estimates of Quantities and Concentration of Substances Expected to Enter the Environment through Use and Disposal of the Product

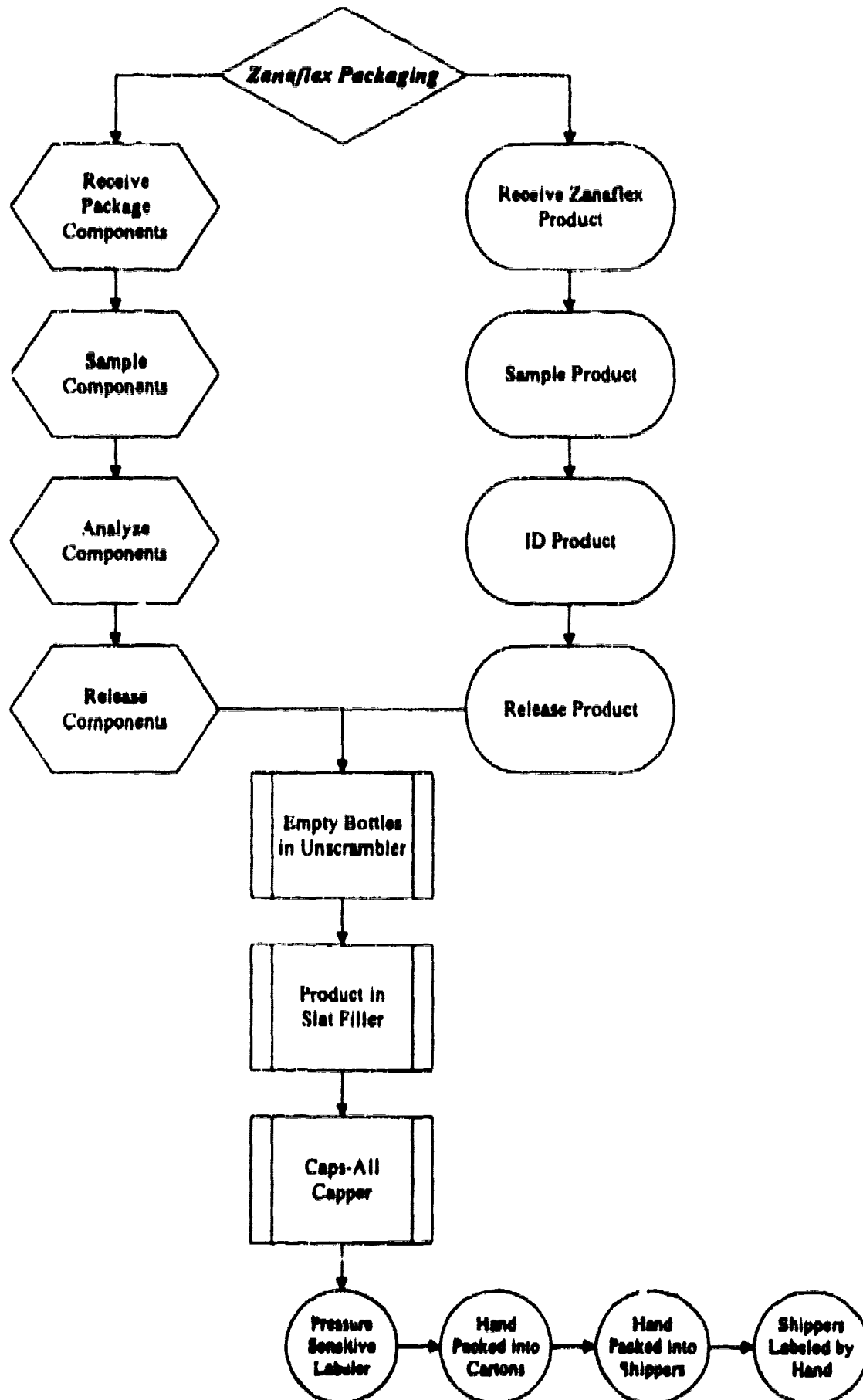
The two routes by which the drug product may potentially enter the environment, disposal of the product and patient use, are discussed below.

6.2.1 Disposal of the Product

Rejected, returned or expired tablets are currently delivered to [redacted] and disposed by the licensed treatment facility

[redacted] compliance with [redacted] standards. Certificates of destruction will be issued by [redacted]

FIGURE 1: ZANAFLEX PACKAGING MATERIALS AND OPERATIONS FLOW CHART



Empty tizanidine containers will be disposed at institutions and clinics in accordance with applicable federal, state and local standards. For home use, empty containers will be disposed as household trash throughout the U.S. This waste will constitute an extremely small and insignificant addition to solid waste streams typical of hospitals, medical centers and households. A Material Safety Data Sheet (MSDS) outlining appropriate safety and disposal practices will be available to administering personnel. An MSDS for tizanidine is included on page 8.

6.2.2 Use of the Product

The major source of entry of tizanidine into the environment will be through actual patient use. The concentration and quantities of tizanidine that may enter the environment through patient use are related to dose, treatment duration, location of use, metabolism and excretion properties of tizanidine and the treatment of excreted materials.¹ Consumed product will eventually enter the aquatic environment following treatment by local waste water treatment plants (WWTPs) throughout the country. It has been determined that up to 4.9% of consumed tizanidine is excreted intact in urine and feces combined.^{2,3} In addition, metabolites of tizanidine have been identified in human urine, including two metabolites (4 and 10) that are present at quantities greater than 10% of the total drug and metabolites excreted (refer to Table 2 on the following page). Refer to Figure 2 in Section 7 for the probable metabolic pathway of tizanidine.

6.2.2.1 Calculation of Maximum Expected Emitted Concentrations

The method used for calculating the concentration of drug that would be released to WWTPs, given in *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA* (PMA, 1991), is shown below. In this method, the annual production of the drug is multiplied by 8.9×10^{-9} to obtain the Maximum Expected Emitted Concentration (MEEC) in ppm (or mg/L).

MEEC (ppm) = (A)(B)(C)(D)(E)(F), where:

A = pounds of product per year production

B = year/365 days

C = day person/150 gallons

D = 1/246 million persons (population of U.S.)

E = gallons/8.34 pounds

F = one million

(B)(C)(D)(E)(F) = 8.9×10^{-9}

During the first 5 production years, the maximum amount of tizanidine that will be manufactured is estimated to be less than _____ per year. This calculates to a worst-case MEEC for tizanidine of _____ ppm. This calculation does not take into account metabolic degradation (assumes 100% would enter the WWTP intact), and is a very conservative estimate of the maximum concentration of tizanidine that might be introduced to WWTPs through actual use of the product. More precise estimates of the manufacturing volumes for the first 5 production years are provided in Appendix D (confidential). The effect of biodegradation on the concentration and dissipation of released product are discussed in Section 7.

