DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 5 1999

TRANSMITTED VIA FACSIMILE

Albert P. Mayo
Director, Regulatory Affairs
Organon
375 Mount Pleasant Avenue
West Orange, NJ 07052

RE: NDA# 20-415
Remeron (mirtazapine) Tablets
MACMIS# 6950

Dear Mr. Mayo:

As part of our routine monitoring and surveillance, the Division of Marketing, Advertising, and Communications (DDMAC) has reviewed various promotional materials for Remeron (mirtazapine) Tablets, submitted by Organon on FDA Form 2253. These materials include, but are not limited to, journal ads (ID# ORG-43933, ORG-44542), fact sheets (ID# ORG-43864, ORG-43720, ORG-43727), a visual aid (ID# ORG-43620), brochures (ID#ORG-44330, ORG-44674, ORG-43723), and a letter (ID# ORG-43720). DDMAC finds these materials to be false, misleading, and/or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Specifically, DDMAC has the following objections:

1. Materials that represent Remeron as particularly effective in treating anxiety are false or misleading because Remeron is not an anxiolytic. Adequate and well-controlled studies demonstrate that Remeron is effective in treating depression. Remeron may relieve depression-associated anxiety to the extent that the anxiety is a symptom that is sometimes associated with depression. However, a claim that Remeron is effective in relieving anxiety and materials that focus on Remeron's ability to relieve anxiety are not substantiated. Furthermore, the approved product labeling (PI) for Remeron lists anxiety as a frequent adverse event, thus Remeron has the potential of causing anxiety itself.

2. Claims that Remeron can relieve anxiety induced by selective serotonin reuptake inhibitors (SSRIs) or presentations that imply

that Remeron cannot cause SSRI-induced anxiety, are false or misleading because they lack substantiation.

3. The claim that Remeron can improve symptoms of anxiety "as early as week 1" is false or misleading because it implies, without substantiation, that Remeron has antidepressant effects within the first week. Although early improvements may be seen in non-specific symptoms (such as "sleep disturbance" because a common adverse event of Remeron is somnolence, reported by 54% of patients in the clinical trials), these are not considered to be equivalent to the true antidepressant response that takes several weeks of treatment to achieve.

4. Claims that state or imply that Remeron is safer or more effective because it is more selective than SSRIs are false or misleading because they imply superiority without adequate substantiation from adequate and well-controlled comparative clinical trials. Furthermore, such claims are based on a theoretical mechanism of action derived from pre-clinical studies. This includes, but is not limited to, claims such as: "selecting an agent with serotonin receptor-specific action can reduce the anxiety level dramatically," " [efficacy] with minimal serotonergic side effects," or "anitdepressants with serotonin receptor-specific action offer an effective pharmacologic alternative."

   Similarly, the claim that Remeron is "the only agent that through alpha-2 antagonism [blocks receptors] believed to be responsible for many serotonergic side effects," is false or because there are other alpha-2 antagonists and because the claim is not substantiated by adequate and well-controlled clinical trials.

5. These materials are lacking in fair balance because the risk information is not presented with a prominence and readability that is reasonably comparable to the presentation of information relating to effectiveness. In most cases, the risk information is presented in tiny font as a footnote to the ad or sales aid. Also, risk information is not included in the body of the letter, but is listed in tiny font on the reverse side of the one-page letter along with the references.

6. The claim that Remeron has "no significant inhibition of cytochrome P450 enzymes..." is false or misleading because there have been

no formal drug interaction studies to substantiate this claim. Furthermore, the PI states that Remeron is a substrate for several of these enzymes, and, due to the lack of formal studies, it is not possible to make definitive statements about the risks of coadministration of Remeron with such drugs. The disclaimer used with this claim in promotional materials is not sufficient to correct the impression that there is evidence that there would be little or no interaction with this enzyme system.

7. Presentations that focus on Remeron's lack of adverse events related to sexual dysfunction are misleading and lacking in fair balance because the claims are based on the theoretical mechanism of action for Remeron, and they lack substantiation from clinical trials designed to examine the effect of Remeron on sexual function.

8. The case studies for Remeron (ID#s ORG-44330 and ORG-43723) are misleading because they present Remeron as effective therapy after failure of specific SSRIs and other therapies. In the absence of adequate and well-controlled clinical trials, there is no substantiation for the claim or implication that Remeron would be effective when other SSRI therapy was not. In addition, these case studies are false, misleading, and/or lacking in fair balance due to many of the issues listed above.

To address these concerns, DDMAC recommends that:

a. Organon immediately cease distribution of materials that state or imply these violative messages and/or unbalanced presentations.

b. Provide DDMAC with a written response stating Organon's intent to comply with DDMAC's request. This letter should be received no later than January 19, 1999, and should include a complete listing of the materials that are discontinued as a result of this letter, as well as a list of those materials that will remain in use.

If Organon 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-040, 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 #6950 in addition to the NDA number.

Sincerely,

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