CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-447

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

ELAN PHARMACEUTICALS TIZANIDINE HCL CAPSULES

NEW DRUG APPLICATION ITEM 13

13. PATENT INFORMATION

US Patents 3,843,668 and 4,053,617 for Zanaflex® have expired. Zanaflex is a registered trademark of Elan Pharmaceuticals, Inc. under license from Novartis Pharma, AG, Basel, Switzerland. The exclusivity (listed in the current Orange Book) for Zanaflex (tizanidine hydrochloride), NDA 20-397 expires on November 27, 2001.

ELAN PHARMACEUTICALS
NEW DRUG APPLICATION

TIZANIDINE HCL CAPSULES
ITEM 14

14. PATENT CERTIFICATION

See attached.

APPEARS THIS WAY
ON ORIGINAL

élan
pharmaceuticals

Elan Pharmaceuticals

7475 Lusk Boulevard, San Diego, CA 92121

Telephone (858) 457-2553

Fax (858) 457-2555

PATENT CERTIFICATION

In accordance with 21 CFR Part 314.53(c)(3), in the opinion and to the best knowledge of Elan Pharmaceuticals, Inc., there are no patents that claim the drug or drug product.

US Patents 3,843,668 and 4,053,617 for Zanaflex® have expired. Zanaflex is a registered trademark of Elan Pharmaceuticals, Inc. under license from Novartis Pharma, AG, Basel, Switzerland. The exclusivity (listed in the current Orange Book) for Zanaflex (tizanidine hydrochloride), NDA 20-397 expires on November 27, 2001.

Michael C. Scaife

Micahael C. Scaife, Ph.D.
Vice President, Global Regulatory Affairs

31 October 2001

Date

EXCLUSIVITY SUMMARY for NDA # 21-447 SUPPL # _____

Trade Name (none) Generic Name Tizanidine

Applicant Name Elan HFD- 120

Approval Date August 29, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ x / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / x /

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO / x /

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      Bioequivalence study to show 6 mg capsule is bioequivalent to (4 mg + 2mg) tablet (no 6 mg tablet available)

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO / x /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-397 Tizanidine Tablets

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_x_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Lana Chen, R.Ph. 8/30/02
Signature of Preparer Date
Title: Project Manager

Russell Katz, M.D. _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA # : NDA 21-447 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: November 1, 2001 Action Date: September 1, 2002

HFD-120 Trade and generic names/dosage form: Tizanidine Capsules

Applicant: Elan Therapeutic Class: 3S

Indication(s) previously approved: Spasticity

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Spasticity

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

■ No: Please check all that apply: ____Partial Waiver __x__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min	**0**	**kg**	**mo.**	**yr.** X	**Tanner Stage**
Max	**16**	**kg**	**mo.**	**yr.** X	**Tanner Stage**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: _____

Date studies are due (mm/dd/yy): 12/31/05

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min		**kg**	**mo.**	**yr.**	**Tanner Stage**
Max		**kg**	**mo.**	**yr.**	**Tanner Stage**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lana Chen, R.Ph.
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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

/s/

Lana Chen
8/27/02 01:41:25 PM
CSO
Ok'd by Armando Oliva, MD, Neurology Team Leader (8/23/02)

ELAN PHARMACEUTICALS
NEW DRUG APPLICATION

TIZANIDINE HCL CAPSULES
ITEM 16

16. DEBARMENT CERTIFICATION

See attached.

Elan Pharmaceuticals

7475 Lusk Boulevard, San Diego, CA 92121

Telephone (858) 457-2553

Fax (858) 457-2555

DEBARMENT CERTIFICATION

Elan Pharmaceuticals, Inc., hereby certifies that, to the best of its knowledge, it has not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) of the Food, Drug, and Cosmetic Act, in connection with this application. In addition, to the best of its knowledge, Elan Pharmaceuticals states that neither Elan Pharmaceuticals nor any individuals, partnerships, corporations, or associations responsible for the development or submission of this application have been convicted as described in Section 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act.