Most of the chemicals introduced into the environment through human elimination will be metabolites and not the parent compound, tizanidine. The MEECs for each metabolite identified in human urine samples are listed in Table 2. Structures for these metabolites are provided in Figure 2 in Section 7. Two of the metabolites, 4 and 10, are considered major metabolites because they have been measured at quantities greater than 10% of the total drug and metabolites excreted. The fate and effects of these major metabolites are discussed in Sections 7 and 8.

TABLE 2: METABOLITE CONCENTRATIONS IN HUMAN URINE AND MEECS

Tizanidine Metabolite	% Excreted ¹	MEEC ²
3	< 6	2×10^{-7}
4	< 12	4×10^{-7}
7	< 7	2×10^{-7}
9	< 5	2×10^{-7}
10	< 12	4×10^{-7}

¹ Calculated from % radiolabeled metabolite excreted in urine after oral dosing with ¹⁴C-tizanidine.

² MEEC calculations are based on the maximum annual production volume of 400 lbs tizanidine.

Values calculated to reflect metabolite concentrations corrected for molecular weight of hydrochloride.



ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company SANDOZ PHARMA LTD operates facilities for chemical and pharmaceutical manufacturing at the following address:

SANDOZ PHARMA LTD
Lichtstrasse 35
CH-4002 Basel
Switzerland

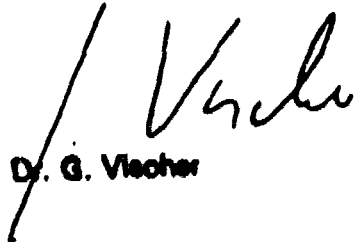
2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permits are laid down the purpose for which buildings and plants may be used and the legal conditions with which the Company must comply.
3. The above-described permits also cover the preparation of the galenical dosage form

Sirdalud tablets (Tizanidin hydrochloride)

in different strength.
4. All buildings and plants of the company SANDOZ PHARMA LTD must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment and working conditions.
5. The relevant departments of the Cantonal Authorities perform periodic inspections.
6. It can here be stated that the undersigned Governmental Office has proved the correct building and producing permits are given.

BAUDEPARTEMENT BASEL-STADT
Der Departementssekretär

Basel, den 9. September 1993


D. G. Vöcher

SANDOZ PHARMA AG OUTLINE FOR ADHERENCE TO LAWS RELATING TO AIR,
WATER AND WASTES

by Dr. Z. Bidlo

PRESERVATION OF CLEAN AIR AT SANDOZ PHARMA AG

1. Preservation of Clean Air Law in Switzerland

The Preservation of Clean Air Law is based on the Environmental Protection Act (Umweltschutzgesetz, USG) of Oct. 7, 1983. Supported by this law, the following regulations subsequently became effective. In addition to the exhaust gas regulation for automobiles, the most important decree, the Preservation of Clean Air Ordinance (Luftreinhalteverordnung, LRV) for stationary installations was introduced on Dec. 16, 1985.

The LRV consists of a two-step outline with generally precautionary 'immission' limits regulated in Appendices 1-3 and measures which must be taken when the 'immission'* limits according to Appendix 7 are exceeded.

The general precautionary 'immission' limits which conform to the state-of-the art and economic condition of the plant, must always and everywhere be realized. If the 'immission' limits in Appendix 7 are exceeded in one area, then the responsible officials according to Articles 31-34 must clarify the source responsible. The officials draw up an action plan. The measures taken can be realized in the area of the stationary installation in a decreed or prescribed manner and as a rule contain heightened emission limits.

In the Basel area, this was achieved via the regulatory method. On Aug. 14, 1990, the Ordinance for Strengthening of Emission Limits in stationary installations, abbreviated the Cantonal Measures Ordinance, became effective.

2. Performance of the Preservation of Clean Air Law in the SANDOZ Basel Site

The waste air stream in the Basel site is dealt with on the basis of the multiplicity of various regulations. In the following, the waste air stream is arranged into classes, and both the associated purification method and the relevant regulation to carry it out are described:

* 'Immission' is a German word defined as any emission which results in environmental changes damaging to humans, animals and plants.

<u>Class</u>	<u>Method of Purification</u>	<u>Regulation</u>
a) Waste air from chemical processes; waste air with inorganic gases	Wet scrubber	LRV 86
b) Waste air from chemical processes; waste air with organic nonhalogenated material	Thermal oxidation	LRV 86 Cantonal Measures Ordinance
c) Waste air from chemical processes; waste air with halogenated material	Oil Scrubber	LRV 86 Cantonal Measures Ordinance
Strengthening for individual materials		LRV 92
d) Exhaust gases from heating plants	DENOX (apparatus to reduce NOX emissions)	Cantonal Measures Ordinance
e) Exhaust gases from incineration plants	Wet scrubber DENOX	LRV 86 & 92 Cantonal Measures Ordinance

The methods of purification for the waste air streams in Classes a-c) are in practice or will shortly be in operation. For exhaust gases in Classes d) and e), the purification methods will be placed in operation in the coming years. Here we must still make a great effort, especially in the area of DENOX installations.

3. Waste Gas Register

According to LRV Article 12, each plant manager is obligated to provide authorities with information on:

- a) the type and amount of emissions;
- b) the site, height and timely course of the exhausts;
- c) any other information necessary for the assessment of the emissions.

In the SANDOZ Basel site this will be achieved with a data bank-based Waste Gas Register. This Register contains the master files of the waste gas installation and the measurement results of the air hygiene laboratory. The data will be kept up to date and once a year is forwarded to the authorities.

WASTE WATER DISPOSAL AT SANDOZ PHARMA AG

1. SANDOZ Structure

On Jan. 1, 1990, SANDOZ AG was converted into a Holding Company. Under the six new divisional companies, SANDOZ PHARMA AG was founded in Basel. To date, several dyestuff production units also remain there.

2. Swiss Legislation

Supported by the Federal Water Protection Law (1971), the Ordinance for Waste Water Discharge was issued (1975). This Ordinance defined the aimed-for quality of receiving waters (e.g., rivers, lakes), and sets quality criteria under which the waste water from any source could be discharged into the receiving waters or sewer. All waters which are discharged from built-over areas are designated as waste water.

3. Waste Water Treatment at SANDOZ PHARMA AG

The Basel site has its own separate sewers for different types of waters. The nonpolluted waters, designated WAR (rain and cooling waters) are conducted over a retention basin for incidents and emergencies where their quality is continually monitored, and then, with the approval of responsible authorities, flow directly into the Rhine.

