DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Louise C. Johnson
Director, Regulatory Affairs
Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Re: NDA # 20-397
Zanaflex (tizanidine HCl) Tablets
MACMIS # 10596

Dear Ms. Johnson:

This letter concerns the dissemination of promotional materials for Zanaflex (tizanidine HCl) Tablets. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a visual aid (#ZFX-980) submitted under cover of Form FDA 2253 by Elan Pharmaceuticals (Elan). The visual aid promotes Zanaflex in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations. Specifically, DDMAC has the following objections:

Lack of Fair Balance

The visual aid lacks fair balance because there is no risk information provided in the body of the visual aid. Risk information provided by the accompanying approved product labeling (PI) does not provide adequate communication of contraindications, warnings, precautions, and adverse reactions with a prominence and readability that is reasonably comparable to the presentation of information relating to the effectiveness of the drug.

Inadequate Communication of Approved Indication

According to the PI, "Tizanidine is a short acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important."

The visual aid fails to adequately convey either the approved indication or its limitations. For example, the claim "#1 antispasticity agent" fails to communicate that Zanaflex is a short acting drug. Therefore, this presentation misleadingly broadens the indication and implies that Zanaflex is approved for use in a broader range of conditions than has been demonstrated by substantial evidence.

Unsubstantiated Efficacy Claims

The claim "Zanaflex provided a 32% reduction in frequency of interference with daily activities" is misleading because it is inconsistent with the information provided in the PI. Specifically, the PI states that "The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) *but also did not lead to any consistent advantage of tizanidine treated patients on measures of activities of daily living.*" (Emphasis added)

The statement "Begin treatment with 2 mg dose and continue titration to desired effect (up to 36 mg/day)" is misleading because it is inconsistent with the PI. The dosage and administration section of the PI states "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 adverse events make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose)." Therefore, the visual aid misleadingly implies that Zanaflex is effective at a lower dose than has been demonstrated.

The claims "Get Life Moving Again" and "Freer Movement for a More Active Life" constitute an overstatement of the efficacy of Zanaflex. Specifically, these claims misleadingly imply that Zanaflex will improve activities of daily living, and other outcomes that may impact life, when this has not been demonstrated by adequate and well-controlled clinical trials. Similarly, the lenticular graphic of the woman walking away from her shackles implies a much broader freedom of movement that cannot be achieved by short term alleviation of spasticity.

To address these objections, DDMAC recommends that Elan do the following:

1. Immediately discontinue the use of this visual aid, as well as any other promotional material and practices with the same or similar messages.

2. Respond to this letter within ten days. Your response should include a statement of your intent to comply with the above, a list of all promotional materials with the same or similar issues, and your methods for discontinuing these promotional materials.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 10596 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