Elan Pharmaceuticals, Inc.,

Michael C. Scaife

Michael C. Scaife, Ph.D.
Vice President, Global Regulatory Affairs

October 31 2001

Date

élan pharmaceutical technologies

Monksland, Athlone, County Westmeath, Ireland
Telephone (+353 902) 95000
Fax (+353 902) 95803

DEBARMENT STATEMENT

Elan Pharmaceutical Technologies, the developers of the Tizanidine IR Capsules (2,4 & 6mg) hereby certifies that it did not and will not use, in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with the New Drug Application for this product.

Geraldine Carr-Mulry.

Geraldine Carr-Mulry. M.Sc.
Head of Regulatory Operations – Athlone

Date: 30/10/01

19. OTHER

19.1 Financial Disclosure

See attached.

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

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

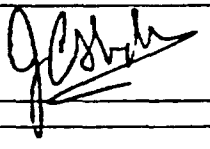
Please mark the applicable checkbox.

✓ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	—— MB, MRCGP	
	—— , MB, MRCGP	
	—— , MB, MRCGP	

✓ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

✓ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Jaymin Shah, PhD	Director, Clinical Pharmacology
FIRM/ORGANIZATION Elan Pharmaceuticals, Inc.	
SIGNATURE 	DATE 10/31/01

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

MEMORANDUM

DATE: August 29, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-447

SUBJECT: Action Memo for NDA 21-447, for the introduction of Zanaflex (tizanidine hydrochloride) capsules

NDA 21-447, for the introduction of Zanaflex (tizanidine hydrochloride) capsules, was submitted by Elan Pharmaceuticals on 10/31/01. Currently, Zanaflex is approved as 2 and 4 mg tablets for the treatment of spasticity; the current application proposes the introduction of 2, 4, and 6 mg capsules. The application contains the results of a number of pharmacokinetic and bioequivalence trials, as well as CMC information. The application also contains reports of additional safety data accrued with the approved tablet.

The application has been reviewed by Dr. Eric Bastings, medical officer (review dated 8/13/02), Dr. Ron Kavanagh, Office of Clinical Pharmacology and Biopharmaceutics (review dated 5/30/02), Dr. Janusz Rzeszotarski, chemist (review dated 8/28/02), and Dr. Armando Oliva, Neurology Drugs Team Leader (memo dated 8/28/02). The review team recommends that the application be approved.

While there are a number of minor issues raised in the application, there are 2 issues that require discussion.

As the various reviewers noted, the tablet and capsule have been shown to be bioequivalent in the fasted state. However, as the review team has also noted, the capsule and tablet are not bioequivalent in the fed state. Specifically, the Cmax of the capsule is about 2/3 that of the tablet in the fed state, and the Tmax of the capsule is about twice that of the tablet in the fed state. As would be expected from this finding, the Cmax of the capsule in the fed state is less than that in the fasted state, but the Cmax of the tablet is higher in the fed state than in the fasted state (exactly the opposite effect seen with the capsule). The combined effects result in the lack of bioequivalence seen between the tablet and capsule in the fed state.

As the review team notes, this has implications for dosing recommendations, especially when patients switch from one dosage form to the other after a meal. This may be particularly problematic with this treatment, where it is taken essentially as needed; we cannot be certain that it will be needed at the same time in relation to meals each day. It is further particularly problematic because

the peak effect of the drug probably corresponds, at least roughly, to the Tmax, which is also effected by food.

Apparently, there is a food effect for the tablet by itself (one opposite that seen with the capsule), the Cmax being greater with food than in the fasted state. Additionally, we don't really know how long after a meal the effect can be seen, nor do we know the specific effects of different meals (presumably the effects seen were in relation to a high fat, FDA standard meal; the effects of other foods are not known). All of these factors can conspire to make dosing recommendations quite complex; as such, it seems that trying to provide explicit dosing recommendations to cover every possible eventuality (e.g., switching from tablet to capsule, either while the patient has just eaten or not, etc.) would be unproductive.