The polluted water, designated WAI, is conducted to a waste water treatment plant. This treatment plant consists of a neutralization (lime) with a primary settling tank, waste water storage tanks with a sufficient buffer volume, and an activated sludge biology with a secondary settling tank. The neutralization and surplus sludges are burned in a fluidized bed furnace, and the ashes deposited in a controlled landfill according to legislation by authorities.

All process waste waters are analyzed for the most important official water quality criteria, and in addition, for ecologically relevant organic substances. These pollution criteria are given as concentration limits (no loads) and these limits cannot be reached by dilution. The Safety and Environmental Protection Department (OSW) accordingly then decides whether the process waste water can be discharged directly into the waste water treatment plant or whether it must be treated at the source.

4. Fulfillment of Requirements in the Ordinance for Waste Water Discharge

SANDOZ PHARMA AG fulfills practically all 52 requirements noted in the Ordinance. Only the total undissolved material and the volatile phenols exceed the Ordinance limits. The necessary steps for improving both performance parameters have been defined with the authorities.

5. Additional Actions Planned

Since it was known that future Swiss legislation would be strengthened, three years ago SANDOZ PHARMA AG undertook the initiative to meet the expected new requirements. At the end of 1992, it will be decided whether to begin an intensified program for the treatment of process waste water at the source, or whether a further treatment step would be built in the waste water treatment plant (activated charcoal).

WASTE DISPOSAL SANDOZ PHARMA AG

Statutory Basis

Based on the Environmental Protection Act of Oct. 7, 1983, disposal of wastes is to be conducted according to the following laws, ordinances and internal guidelines.

- Ordinance on Commerce with Hazardous Wastes (VVS); Verordnung ueber den Yerkehr mit Sonderabfaellen.
- Technical Ordinance on Wastes (TVA); Technische Verordnung ueber Abfalle.
- SANDOZ internal guidelines for environmental protection.

The Ordinance on Commerce with Hazardous Wastes (VVS) regulates commerce with special wastes. The VVS contains a waste list. Products on this list are considered hazardous wastes and must be accompanied by the appropriate documents.

The Technical Ordinance on Wastes (TVA) defines the conditions of deposition of the waste. It contains acceptance criteria for the combustion plant and describes the three allowed deposition types:

- Inert material deposits (lowest eluate value);
- Residual material deposits (ca. 10% higher eluate values);

The content of organic material is limited in both.

- Reactor deposits (for domestic wastes where combustion is unavailable).

The internal SANDOZ guidelines regulate the management of waste handling at the site.

Preparation for Disposal at the Basel Site

Before beginning production, the expected wastes are reported to the central authority OSW. There they will be examined for disposability or combustibility. If the possibility for disposal exists, then the wastes are recorded in the Waste Register and a permit is issued to the plant manager to produce the wastes. Under this permit number, the producer can hand over this waste to the internal transport group in the future. For wastes which do not correspond to the acceptance criteria of a disposer, or an external waste management firm, a revision in the workup or a process modification can be requested.

Management in the Plant Site

The plants place their internally accepted wastes in prepared standard containers and signify their readiness to a central transport organization. These transport groups collect the wastes and prepare the necessary papers for an external disposal or combustion. The data is recorded at the same time on the basis of the waste permit number under the VVS code, and reported quarterly to authorities of the Canton of origin and the Federal government. After disposal, a copy of the accompanying document is returned to the producer. This printed form confirms that the waste has been disposed of or combusted.

4 Pages

Purged

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Introduction

The environmental fate of Zanaflex can be predicted by the physical and chemical properties and environmental fate of its active ingredient, tizanidine. In addition to tizanidine, major metabolites (4 and 10) may be introduced into the environment. The structures of these metabolites are similar to their parent compound, tizanidine, in that the core benzothiadiazole structure is present and, therefore, predictions about the environmental fate of Zanaflex may be based solely on that of tizanidine. These predictions will likely be conservative for the reasons discussed below.

