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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fisher Lane
Rockville, Maryland 20852

Re: Docket No. 02P-0249
Comments on Suitability Petition for 7.5 mg Tablets of Mirtazapine

Dear Madam/Sir:

We represent Organon Inc., 375 Mt. Pleasant Avenue, West Orange, New Jersey 02052 ("Organon"). On behalf of Organon, we herewith submit the following comments on the May 29, 2002, Citizen Petition filed by AAC Consulting Group, Docket No. 02-0249 (copy attached). The Citizen Petition requests that the FDA determine that a low-dose tablet of mirtazapine be suitable for an ANDA based upon Organon's NDA 20-415 covering REMERON® (mirtazapine) Tablets. Specifically, AAC Consulting Group requests that a 7.5 mg tablet of mirtazapine be eligible for an ANDA despite the fact that no 7.5 mg tablet is presently on the market and despite the fact that the only approved formulations for the reference listed drug, REMERON® Tablets, are 15, 30 and 45 mg tablets. Because the granting of the Citizen Petition would jeopardize the safe and effective use of mirtazapine, Organon respectfully requests that the FDA deny the Petition in its entirety.

At the outset it must be noted that, in its Citizen Petition, AAC Consulting Group provides no analysis whatsoever of the safety and efficacy issues raised by a potential approval of a 7.5 mg mirtazapine tablet. Instead, the Consulting Group merely recites the same boilerplate language

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that it has used in other suitability petitions.¹ Organon submits that this is far from sufficient to warrant approval of a mirtazapine suitability petition since even a cursory review of the approved labeling for the reference listed drug - that is, for REMERON® Tablets - demonstrates that a 7.5 mg tablet is not appropriate for an ANDA.

I. A 7.5 mg. dosage form of mirtazapine raises serious efficacy issues that were not addressed in the Citizen Petition.

Under the approved labeling for REMERON® Tablets, the minimum recommended “starting dose” is 15 mg/day, administered in a single dose “preferably in the evening prior to sleep.” Organon (and the FDA) did not select this dose randomly or arbitrarily; rather, this dose was based upon voluminous data obtained from the controlled clinical trials submitted with the NDA. These clinical data suggest that some patients may not fully respond to the initial 15 mg/day starting dose, and may benefit from dose increases up to a maximum of 45 mg/day. Therefore, the approved labeling recommends a dose range of between 15-45 mg/day to achieve the antidepressant efficacy of REMERON®. None of the clinical data supports the administration of a dose below 15 mg/day - and, indeed, **nowhere** in the world is the recommended starting dose as low as 7.5 mg/day.

Moreover, a *post hoc* statistical analysis of the clinical trial data demonstrates that the proportion of patients responding increases incrementally with the higher dose levels - for example, at the 30 mg and 45 mg dose. Nothing in the Citizen Petition suggests that there is any

¹ See, e.g., Citizen Petition, dated May 29, 2002, filed by AAC Consulting Group, requesting a determination that a 50 mg clozapine tablet drug product is suitable for an ANDA based on the listed drug Clozaril® Tablets, 25 mg. (copy attached).

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benefit to starting with a dose lower than 15 mg. In addition, there is no evidence provided in the Petition that such a lower dose of mirtazapine would in any way reduce any adverse effects.

Remarkably, AAC Consulting asks FDA to declare suitable for an ANDA a dosage strength that is only one-half of the minimum recommended starting dose. As the sole support for this request, the Citizen Petition claims that a 7.5 mg. tablet “will make it easier and more convenient for patients prescribed smaller daily doses of mirtazapine tablets to take their medication.” In reality, however, approval of a generic 7.5 mirtazapine tablet is only likely to cause serious and harmful confusion among physicians, pharmacists, and/or patients.

II. A 7.5 mg. dosage form of mirtazapine raises substantial and critical safety issues that were likewise not addressed in the Citizen Petition.

Many patients accustomed to completing their day’s antidepressant regimen by taking a single REMERON® tablet may now inadvertently take a single 7.5 mg tablet of their “new” prescription. These patients will be dangerously undermedicated. The risks of undermedication are obvious: REMERON® tablets are indicated for the treatment of patients with major depressive disorders, a condition that when left un- or under-treated poses grave risk to the patient, and to others.

Moreover, because the currently approved strengths of REMERON® tablets are 15, 30, and 45 mg, the approval of a generic 7.5 mg tablet might very well result in prescription errors that could also have disastrous effects on patient safety. For example, a pharmacist could mistake a physician’s notation for a 7.5 mg tablet for that of a prescription for 45 or 75 mg/day, and thus inadvertently overmedicate a patient.