In light of this, I believe that the most efficient approach would be to alert prescribers to these facts, and caution them to be aware of the consequences that may arise from varying dosage forms and/or dosing in relation to meals.

The second issue relates to a finding noted in the inspection of the study that demonstrated bioequivalence of the products (6 mg single dose) in the fasted state, a study performed in [redacted] by [redacted] The inspection, performed 6/10-14/02, revealed that the plasma samples from Period 1 (this was a standard 2 period cross-over study) were taken out of the storage freezer on 10/9/01, to be shipped for analysis to Elan, but were actually not shipped to Elan until 10/16/01. The storage location during this period was not documented, and the Division of Scientific Investigations (DSI) recommended, in a memo dated 7/9/02, that the sponsor address this question. In addition, there were also questions about complete reporting of hypotensive episodes in the study.

On 7/5/02, the sponsor responded to these issues (this submission was made in response to a 483 issued after the inspection; the 483 was issued well before the 7/9/02 memo was written). They noted that, in fact, the samples were immediately returned to the freezer on 10/9/01 when the shipment to Elan did not occur, and were kept frozen until 10/16/01, when the shipment was made. The study site acknowledged that this was not documented. In addition, they addressed the "underreporting" of hypotensive episodes by stating that they had only intended to report such episodes if associated with symptoms, given that hypotension itself is a known adverse reaction to tizanidine (they also noted that the actual blood pressures for all patients were included in the study report).

In a subsequent memo from DSI dated 8/9/02, they concluded that the sponsor's explanations relating to the storage conditions were inadequate, and that the data from Period 1 should not be accepted, unless additional documentation about the storage conditions during that time period could be produced. We

have just received, in a fax of several documents from the sponsor dated 8/28/02, additional documentation relating to this issue. The one relevant document is a signed (undated) statement from the person who presumably actually did the transferring of the samples. This person, [redacted] asserts (although undated, the memo was clearly written after the fact) that he removed the samples from the freezer on 10/9/01, but realized that there was not an adequate supply of dry ice in which to package the samples for shipment. As a result, he immediately re-placed the samples into the freezer until 10/16/01, when they were removed and shipped to Elan for analysis (the sponsor has also included receipts in the fax that document that the samples were received frozen). [redacted] acknowledges that he did not record the fact that the samples were re-placed into the freezer on 10/9/02.

Dr. Oliva has extensively addressed this issue in his memo. He notes that any potential degradation of tizanidine levels in inadequately stored plasma samples should have affected samples from tablet and capsule equally. Further, there is no period effect in the study; that is, the results in Period 1 are not significantly different than those in Period 2 (samples from Period 2 were documented to have been handled appropriately). It is true that the results were not identical in both periods, but this is not unexpected. In addition, another separate study also has documented the equivalence of the tablet and capsule in the fasting state (this study has not been inspected).

Dr. Oliva further notes that Dr. Kavanagh has a number of difficulties with these conclusions. Dr. Kavanagh posits that there might be a concentration dependent difference in degradation, as well as a possible masking of a period effect. Dr. Kavanagh does acknowledge, however, that there is no affirmative evidence that the plasma levels in Period 1 are problematic. His objections are based on the view that in the absence of evidence that the samples were stored properly, it is reasonable to assume that they were not, and that if they were not, in the absence of evidence that samples stored at room temperature do not degrade (differentially), it is reasonable to assume that they might. He would prefer that the sponsor perform a simple stability test of drug in plasma kept at room temperature to definitively address the question. Dr. Oliva concludes that such testing is not necessary.

I agree with Dr. Oliva. I find his arguments persuasive. It is important to note that his arguments are compelling even if we knew that the samples were kept at room temperature for the period in question. However, the sponsor states that, in fact, the samples were stored appropriately, and has recently supplied us with a signed statement from the responsible party that indeed the samples were stored appropriately; if we accept this as true (and I am certainly inclined to do so), there would be not question about the results. In summary, then, I find Dr. Oliva's rationale for accepting the results of this study without further stability data compelling even if the samples were inappropriately stored, but I am further reassured that the samples were stored appropriately, despite the absence of

contemporaneous documentation of this. For these reasons, I do not believe that the studies recommended by Dr. Kavanagh need be done. I also find the sponsor's explanation about the reporting of cases of hypotension acceptable, although I too would have preferred them to report asymptomatic cases of hypotension explicitly.