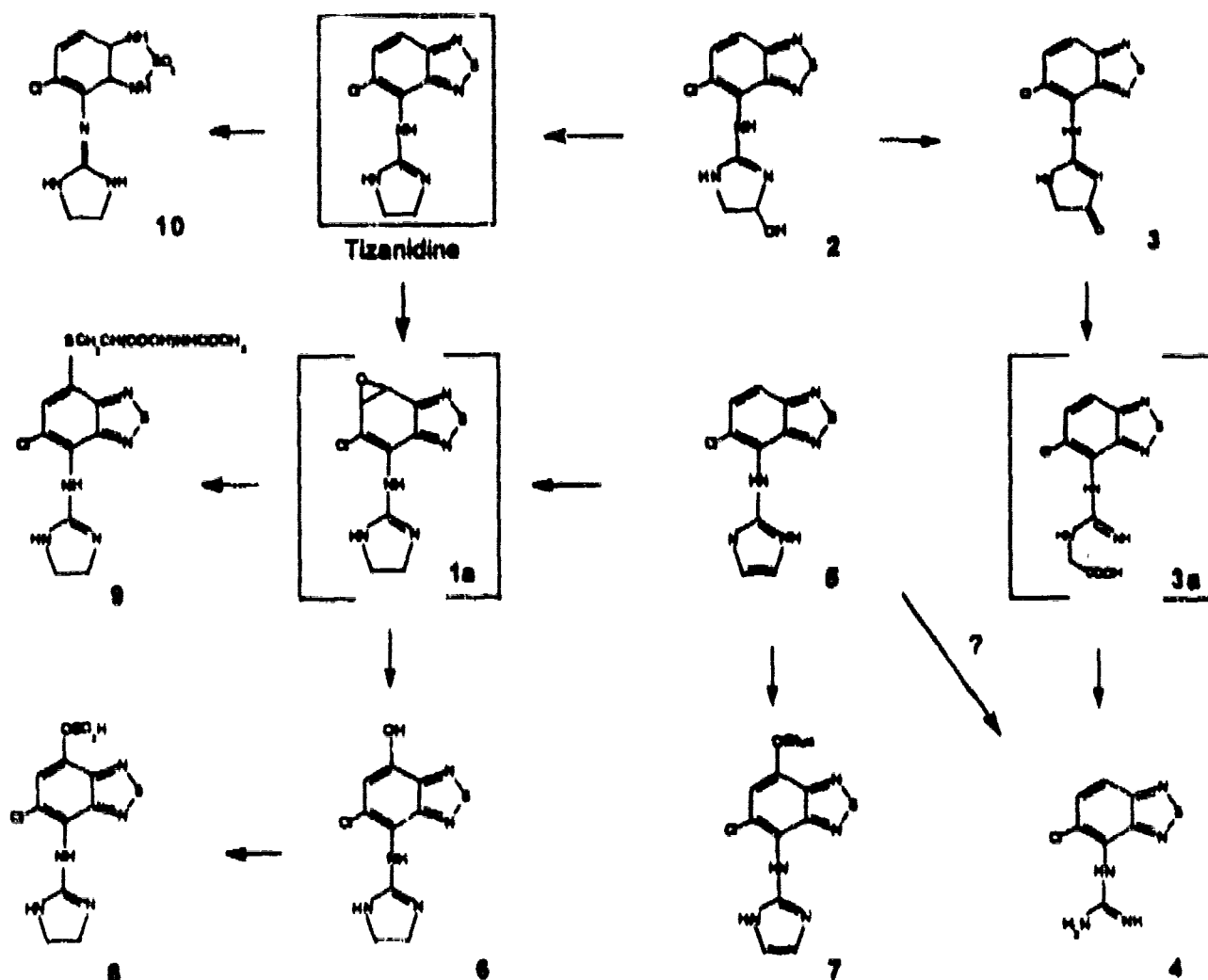
7.1 Action and Metabolism of Tizanidine

Tizanidine is a centrally acting muscle relaxant with a chemical structure different from other muscle relaxants. Tizanidine acts as an α_2 -adrenergic agonist by a mechanism which is similar to that of the well known drug, clonidine.

Orally administered tizanidine is well absorbed, extensively metabolized and rapidly excreted.^{2,3} In humans, approximately 60% of a single dose is excreted within 24 hours. Urine is the major route of elimination; cumulative excretion of radioactivity for 5 days after a single dose was reported as 53 - 58% in urine and 19-23% in feces. Tizanidine is primarily metabolized in the liver with extensive first pass metabolism. Little tizanidine (less than 4.9% of total drug and metabolites) is excreted unchanged.

Seven metabolites of ¹⁴C-tizanidine have been identified in human samples (Table 2). After isolation, the structures of these metabolites were established either by comparison to synthetic reference compounds or by spectroscopic analysis (¹H-NMR and mass spectroscopy). Probable metabolic pathways of tizanidine are shown in Figure 2.

FIGURE 2: PROBABLE METABOLIC PATHWAYS OF TIZANIDINE^{2,3}



The amount of each urinary metabolite is shown in Table 2. Two of the metabolites (metabolites 4 and 10) are excreted at levels >10% of the total radioactivity recovered. Metabolite 4 is a guanidine and metabolite 10 is a sulfone. Based on structure analysis and reversed phase HPLC elution order, both metabolites are significantly more polar than tizanidine.

The environmental fate and effects of the metabolites were not evaluated directly but are based on tests with tizanidine. This conservative approach will predict the worst-case for environmental contamination and hazard. Both metabolites are more polar and expected to be less persistent in the environment than tizanidine. The metabolites are likely to undergo further metabolism and degradation in the environment. For instance, oxidation and hydrolysis of the imidazole ring of

metabolite 10 would lead to a guanidine, oxidation of the benzothiadiazole ring of metabolite 4 would produce a sulfone, and oxidation of the aromatic moiety in either metabolite 4 or 10 could occur, as in the formation of metabolite 6. Further degradation of metabolites could occur by abiotic processes, such as indirect photodegradation as noted for tizanidine. All of these changes would lead to compounds that are more polar, likely to be less toxic and hence even less of an environmental hazard than tizanidine.

The environmental fate of tizanidine can be predicted by estimating the distribution between air, water and land compartments and the potential for motility, accumulation and depletion. The results of environmental fate and effects testing of tizanidine are summarized below and in Appendix A, Tables 4 and 5.

7.2 Distribution Between Air, Water and Terrestrial Compartments

7.2.1 Air

The physical and chemical properties of tizanidine are described in Table 1. The vapor pressure of tizanidine is estimated to be less than 10^{-6} torr based on the high melting point. The low vapor pressure and high water solubility of tizanidine indicate that volatility will be minimal and distribution of tizanidine into the atmospheric compartment can be assumed to be negligible.

7.2.2 Water

Tizanidine and its metabolites will be introduced into the aqueous environment via patient use and excretion to WWTPs. Distribution to the solid phase of the WWTP is expected to be minimal because the potential to sorb is low. This is because the calculated soil adsorption coefficient, K_{oc} , (based on the octanol/water partition coefficient, K_{ow}) is low (≤ 100). The maximum concentration of tizanidine and metabolites that would result from the proposed action is expected to be 4×10^{-6} ppm (Section 6.2.2.1). Release from WWTP in a worst-case scenario, i.e., no abatement, would consider dilution using a typical dilution factor of 10^{-3} for WWTP effluent into rivers. Prediction of the worst-case levels in surface water that receive WWTP effluent would be 4×10^{-9} ppm. Tizanidine and its metabolites would be affected by numerous environmental processes during the WWTP residence, some of which would virtually eliminate tizanidine from the effluent before release from the WWTP. These environmental processes and important properties of tizanidine that have an impact on the fate of Zanaflex are individually discussed in the following sections.

7.2.2.1 Photolysis

The photodegradation potential of tizanidine was evaluated in laboratory studies based on FDA Technical Assistant Document (TAD) 3.10 (Report #42322). In these studies, a xenon arc lamp was used as an artificial light source, with light intensity at the samples equivalent to natural sunlight at equinox 40°N. ¹⁴C-tizanidine was prepared at a nominal 10 µg/mL in sterile aqueous solutions of pH 5, 7 and 9. Tizanidine absorbs electromagnetic radiation in the sunlight wavelength range, with molar absorptivities >10 K/M/cm for wavelengths 290 - 310 nm. Although direct photolysis might have been expected for tizanidine, negligible breakdown was identified in preliminary laboratory studies; the estimated $t_{1/2}$ was 164 - 272 hours. In contrast, tizanidine readily degraded at all pHs under indirect photolysis conditions, with a $t_{1/2}$ < 4 hours with 1% acetone as a sensitizer. Three photodegradation products were observed by HPLC and all were more polar than the parent compound based on HPLC elution order. Two of these photodegradates were minor, i.e., less than 10% of applied tizanidine. The major degradate was 60 - 80% of radioactivity and appeared to be the same at all pHs. The degradate was analyzed by liquid chromatography followed by mass spectrometry (LC/MS) but could not be fully identified. Based on observed features (loss of chlorine, even number of nitrogen atoms and base molecular ion of 224) the photodegradate structure was proposed as 2-(2-amino-3,5-dihydroxy-phenyl-imino)-4-hydroxyimidazoline. The scientific literature was searched, but no information was reported for this compound. Since it is a much simpler structure than tizanidine and more polar, it is likely to have an even lower potential than tizanidine to persist in the environment or be harmful to environmental life.