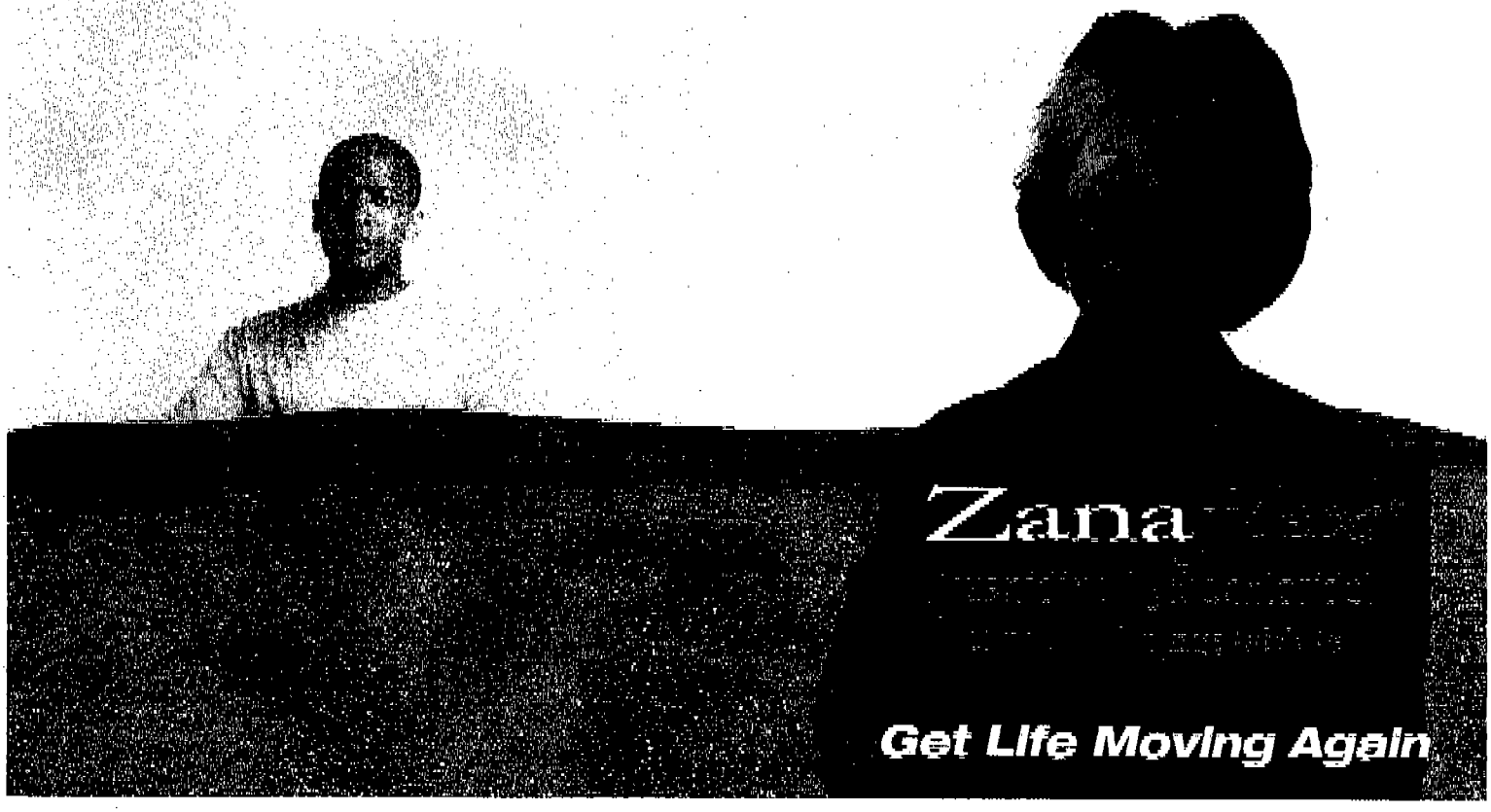
Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