Finally, as Dr. Oliva has noted, one packaging site in New Jersey has failed a compliance inspection. We have secured the sponsor's agreement to withdraw this site from the application (on 8/28/02); there is another acceptable site that performs this function in the application.

For the reasons stated above, then, I will issue the attached Approval letter with appended labeling, with which we have obtained agreement from the sponsor.

Russell Katz, M.D.

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

/s/

Russell Katz
8/29/02 05:14:24 PM
MEDICAL OFFICER

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ication:	NDA 21447/000	Action Goal:	
Stamp:	01-NOV-2001	District Goal:	03-JUL-2002
Regulatory Due:	01-SEP-2002	Brand Name:	ZANAFLEX (TIZANIDINE
Applicant:	ELAN PHARMS	Estab. Name:	HCL) 2,4,6 MG CAPS
	7475 LUSK BLVD	Generic Name:	TIZANIDINE HCL
	SAN DIEGO, CA 92121		
Priority:	3S	Dosage Form:	(CAPSULE)
Org Code:	120	Strength:	2MG, 4MG, 6 MG

Application Comment: 1. ELAN HOLDINGS GAINESVILLE, GA HAS NOT BEEN AP FOR 20-397/ [redacted] (INJUNCTION IN AUG 2000). PLEASE LET ME KNOW THE CURRENT STATUS OF THIS FACILITY AS IT APPEARS RED IN EES (ALTERNATE PACKAGER AND RELEASE TESTER FOR THIS NDA).
2. IS [redacted] (CFN [redacted] AT [redacted] THE SAME AS [redacted]
3. IS [redacted] (CFN [redacted] THE SAME AS [redacted]
4. PLEASE ALSO ADVICE IF [redacted] NEED TO BE INSPECTED.
THANKS
(on 19-DEC-2001 by D. CHRISTODOULOU (HFD-810) 301-594-5554)

FDA Contacts:	L. CHEN	(HFD-120)	301-594-5529	, Project Manager
	W. RZESZOTARSKI	(HFD-120)	301-594-2850	, Review Chemist
	M. GUZEWSKA	(HFD-120)	301-594-5571	, Team Leader

Overall Recommendation: ACCEPTABLE on 28-AUG-2002by J. D AMBROGIO(HFD-324)301-827-0062
WITHHOLD on 28-AUG-2002by S. ADAMS (HFD-324)301-594-0095

Establishment: CFN [redacted] FEI 3002806531

DMF No: AADA:
Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-DEC-2001				CHRISTODOUL
SUBMITTED TO DO	19-DEC-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	20-DEC-2001	GMP			GARCIAM
INSPECTION SCHEDULED	13-JUN-2002		07-AUG-2002		IRIVERA
PECTION SCHEDULED	10-JUL-2002		15-SEP-2002		GARCIAM
PECTION PERFORMED	15-AUG-2002		07-AUG-2002		IRIVERA

NO FD-483 WAS ISSUED. FIRM IS ACCEPTABLE.

DO RECOMMENDATION	28-AUG-2002	ACCEPTABLE INSPECTION	ADAMSS

BASED ON INVESTIGATOR'S RECOMMENDATION. AWAITING EIR.

OC RECOMMENDATION	28-AUG-2002	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9611013 FEI 3002806873
ELAN CORP PLC
WESTMEATH COUNTY, ATHLONE, EI

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: CHG OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
MITTED TO OC	19-DEC-2001				CHRISTODOUL
SUBMITTED TO DO	19-DEC-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	20-DEC-2001	GMP			GARCIAM
INSPECTION SCHEDULED	03-JUL-2002		26-AUG-2002		GARCIAM
INSPECTION PERFORMED	23-AUG-2002		23-AUG-2002		IRIVERA
DO RECOMMENDATION	28-AUG-2002			ACCEPTABLE INSPECTION	ADAMSS

BASED REVIEW OF 483 AND INVESTIGATOR'S RECOMMENDATION. AWAITING FIRM'S RESPONSE AND EIR.