To avoid the problematic fact that a 7.5 mg tablet falls far below the minimum recommended dose of mirtazapine, AAC Consulting asserts that some patients take 22.5 mg/day of REMERON®. However, the number of patients in this subset is very small, even assuming that AAC has accurately reported IMS data - only about 7 percent. The slight convenience afforded to this very small patient cohort is far outweighed by the potential dangers outlined above - namely the possibilities of both undermedication, leaving patients seriously un- or under-treated at the 7.5 mg. dosage level, and overmedication if prescription errors result. And the “convenience” is, indeed, slight. Already Organon has scored its 15 mg tablet to accommodate the 7% or fewer number of patients who daily may be prescribed a 22.5 mg dose of REMERON®. AAC Consulting fails to explain why scoring the 15 mg tablet is not an adequate solution.

Finally, it should be noted that a scored 15 mg tablet is a far safer mechanism for administering a 22.5 mg dose of mirtazapine than the “solution” proposed by AAC Consulting. Whereas those few patients that are prescribed 22.5 mg./day of mirtazapine need only take one and one-half 15 mg. tablets of REMERON®, AAC Consulting’s proposal would result in those patients being required to take three 7.5 tablets to achieve that same small daily dose. Such a result poses unnecessary risks to the safe and effective use of mirtazapine. It is far more manageable for patients -- particularly the elderly and others who must keep up with many different medications on a daily basis -- to take only one and one-half tablets of mirtazapine rather than having to keep track of three tablets at a time. In fact, this is one of the reasons that Organon has chosen to have approved formulations of REMERON in 15, 30, and 45 mg tablets; that is,

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depending on the prescribed daily dose, patients need only take one or one and one-half tablets daily rather than having to juggle multiple tablets to achieve the prescribed dose.

III. A 7.5 mg dosage form of mirtazapine using an unscored tablet violates long-standing FDA Policy.

The Petition's request to produce an unscored tablet presents an additional problem. Under a Policy Guide issued by the FDA's Office of Generic Drugs, the scoring configuration of generic tablets in an ANDA must be identical to that of the reference listed drug. *See* "Scoring Configuration of Generic Drug Products," MAPP 5223.2 (Nov. 1, 1995). In other words, if the listed drug is scored, the generic tablet **must** also be scored, and vice versa. Yet the Petition requests ANDA approval of an unscored tablet despite the fact that the reference listed drug - REMERON® - is scored.

The purpose of FDA's scoring policy is evident: Consistent scoring of listed and generic drugs enables the patient to switch between manufacturers of the same product without encountering problems related to the dose. The goal is obviously to avoid the very risks that will arise should the instant Citizen Petition be granted - specifically, different scoring configurations cause confusion among physicians, pharmacists, and/or patients, and this confusion results in under- or overmedication. Yet the Petition would have FDA ignore this sound reasoning.²

Additionally, consistent scoring assures that neither the generic product nor the listed drug may have an advantage in the marketplace because of a difference in scoring. As FDA notes in

² Petitioner does not even attempt to reconcile FDA's scoring configuration policy with its request for an unscored tablet, despite the fact that the reference listed drug is scored. Instead, Petitioner remains silent on the entire issue.

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the above-referenced Policy Guide, permitting such an advantage is contrary to the intent of the Drug Price Competition and Patent Term Restoration Act of 1984. *Id.* at 1.

Under the FDA's scoring configuration policy therefore, AAC Consulting Group's 7.5 mg unscored tablet of mirtazapine is ineligible for approval under the ANDA process set forth in 21 U.S.C. § 505(j). Therefore, the Petition must be denied.³

IV. Conclusion

In conclusion, the granting of AAC Consulting Group's Citizen Petition would pose significant risks to the safe and effective use of mirtazapine for the treatment of major depressive disorders. Further, the approval of the Petition would conflict with FDA's longstanding

³ FDA's only exception to this policy to date does not apply here. That exception involved a patented scoring configuration, which the innovator company had developed in conjunction with approval of a new titration dosing schedule. When the NDA holder obtained supplemental approval of, and a patent for, its 25 mg dosing schedule, it chose to score its 50 mg reference listed drug. Thus the reference listed drug was scored only after its initial approval at 50 mg and only in order to permit the patented 25 mg titration dosing regimen. FDA agreed that although the generic product's labeling could not include the protected 25 mg titration schedule, it could include the dosing regimen of 50 mg/day because that dose was no longer subject to a period of marketing or patent exclusivity. In short, FDA permitted the unscored 50 mg tablets because this was entirely consistent with the dosing regimen originally approved for the reference listed drug (*i.e.*, one 50 mg tablet daily).

The instant case, however, is readily distinguishable. The approved labeling for REMERON® Tablets does not include a starting dose of 7.5 mg nor does it include a 7.5 mg titration dosing schedule. As previously explained, the recommended starting dose -- 15 mg/day -- can be achieved with a 15 mg/day tablet. Approval of a 7.5 mg tablet is not only entirely unnecessary, but it also poses great risk to the safety and efficacy of the approved use of mirtazapine.



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configuration scoring policy. For the foregoing reasons, Organon respectfully submits that the
Petition should be denied.

Sincerely,

A handwritten signature in black ink that reads "Wayne H. Matelski/dms". The signature is written in a cursive style with a vertical line through the end of the name.

Wayne H. Matelski
Counsel to Organon Inc.

Enclosures