7.2.2.2 Biodegradation

The biodegradation of tizanidine (at 10.0 mg carbon/L) to CO₂ was evaluated in an aquatic test system using a microbial inoculum of WWTP activated sludge and secondary effluent (Report #41224). At the end of the 28 day study, the mean percent cumulative theoretical CO₂ evolution was 0.94 - 1.26%.

The results of the study indicated that tizanidine was not significantly mineralized (measured as CO₂ evolution) under the test conditions, and therefore did not readily biodegrade in this test system. The FDA TAD 3.11 for biodegradation recommends including soil culture in the inoculum and adapting the inoculum to the test chemical. These techniques are included to improve the potential of the laboratory test to detect biodegradation but were not used in the tizanidine test. Negative results in this laboratory study do not necessarily mean that tizanidine is not biodegradable. There are several reasons for false negative results, explained in the FDA TAD 3.11, including partial degradation (i.e., degradation but not all the way to CO₂) or differences between the test conditions and the environment. Another explanation

for false negative results could be that the test material is inhibitory or toxic at the concentration tested. This explanation does not appear to apply to the tizanidine test because microbial viability, as measured by microbial enumeration, was not affected by tizanidine.

7.2.2.3 Hydrolysis

The potential for tizanidine to hydrolyze was not evaluated directly. However, tizanidine hydrolysis appears to be slow or negligible based on observations during the water solubility test performed at [redacted]. During the approach to equilibrium, 3 - 7 days depending on pH, there was no sign of hydrolysis as might be indicated by significant decreases in the tizanidine concentration. Similarly, the dark control samples in the [redacted] photolysis study did not show any evidence of hydrolysis as measured by changes in concentration. Therefore, tizanidine is unlikely to undergo significant hydrolysis.

7.2.2.4 Octanol/Water Partition Coefficient

The octanol/water partition coefficient (K_{ow}) of tizanidine was determined using the shake flask method at $25 \pm 1^\circ\text{C}$ (ABC Report #42321). Solutions of 0.07 and 0.7 mM tizanidine in pH 5, 7, and 9 buffers saturated with octanol were equilibrated with octanol saturated with the appropriate buffer. The concentration of tizanidine in each phase was determined and the partition coefficients were calculated.

The tizanidine K_{ow} in the pH 5 and 7 systems were less than 10. The tizanidine K_{ow} in the pH 9 system was 14.1 ± 0.2 and 14.3 ± 0.2 for the 0.07 and 0.7 mM solutions, respectively. Chemicals with n-octanol/water partition coefficients less than 10 are not expected to bioconcentrate in living things or sorb to organic particles significantly. Significant environmental sorption or bioaccumulation potential is not reached until the partition coefficient is 10^4 . Therefore, regardless of environmental pH, tizanidine would not be likely to bioconcentrate or sorb to soil or sediment.

7.2.2.5 Water Solubility

The water solubility of tizanidine at pH 5, 7 and 9 at 25°C was determined using the oversaturation/undersaturation method ([redacted] Report #42320). Tizanidine (in excess of estimated water solubility) was added to reagent water and the pH adjusted to 5, 7 or 9. Samples for approach to equilibrium from undersaturation were kept at 25°C and shaken until equilibrated, up to 7 days. The oversaturation samples were initially heated to 40°C and then shaken at 25°C until equilibrated. Equilibration was defined by similar (i.e., less than 5% difference) tizanidine concentration between over and undersaturation samples. Density was also measured in the terminal pH 5 solution.

Equilibration was reached within 3 days for the pH 5 and 9 solutions and 7 days for pH 7. The water solubility of tizanidine (mean $\pm$ SD) was 59.2 ± 1.1 (pH 5), 1.11 ± 0.07 (pH 7) and 0.255 ± 0.006 mg/mL (pH 9). The pH was stable during the experiment, terminal measurements were: 5.04 ± 0.02 , 6.88 ± 0.04 and 9.01 ± 0.03 . The density of the pH 5 tizanidine solution was 1.017 ± 0.001 . The estimated K_{oc} (soil adsorption coefficient) of tizanidine based on $K_{oc} = 3.64 - 0.55 \log S$ with water solubility (S) in ppm, is 10.5 (pH 5), 91.2 (pH 7) or 204 (pH 9). Tizanidine is likely to be quite mobile in the environment based on the low K_{oc} .

7.2.3 Terrestrial Compartment

Tizanidine is unlikely to accumulate in the terrestrial compartment based on the K_{ow} and estimates of the bioconcentration factor and soil/water partition coefficient. Tizanidine K_{ow} is low, < 10 at pH 5 and 7, and approximately 14 at pH 9. Chemicals with K_{ow} less than 100 are not expected to significantly bioaccumulate or sorb to soil/sediment.

7.3 Summary of Environmental Fate Analyses

Tizanidine is most likely to be introduced to the environment through the aquatic compartment via patient discharge into waste water treatment plants (WWTP). Tizanidine will be essentially completely removed from WWTP effluent prior to release. This conclusion is based on the ready degradation ($t_{1/2} < 4$ hours) via indirect photolysis and an average of 24 hour residence in WWTP. Photodegradation is one of the most important routes of abiotic depletion processes since solar radiation is the largest source of environmental energy and sensitizers are naturally abundant, e.g., humic acid.⁴ Biotic removal may be a less significant process, based on lack of mineralization in the aerobic aquatic biodegradation test. Tizanidine's low partition coefficient and high water solubility mean that it will stay in the aquatic phase (until removed by indirect photolysis) and will not distribute into soil/sediment or bioaccumulate.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Introduction

Although tizanidine is extensively metabolized prior to elimination in the urine, evaluation of environmental effects was based on studies of the parent, tizanidine. The metabolites are likely to be less toxic than the parent material based on mammalian pharmacology activity and toxicity. The biological activity and toxicity of metabolite 4 was evaluated both directly and indirectly while assumptions regarding metabolite 10 are based on indirect studies and structure activity relationships. Metabolite 10 has not been tested directly since it can not be synthesized.