OC RECOMMENDATION	28-AUG-2002	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 1035761 FEI 1035761
ELAN PHARMACEUTICAL RESEARCH CORP
1300 GOULD DR
GAINESVILLE, GA 30504

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: CHG OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
MITTED TO OC	19-DEC-2001				CHRISTODOUL
MITTED TO DO	19-DEC-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	19-DEC-2001	PS			LANDREWS

INSPECTION SCHEDULED	03-JAN-2002			LANDREWS
INSPECTION PERFORMED	12-MAR-2002	07-MAR-2002		LANDREWS
DO RECOMMENDATION	12-MAR-2002		ACCEPTABLE INSPECTION	LANDREWS
1 ITEM 483 ISSUED. NO SIG OBSERVATIONS NOTED.				
OC RECOMMENDATION	13-MAR-2002		ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
INSPECTION SCHEDULED	14-MAR-2002	01-APR-2002		LANDREW1@OR
DO RECOMMENDATION	09-APR-2002		ACCEPTABLE INSPECTION	LANDREWS
DUPLICATE ENTRY DO RECOMMENDATION PREVIOUSLY MADE.				
OC RECOMMENDATION	09-APR-2002		ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
INSPECTION PERFORMED	30-MAY-2002	07-MAR-2002		LANDREW1@OR
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED				
See endorsement text.				
DO RECOMMENDATION	03-JUN-2002		ACCEPTABLE DUPLICATE MILESTONE FROM FACTS	LANDREWS
DO REC PREVIOUSLY MADE				
OC RECOMMENDATION	03-JUN-2002		ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-DEC-2001				CHRISTODOUL
SUBMITTED TO DO	19-DEC-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	19-DEC-2001	PS			LANDREWS
INSPECTION SCHEDULED	03-JAN-2002				LANDREWS
INSPECTION PERFORMED	12-MAR-2002		07-MAR-2002		LANDREWS
1 ITEM 483 ISSUED. NO SIG. OBSERVATIONS NOTED					
DO RECOMMENDATION	12-MAR-2002			ACCEPTABLE INSPECTION	LANDREWS
INSPECTION OF 2/12-3/7/02 REVEALED NO SIG. OBSERVATION. A 1 ITEM 483 WAS ISSUED.					
OC RECOMMENDATION	13-MAR-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
INSPECTION SCHEDULED	14-MAR-2002		01-APR-2002		LANDREW1@OR
DO RECOMMENDATION	09-APR-2002			ACCEPTABLE INSPECTION	LANDREWS
DUPLICATE ENTRY, DO RECOMMENDATION PREVIOUSLY MADE.					
OC RECOMMENDATION	09-APR-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
INSPECTION PERFORMED	30-MAY-2002		07-MAR-2002		LANDREW1@OR
endorsement text.					
DO RECOMMENDATION	03-JUN-2002			ACCEPTABLE	LANDREWS

DUPLICATE MILESTONE FROM FACTS

DO REC. PREVIOUSLY MADE.
OC RECOMMENDATION 03-JUN-2002 ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION

Establishment: CFN FEI

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-DEC-2001				CHRISTODOUL
MITTED TO DO	19-DEC-2001	GMP			DAMBROGIOJ
IGNED INSPECTION T	20-DEC-2001	GMP			GARCIAM
SPECTION SCHEDULED	03-APR-2002		08-MAY-2002		IRIVERA
INSPECTION PERFORMED	17-MAY-2002		07-MAY-2002		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	26-JUL-2002			ACCEPTABLE INSPECTION	ADAMSS
BASED ON INVESTIGATOR'S RECOMMENDATION. AWAITING EIR.					
OC RECOMMENDATION	26-JUL-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN FEI 3002807964