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

/s/

Lisa Stockbridge
1/16/02 04:55:43 PM

Freer Movement
for a More Active Life

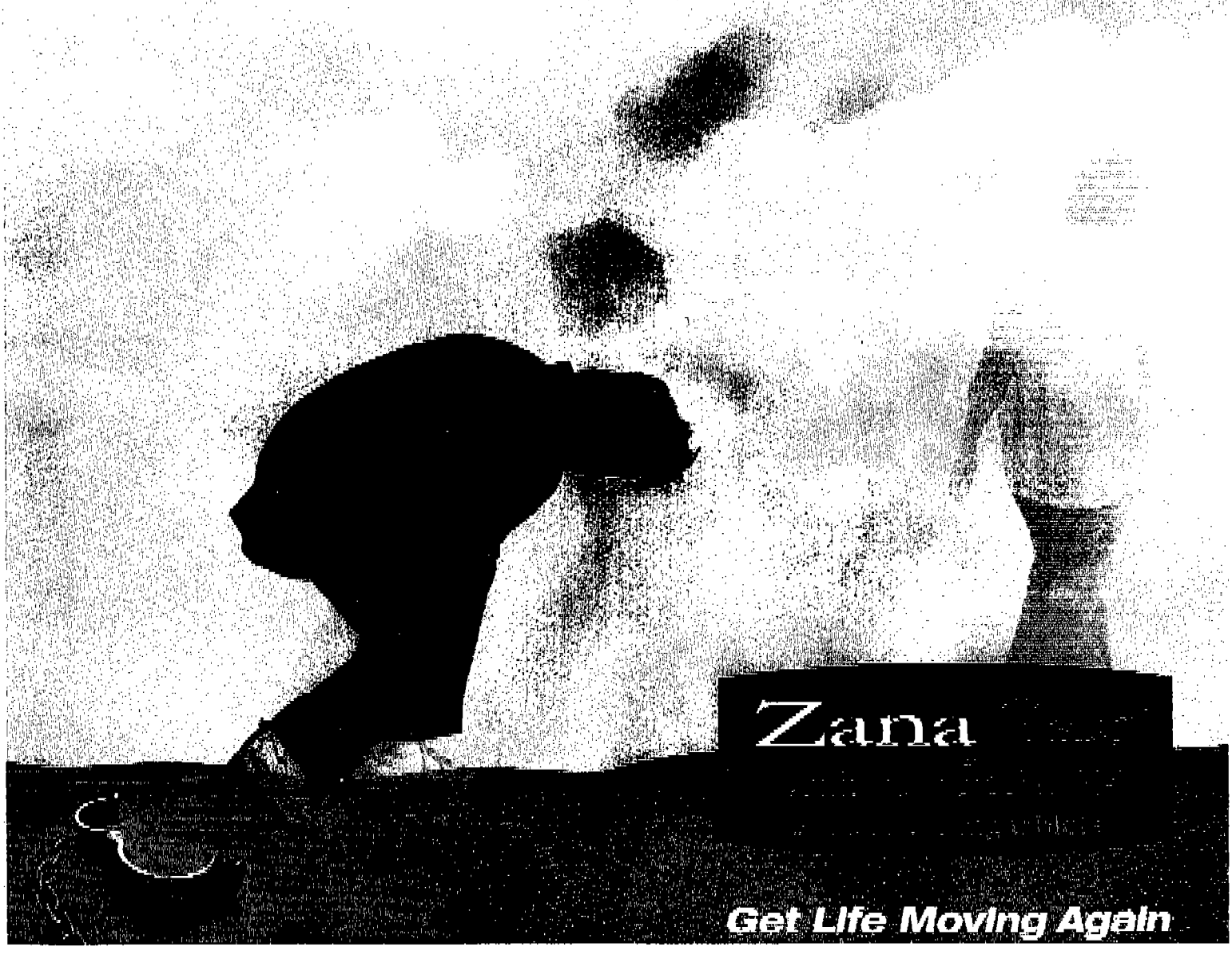


Help Release Patients From Chronic Neuromuscular Symptoms

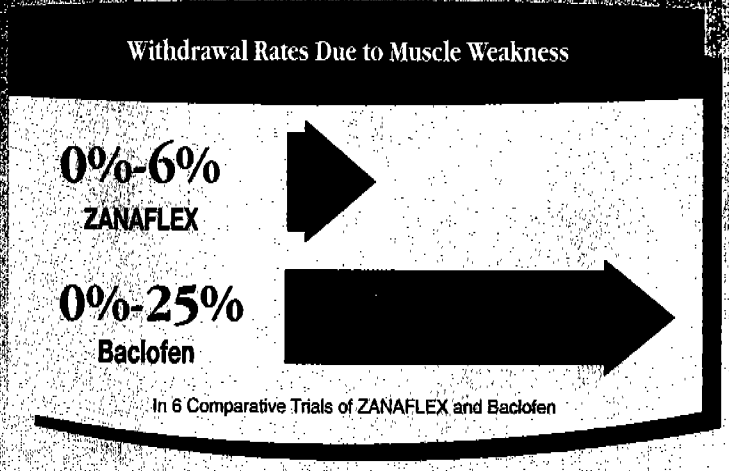
Increase Functionality

- **ZANAFLEX provided a 32% reduction in frequency of interference with daily activities*[1]**

* In stroke patients; daily activities evaluated included mobility, eating, bathing, grooming and dressing.



Increase Functionality Without Affecting Healthy Muscle Strength[2]



- ZANAFLEX demonstrates lower rates of withdrawal due to muscle weakness than baclofen
- Non-opioid

Begin treatment with 2 mg dose and continue titration to desired effect (up to 36 mg/day)[3]

*#1 Prescribed Antispasticity Agent**

**Source™ Prescription Audit (SPA)*; May 2001 Scott-Levin, Inc.

References:
1. Gelber D, Dromerick A, Richardson M, Sergay S. An open label dose titration safety and efficacy study of Zanaflex® (tizanidine HCl) in the treatment of spasticity associated with chronic stroke. Data on file, Athena Neurosciences. 2. Brenner R, Hyman N, Knobler R, O'Brien M, Stephan T. An approach to switching patients from baclofen to tizanidine. *Hosp Med.* 1999;59:778-782. 3. ZANAFLEX® (tizanidine hydrochloride) prescribing information.

élan pharmaceuticals

Zanaflex®
(tizanidine hydrochloride)
2 mg and 4 mg tablets

Get Life Moving Again