8.1 Metabolite Mammalian Activity and Toxicity

The pharmacologic activity of metabolite 4 has been evaluated in three different animal models: a primary observation test in the mouse, inhibition of droperidol + fentanyl-induced muscle rigidity in the rat, and inhibition of tonic stretch reflex in the rabbit. The results indicated that metabolite 4 was devoid of significant pharmacological activity in mice, rats and rabbits. In the rabbit, a pharmacodynamic evaluation also suggested that tizanidine-induced muscle relaxation is directly related to tizanidine, rather than to metabolites.

The acute toxicity of metabolite 4 in mice was evaluated in a limit test. From this test, the mouse LD₅₀ for metabolite 4 may be estimated to be > 1000 mg/kg. In contrast, tizanidine is more toxic, with a mouse LD₅₀ of 264 mg/kg.

The metabolites do not appear to be genotoxic based on mutagenicity testing results with tizanidine. For *in vitro* testing, tizanidine was incubated with an induced rat liver microsomal preparation (S9) which would be expected to produce both metabolites 4 and 10 as well as other rat-specific metabolites. There was no sign of mutagenicity in an Ames test, a V79/HGPRT locus mutation test, or a chromosomal aberration test. Moreover, all *in vivo* mutagenicity tests (unscheduled DNA synthesis in mice, dominant lethal test in mice, bone marrow micronucleus test in mice, bone marrow micronucleus and cytogenicity tests in hamsters) were also negative. Based on these data, tizanidine metabolism is a detoxification process since metabolites 4 and 10 are less toxic than tizanidine.

8.2 Tizanidine Mammalian Toxicity

Tizanidine toxicity has been comprehensively studied in mammals. Acute toxicity is moderate, with oral LD₅₀ for tizanidine > 200 mg/kg for rats and mice, and approximately 90 mg/kg for rabbits. Tizanidine has been evaluated for potential mutagenic and carcinogenic properties and was not shown to be mutagenic or

carcinogenic in the *in vivo* or *in vitro* studies performed. Reproductive toxicity effects in test animals were limited to very high doses of tizanidine, ≥ 10 mg/kg/day or at least 14 times the recommended maximum therapeutic dose in man (based on 50 kg patient). Tizanidine demonstrated no teratogenic potential, even at high, non-lethal doses.

8.3 Environmental Toxicity

Environmental effects testing of tizanidine was performed for Sandoz by

according to international (OECD) methods, under Good Laboratory Practices (GLP). A summary of the results are listed in Appendix A, Table 5 and summaries of the reports are included in Appendix E (confidential). Athena also sponsored environmental effects testing to support and confirm the Sandoz data. This testing was conducted for Athena by according to FDA or OECD test guidelines under GLP. These data are summarized in Appendix A, Table 5, and the reports included in Appendix F (confidential).

8.3.1 Microbial Inhibition

Results of microbial inhibition testing are relevant to the effect of tizanidine to WWTP as well as the general environment. Widespread microbial growth inhibition would indicate adverse disturbances to natural nutrient cycles and potential interference with natural degradative functions that microorganisms play in transformation of man made chemical wastes.

Tizanidine was tested on several ubiquitous microorganisms including *Azobacter chroococcum*, *Pseudomonas fluorescens*, *Nostoc* sp., *Chaetomium globosum*, and *Aspergillus flavus* at maximum concentrations of 1000 mg/L (or 1000 ppm) with no inhibition observed for any microbial population. These tests were performed by under Good Laboratory Practices using methods based on FDA TAD 4.02 Report #41249). One thousand ppm is 8 to 9 orders of magnitude higher than the level of tizanidine expected in the WWTP. Based on its demonstrated lack of toxicity to microbial cultures, tizanidine is not expected to interfere with WWTP function or to disturb the environment.

8.3.2 Algae Toxicity

Tizanidine acute toxicity to green algae, *Scenedesmus subspicatus*, was tested under static conditions following OECD 201 procedures Report #42323). The test was designed to calculate 24, 48 and 72 hour EC_{50} (E_bC_{50} and/or E_rC_{50}) values and the 72 hour no-observed effect concentration (NOEC).

The test species was exposed for 72 hours to 0, 3.2, 6.3, 12.5, 25 and 50 mg/L of tizanidine. Tizanidine was measured in samples collected at 0 and 72 hours and averaged 0, 3.0, 6.1, 11.7, 24 and 47 mg/L. All results are based on the mean measured concentrations. Test water pH and temperature ranged from 7.0 to 8.4 and 24 to 25°C, respectively, when measured at 0 and 72 hours.

The tizanidine 72 hour NOEC was 3.0 mg/L. The E_bC_{50} and 95% confidence limits for 0 - 48 hours and 0 - 72 hours were 16.6 (14.3 - 18.8) and 6.9 mg/L (5.6 - 8.2), respectively. The E_rC_{50} and 95% confidence limits for 24 - 48 hours and 48 - 72 hours were 30 (24 - 36) and 10.5 mg/L (7.4 - 13.7), respectively.

The results of the ABC study agree well with those of the Ciba-Geigy study for both the NOEC and the E_bC_{50} . Tizanidine was moderately toxic to green algae, *Scenedesmus subspicatus*, in contrast to the above noted insensitivity of microbes, including a blue-green algae, *Nostoc* sp. This degree of difference in species specificity, i.e., 3 orders of magnitude, is not common but has been reported for other chemicals. For instance, nitrilo triacetic acid was toxic to a green algae, *Scenedesmus quadricauda*, at 8.3 ppm while a bacteria, *Pseudomonas putida*, was not sensitive, i.e., no toxicity at >10000 ppm.⁵

8.3.3 *Daphnia magna* Toxicity

Tizanidine acute toxicity to *Daphnia magna* was tested under static conditions following procedures based on FDA 4.08 (Report #42325). The tizanidine immobilization EC_{50} (median effective concentration for immobilization) values and sublethal/behavior responses were determined at 24 and 48 hours. The test animals were first-instar daphnids (<24 hours old), 5/replicate with 4 replicates/test concentration. Test concentrations of tizanidine were 0, 5.3, 9.5, 17, 31, 56, 100 and 180 mg/L. The test concentrations were analyzed at 0, 24 and 48 hours and all results were based on the mean measured concentrations. Water quality (temperature, dissolved oxygen, pH, hardness and alkalinity) were measured throughout the test and were within acceptable limits.

The 48-hour EC_{50} value was 11 mg/L with 95% confidence limits of 8.7 and 14 mg/L. The 48 hour dose-response line slope was 2.9. Abnormal behavior, immobility, on bottom of test chamber, erratic movement, trailing extraneous material and/or quiescence were observed in all test concentrations except the control.