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
MITTED TO OC	19-DEC-2001				CHRISTODOUL
MITTED TO DO	19-DEC-2001	10D			DAMBROGIOJ
DO RECOMMENDATION	20-DEC-2001			ACCEPTABLE	GARCIAM

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

BASED ON FILE REVIEW

8/15/01
OC RECOMMENDATION 20-DEC-2001 ACCEPTABLE GARCIAM
DISTRICT RECOMMENDATION

Establishment: CFN [redacted] FEI 2518332

DMF No: 397 AADA:
Responsibilities: [redacted]

Profile: CHG OAI Status: NONE

Estab. Comment: PLEASE COMPLETE PAGE TWO OF THIS ASSIGNMENT AND FORWARD TO THE PRE-APPROVAL MANAGERS OFFICE AT THE COMPLETION OF THE INSPECTION. FORWARD A COPY TO COMPLIANCE BRANCH. LAST EI WAS 10/25/99. (on 07-JAN-2002 by D. PAGANO (HFR-CE100) 215-597-4390)

estone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-DEC-2001				CHRISTODOUL
SUBMITTED TO DO	19-DEC-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	07-JAN-2002	PS			DPAGANO
INSPECTION SCHEDULED	09-JAN-2002		06-FEB-2002		DPAGANO
INSPECTION PERFORMED	29-MAY-2002		24-MAY-2002		DPAGANO
DO RECOMMENDATION	29-MAY-2002			ACCEPTABLE INSPECTION	DPAGANO

483 ITEMS DID NOT WARRANT A WITHHOLD RECOMMENDATION. ALSO PRESENT FOR THIS INSPECTION:

OC RECOMMENDATION 29-MAY-2002 ACCEPTABLE ADAMSS
DISTRICT RECOMMENDATION

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-447 _____ - _____

Drug Tizanidine Capsules Applicant: Elan

RPM Lana Chen, R.Ph. Phone 301-594-5529

■505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s) IND 37, 891 Tizanidine Tabs; NDA 20-397 Tizanidine Tablets; NDA 20-397/SLR 014

Application classifications:
Chem Class 3S
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary 9/1/02
Secondary 11/01/02

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ■AP AE ☐NA
- Labeling & Labels
  FDA revised labeling and reviews..... X
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... X
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No
  Immediate container and carton labels X
  Nomenclature review X
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ■ Materials requested in AP letter

- Post-marketing Commitments _____
  - Agency request for Phase 4 Commitments..... _____
  - Copy of Applicant's commitments ..... _____

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ■No
  - Copy of Press Release or Talk Paper..... _____

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)]..... _____
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... _____

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located ..... _____

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings ..... _____
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting ..... N/A
  - Date of Meeting ..... _____
  - Questions considered by the committee ..... _____
  - Minutes or 48-hour alert or pertinent section of transcript ..... _____

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

Continued ⇨

- Safety Update review(s) X

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ■ Deferred
  Pediatric Page..... X
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ■ Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits X
  ☐Clinical studies ■bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability .....

- DMF review(s) .....

- Environmental Assessment review/FONSI/Categorical exemption .....

- Micro (validation of sterilization) review(s) and memoranda .....

- Facilities Inspection (include EES report)
  Date completed _____ ..... ■ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ■ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: April 25, 2002	**DUE DATE:** September 1, 2002	**ODS CONSULT #:** 02-0079

TO: Russell G. Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Lana Yan Chen
Project Manager
HFD-120

PRODUCT NAME:	**NDA SPONSOR:**
Zanaflex (Tizanidine Hydrochloride Capsules) 2 mg, 4 mg, and 6 mg **NDA:** 21-447	Elan Pharmaceuticals, Inc.

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a labeling review of the container labels, carton and insert labeling for a new dosage form (capsule), additional strength (6 mg), and physician sample blister pack for possible interventions to minimize medication errors with the use of the product.

