DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

F.O.I

JUL 22 1998

TRANSMITTED VIA FACSIMILE

Ron Lapre
Senior Director
Watson Laboratories
311 Bonnie Circle
Corona, CA 91820

RE: NDA# 17-525, 17-658, 18-039
Loxitane (loxapine)
MACMIS # 6853

Dear Mr. Lapre:

As part of our routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed various promotional materials submitted by Watson Laboratories (Watson) on Form FDA 2253, for Loxitane, that are considered to be false or misleading, and in violation of the Federal Food, Drug, and Cosmetic Act, and regulations promulgated thereunder. These materials include, but are not limited to, a clipboard (ID # W-13014), a "Dear Pharmacist" letter (no ID number), fliers (ID # W-13000, W-13002, W-13005, W-13006), a BRC (no ID number), and a brochure (ID # W-13001).

Specifically, DDMAC objects to the following in the above-mentioned promotional pieces:

1. The table entitled "Characteristics of Typical Antipsychotic Agents" is false or misleading because it comparatively rates side effect "potential" among antipsychotic agents without substantial evidence from head-to-head clinical trials.

   Further, the presentation of Loxitane as having a comparatively low incidence of side effects (e.g., "lower potential to cause extrapyramidal side effects than...haloperidol an fluphenazine," "lower incidence of sedation, hypotension, and anticholinergic effects than...chlorpromazime and thioridazine") is: (1) lacking in fair balance because it minimizes the side effects of Loxitane and (2) false or misleading because it implies superiority to these other drug products without substantial evidence from adequate and well-controlled comparative trials.

2. The materials are lacking fair balance either because risk information is diminished (*see for example*, fliers) or absent (*see for example*, the BRC and the brochure # W-13001). Where present, the warning regarding tardive dyskinesia is not presented in a manner that has prominence and readability reasonably comparable to the efficacy information. Instead, it is a subparagraph in small type font. Its importance is further diminished by the prefacing phrase "As with all typical antipsychotic agents..." This warning alone is not considered to be adequate risk information for promotional materials. The materials that fail to mention the common side effects for Loxitane are lacking in fair balance.

3. The mechanism of action of Loxitane has not been established. Therefore, presentations that imply mechanism of action by emphasizing affinity for particular receptors are false or misleading. For example, the presentation "pinpointing the Loxitane difference," with the pushpin penetrating flags that represent the D_4 dopamine receptor and the 5-HT_2 serotonin receptor, is false or misleading. Also, discussion of receptor binding for Loxitane is false or misleading without stating that the antipsychotic mechanism of action of Loxitane is unknown and the clinical significance of the particular receptor binding profile is unknown.

4. The claim that Loxitane has "effectiveness comparable to other typical antipsychotic agents" is misleading because it is not substantiated by adequate and well-controlled comparative efficacy studies.

Requested Actions:

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

1. Immediately discontinue the promotional use of these pieces and all other materials that contain the same or similar deficiencies.

2. Respond to this letter, in writing, by August 5, 1998. This response should include Watson's intent to comply with the above, a list of all violative promotional materials that include the same or similar deficiencies, and Watson's methods for discontinuing their use.

If Watson has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm. 17-B-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 # 6853 in addition to the NDA number.

Sincerely,

/S/

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