The results of the study for tizanidine toxicity showed this aquatic invertebrate to be slightly more sensitive than in the This difference is acceptable for inter-laboratory variation for this type of acute test. *Daphnia*

sensitivity to tizanidine is in the same range as aquatic phytotoxicity, i.e., moderately toxic with EC₅₀ 6.9 - 11 ppm.

8.3.4 Trout Toxicity

Tizanidine acute toxicity to rainbow trout (*Oncorhynchus mykiss*) was tested under static conditions following procedures based on FDA 4.11 (Report #42326). Ten fish, with a mean wet weight of 0.74 ± 0.24 g and a mean standard length of 38 ± 4 mm, were tested at each replicate and 2 replicates/concentration. Water quality (temperature, dissolved oxygen and pH) was measured throughout the test and was within acceptable limits. Nominal test concentration of tizanidine were 0, 16, 29, 51, 93, 170 and 300 mg/L. Test concentrations were analyzed at 0, 48 and 96 hours and mean measured concentrations were 13, 25, 44, 82, 150 and 270 mg/L.

The tizanidine 96 hour LC₅₀ was 76 mg/L, with 95% confidence limits 65 - 89 mg/L, based on mean measured concentrations. The slope of the dose-response line was 7.5. Signs of toxicity produced by the test material included mortality, on bottom of the test chamber, loss of equilibrium, surfacing, erratic swimming and/or quiescence. The 96 hour NOEC was 25 mg/L, based on the lack of toxic signs.

There was good agreement between tizanidine trout toxicity in both the
Tizanidine is moderately toxic to fresh water fish with NOEC in
the range of 25 - 58 ppm.

8.4 Summary of Environmental Effects of Tizanidine

The acute toxicity of tizanidine to environmental plants and animals is moderate; concentrations of 10 - 100 ppm and above were generally toxic in laboratory tests. The small amount of tizanidine and/or metabolites that may be released into the environment is expected to have no or negligible impact on environmental flora and fauna. Moreover, tizanidine is not expected to have any adverse affect to WWTP function based on the lack of microbial growth inhibition.

8.5 Overall Summary of the Environmental Fate and Effects of Tizanidine

Use of tizanidine is expected to have no adverse impact on the environment. Tizanidine is unlikely to accumulate or persist in the environment, based on the low partition coefficient and high sensitivity to indirect photodegradation. Indeed, indirect photodegradation will virtually eliminate tizanidine and metabolites from WWTP effluent prior to release into the environment. Tizanidine is not likely to be harmful to the environment at concentrations 5 - 6 orders of magnitude greater than the worst-case maximal expected environmental concentration. This conclusion is based on the algae NOEC, since algae were the most sensitive environmental species studied. The conclusion that the manufacture and use of tizanidine will be harmless to the environment is based on the wide safety margin between environmental toxicity and worst-case (all drug manufactured released intact to the environment and without a depletion mechanism) maximal expected environmental concentrations.

Since the identical drug product has been in commercial use for ten years in Europe and Japan, a comprehensive literature search was performed to identify if any adverse occupational health or environmental consequences have been published. No environmental consequences or adverse occupational health reports due to tizanidine were found. The list of data bases screened is provided on page 40.

According to 21 CFR 25.15(b)(6):

a substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment, i.e., either at any point of entry or any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes, exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level) or exceeds 1/100 of the concentration that causes 50-percent mortality (LC_{50} / EC_{50}) in a test organism species, whichever concentration is less.

In order to determine whether or not tizanidine would be toxic in the environment, comparisons of the worst-case MEEC for tizanidine (400 lb tizanidine/year) are made to the NOECs and to the 1/100 LD_{50} values determined in the environmental testing performed on tizanidine. The NOECs were used instead of the minimum effect levels to provide more conservative estimates. The comparisons are summarized in Table 3.

TABLE 3: COMPARISON OF WORST-CASE TIZANIDINE MEEC TO NOEC AND 1/100 LD₅₀ VALUES

Test Performed	NOEC ¹	% (MEEC ² / NOEC)	LC ₅₀ ³ / EC ₅₀	% (MEEC ² / 1/100 LC ₅₀)
Microbial Inhibition, FDA 4.02	≤ 1000 mg/L	4 x 10 ⁻⁷ %	ND ⁴	---
Acute Toxicity Test - Rainbow Trout, OECD 203	25 mg/L	2 x 10 ⁻³ %	LC ₅₀ = 76 mg/L	0.0005%
Acute Toxicity Test - Daphnia, OECD 202	ND	---	⁵ EC ₅₀ = 11 mg/L	0.0036 %
Growth Inhibition - Green Algae (<i>Scenedesmus subspicatus</i>), OECD 201	7.0 mg/L	0.0001 %	⁶ E ₀ C ₅₀ (0-72 h) = 6.9 mg/L	0.0058%

¹ NOEC = no-observed effect concentration

² Assumption: MEEC = 4 x 10⁻⁶ ppm (worst-case, maximum production ≤ 400 lb tizanidine/year)

³ LC₅₀ = concentration of test chemical that results in death of 50% of test species

⁴ ND = not determined

⁵ EC₅₀ = concentration of test chemical that results in immobilization of 50% of the daphnids

⁶ E₀C₅₀ (0-72 hr) = concentration of test chemical that results in 50% growth reduction, compared to control, between 0 and 72 hours

These comparisons show that even in the most sensitive species, green algae, the MEEC is only 0.0058% of the 1/100 EC₅₀ value and it would take more than 22,000 years, assuming no degradation or dissipation, to reach the minimum definition of potentially toxic in the environment. Based on these comparisons, it is clear that the manufacture and use of tizanidine will not have an adverse environmental effect.

Therefore, we conclude that the manufacture and use of Zanaflex will not adversely impact the site of U.S. packaging operations or sites of use and emission. The amount of tizanidine at its maximum expected use is not anticipated to be toxic to the potentially impacted aquatic environments.