DMETS RECOMMENDATION: DMETS recommends revising the labels and labeling as outlined in Section II of this review.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

CONTAINER LABEL AND CARTON/INSERT LABELING REVIEW

DATE OF REVIEW: July 22, 2002

NDA # 21-447

NAME OF DRUG: Zanaflex
(Tizanidine Hydrochloride Capsules) 2 mg, 4 mg, and 6 mg

NDA HOLDER: Elan Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products to review the container label, carton and insert labeling for the product Zanaflex.

PRODUCT INFORMATION

The currently marketed product Zanaflex contains the active ingredient tizanidine hydrochloride in a tablet formulation under NDA 20-397 of 2 mg and 4 mg. Both are available in a 150-count bottle. The sponsor proposes a new dosage formulation (capsules), and a new strength of 6 mg in addition to a new physician sample package. Zanaflex is a short acting drug indicated for the management of spasticity. The usual dose of Zanaflex is 8 mg, given in six to eight hour increments. Single daytime doses should not exceed 12 mg and the daily dose should not exceed 36 mg. Treatment should be initiated with doses of 4 mg. The dose should be titrated upwards in increments of 2 mg to 4 mg. Patients should be monitored for dose-related adverse events during the titration period. NDA 21-447 is for Zanaflex capsules which will be available in 2 mg, 4 mg, and 6 mg strengths. The daily dose, maximum dose, and titration schedules will be the same for the capsule formulation as it is for the tablet formulation.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of "Zanaflex," DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has reviewed the current container labels, carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (2 mg, 4 mg, and 6 mg – 150 count)

[redacted]

III. RECOMMENDATIONS:

DMETS recommends revising the labels and labeling as outlined in Section II of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
7/22/02 07:48:19 AM
PHARMACIST

Carol Holquist
7/22/02 10:24:12 AM
PHARMACIST

Jerry Phillips
7/22/02 03:24:21 PM
DIRECTOR

FOOD AND DRUG ADMINISTRATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859

Telecopier Cover Sheet

DATE: December 21, 2001
TIME:

DELIVER TO: **Michael Scaife, PhD**
Fax Number: (858) 558-1448

FROM: Lana Chen, R. Ph. (Ph 301.594.5529)
Regulatory Management Officer.

Total number of pages, including cover page: 2

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:

Michael,

RE: NDA 21-447 Tizanidine Caps

Please see our attached requests. In reference to your 12/18/01 fax and subsequent voice mails, your telecon request is under review.

Thanks,
Lana

- Please provide new electronic and hard copies of the proposed labeling that indicates all changes from the current approved text with strikeouts and insertion marks. Additional electronic and hardcopies with editing marks (insertions & deletions) in a side-by-side 3-column format, (Current, Proposed, Annotations), would also be appreciated as it tends to speed review.

- For study AN021-101 please provide or adequately cross-reference, as appropriate, the missing sections of the analytic report (Vol. 1.33). The submitted information begins with Appendix F.

- For the Cognitive Drug Research Report (Vol. 1.32 pg 151 and Vol. 1.37 pg 331) please provide legible copies of the literature articles cited.

- Please provide the raw data & computer code for the Cognitive Drug Research Report (Vol. 1.37 pg 331) in electronic format (single precision for numeric data).

MODE = MEMORY TRANSMISSION START=DEC-21 16:23 END=DEC-21 16:24

FILE NO.= 182

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	#	919585581448	002/002	00:00'35"

-FDA/DNDP

********** - - ***** - 3015942859- *********

FOOD AND DRUG ADMINISTRATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX (301) 594-2859

Telecopier Cover Sheet

DATE: December 21, 2001
TIME:

DELIVER TO: **Michael Scaife, PhD**
Fax Number: (858) 558-1448

FROM: Lana Chen, R. Ph. (Ph. 301.594.5529)
Regulatory Management Officer.

Total number of pages, including cover page: 2

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE:

Michael,

RE: NDA 21-447 Tizanidine Caps

Please see our attached requests. In reference to your 12/18/01 fax and subsequent voice mails, your telecon request is under review.

Thanks,
Lana

39 Page(s) Withheld

78 Page(s) of Draft Labeling Withheld