DATABASES

DIALOG

Aquatic Sciences & Fisheries (1978 - present)
Chemical Safety Newbase (1981 - present)
Diogenes (1976 - present)
Dissertation Abstracts (1861 - present)
Eabase (1974 - present)
Enviroline (1971 - present)
F-D-C Reports (1987 - present)
Medline (1966 - present)
Occupational Health and Safety (NIOSH) (1973 - present)
Pollution Abstracts (1970 - present)
PTS Newsletter (1988 - present)
Toxline (Varies) (Includes the following:
 Aneuploidy File 1970- 1986
 Developmental and Reproductive Toxicology File 1989 to
 present
 Environmental Mutagen Information Center pre-1950 -1990
 Environmental Teratology Information Center pre-1950 to
 1989
 Epidemiology Information System pre-1940 -1988
 Federal Research in Progress 1984 - present
 hazardous Materials Technical Center pre-1981 to 1988
 International Labour Office, CIS Abstracts 1981 - present
 International Pharmaceutical Abstracts 1970 to present
 NIOSH 1984 to present
 Pesticides Abstracts 1966 -1981
 poisonous Plants Bibliography pre-1976
 Toxic Substances Control Act Test Submissions pre-1988 to
 present
 Toxicity Bibliography 1965 to present
 Toxicological Aspects of Environmental Health (BIOSIS)
 1972 to present
 Toxicology Document and Data Depository File (NTIS) Oct.
 1979 to present
 Toxicology Research Projects, NIH Current
Unlisted Drugs (1988 - present)

MEDLARS/TOXNET

Chemid (Current)
Hazardous Substances Databank (HSDB) (Current)
Registry of Toxic Substances (RTECS) (Current)
Environmental Mutagen Information Center File (Pre-1950 to
1990)
Environmental Teratology Information Center File (Pre-1950 -
1989)

DATA - STAR

LMS Drug Alerts Online
European Pharmaceutical Market Research
Pharaline
DHSS-MEDTEK (Medical Toxicology & Environmental Health)

9. USE OF RESOURCES AND ENERGY

For U.S. operations, Zanaflex will be processed for final fill and packaging. At maximum production it is expected to utilize less than 1% of the total utility consumption of the company. Water usage is also considered negligible.

The product will be transported via common carrier within the United States and overseas. The energy required to transport the bulk and finished drug products is not expected to significantly affect the availability of resources.

The use of renewable and non-renewable natural resources is considered insignificant. No effects are expected upon endangered or threatened species or upon property listed in, or eligible for listing in, the National Register of Historic Places.

10. MITIGATION MEASURES

Prior to issuing the Environmental Protection Certificate, the Swiss government evaluated and approved Sandoz' procedures for avoiding or mitigating potential adverse environmental impacts associated with the manufacture of Zanaflex. Spill control procedures and practices are sufficient to comply with federal, state and local regulations.

11. ALTERNATIVES TO THE PROPOSED ACTION

The alternative of "no action" has been considered but has been determined not to be acceptable because it would deny patients a valuable pharmaceutical and because no potential adverse environmental impacts are identified for the proposed action. Zanaflex is a very important drug for treatment of spasticity since experts estimate that in approximately 55% of patients, spasticity is not adequately controlled by currently available therapies.

12. LIST OF PREPARERS

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13. CERTIFICATION

The undersigned certifies that the information presented in the Environmental Assessment is true, accurate, and complete (with the exclusion of proprietary information) to the best of the knowledge of the firm.

Date: 8 Sep 95

Signature: Jan Wallace

Jan Wallace
Vice President, Clinical and Regulatory Affairs
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14. REFERENCES

1. FDA, Environmental Assessment Technical Assistance Handbook, 1987.
2. Tse, F.L. S., J. M Jaffe, and S. Bhuta. Pharmacokinetics of Orally Administered Tizanidine in Healthy Volunteers. *Fundam clin Pharmacol.* 1987. 1: 4799-488.
3. Koch, P., Hirst, D.R., von Wartburg, B.R. Biological Fate of sirdalud in animals and man. *Xenobiotica.* 1989. 19(11): 1255-1265.
4. Minero, C., Pramauro, E., Pelizzetti, E., Dolci, M., Marchesini, A. Photosensitized transformations of atrazine under simulated sunlight in aqueous humic acid solution. *Chemosphere.* 1992. 24(11): 1597 - 1606.
5. Bringman, G., Kuhn, R. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. *Water Research.* 1980. 14: 231- 241.

APPENDIX A

TABLE 4: TIZANIDINE ENVIRONMENTAL FATE DATA SUMMARY

Title	Guideline	Ciba-Geigy Results	ABC Results
Water Solubility (Oversaturation/Undersaturation Method)	FDA 3.01	not done	Mean water solubility: pH 5: 59.2 ± 1.1 mg/mL pH 7: 1.11 ± 0.07 mg/mL pH 9: 0.255 ± 0.006 mg/mL Density at pH 5: 1.017 ± 0.001 g/mL
Octanol/Water Partition Coefficient (Shake Flask)	FDA 3.02	not done	K_{ow} Values: pH 5: < 10 pH 7: < 10 pH 9: 14
Photolysis	FDA 3.10	not done	Light source: xenon lamp. light intensity $\sim 40^\circ$ N latitude at equinox. Sensitizer: 1% acetone Indirect photolysis kinetics: pH 5: 3.54 h pH 7: 3.54 h pH 9: 1.64 h
Aerobic Biodegradation in water (28 day CO ₂ evolution method)	OECD 301B / FDA 3.11	1% ThCO ₂ Tizanidine not biodegradable in this test	< 1% ThCO ₂ Tizanidine not significantly mineralized and hence, not readily biodegradable

APPENDIX A

TABLE 5: TIZANIDINE ENVIRONMENTAL EFFECTS DATA SUMMARY

Title	Guideline	Ciba-Geigy Results	ABC Results
48-hour Static <i>Daphnia magna</i> Acute Toxicity	OECD 202 / FDA 4.08	EC ₅₀ (calc.): 93.2 mg/L NOEC*: 18 mg/L	EC ₅₀ : 11 mg/L
72-hour Static Algae Acute Toxicity (<i>Scenedesmus subspicatus</i>)	OECD 201	NOEC: 3.3 mg/L E ₅ C ₅₀ (0-72 h, calc): 15.4 mg/L	NOEC: 3.0 mg/L E ₅ C ₅₀ (0-72 h): 6.9 mg/L E ₇ C ₅₀ (48-72 h): 10.5 mg/L
96-hour Static Freshwater Fish Acute Toxicity rainbow trout (<i>Oncorhynchus mykiss</i>)	OECD 203 / FDA 4.11	LC ₅₀ : (calc) >100 mg/L NOEC: 58 mg/L	LC ₅₀ : 76 mg/L (65 -89 mg/L), slope: 7.5 NOEC: 25 mg/L
Microbial Growth Inhibition	FDA 4.02	Bacterial toxicity results are referred to on page 4 of the MSDS.	No inhibition of microbial growth at ≤ 1000 mg/L for: <i>Azotobacter chroococum</i> , <i>Pseudomonas fluorescens</i> , <i>Nostoc</i> sp., <i>Chaetomium globosum</i> or <i>Aspergillus flavus</i>

Results reported as nominal (Ciba-Geigy) or mean measured (ABC) concentrations

* NOEC = no-observed effect concentration

END

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