

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-208

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-208

SPONSOR: ORGANON

DRUG: REMERON SOLTAB (MIRTAZAPINE ORALLY DISINTEGRATING TABLETS)

MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER AND SUPPORTING INFORMATION

DATE SUBMITTED: 11/13/00, 11/22/00

DATE RECEIVED: 11/14/00, 11/24/00

MEDICAL OFFICER: ANDREW MOSHOLDER, M.D.

This response includes proposed labeling based upon our approvable letter, a reanalysis of QT data from placebo controlled clinical trials, discussion of 4 postmarketing reports of torsades de pointes, and replies to Biopharmaceutics and Chemistry items in the approvable letter.

Labeling Review

Organon has accepted our proposed labeling, with the following exceptions. The approvable letter labeling they wish to modify relates to the question of cardiac repolarization abnormalities (QT prolongation and torsades de pointes). Language Organon would like to omit is shown in ~~strikeout font~~.

1. Under Precautions-Use in Patients with Concomitant Illness, Organon would like to restore the sentence, "Remeron was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials." This request is based upon their QTc reanalysis (see below).

2. Under Precautions-Drug Interactions, Organon would like to delete the sentence, ~~_____~~

3. Under Adverse Reactions-ECG Changes, Organon proposes the following paragraph:
"Electrocardiograms from Remeron (n=338) and placebo (n=261) groups were compared with respect to (1) mean change from baseline in the QTc interval and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in this variable. No statistically significant differences were observed between the Remeron and placebo treated groups." This would replace our proposed language in the approvable letter, shown below:
~~_____~~
~~_____~~
~~_____~~

4. Organon requests deletion of the following paragraph, in Adverse Reactions:
~~_____~~

QT reanalysis

This Division faxed our recommendations about alternative correction methods for the QT interval to Organon, on 10/19/00. The sponsor had used the Bazett square root correction for calculating QTc, but since mirtazapine raises the heart rate, the square root correction may not be ideal. The suggested alternatives were to determine a fractional exponent X in the expression

$$QTc = QT/RR^X$$

to minimize the effect of heart rate, or to use a linear model

$$QT = a + (b)(RR)$$

in which a and b are derived from the placebo data. Organon employed both approaches. In addition, we requested a reanalysis employing the cube root (Fridericia) correction, which Organon submitted 11/22/00. Finally, we requested an analysis of outliers using a cutoff value of 500 msec, which Organon submitted by email on 11/30/00. The results of these analyses are shown below.

The sponsor included ECG data from 8 placebo controlled trials. To be included, subjects were required to have a baseline ECG and an endpoint ECG obtained no more than two days after discontinuing study medication. A total of 338 mirtazapine subjects, 261 placebo subjects and 168 amitriptyline subjects had the requisite ECG data for this analysis. Organon derived new correction factors for each trial separately, so that there were 8 separate linear models and 8 different exponents applied to the data. That is to say, Organon did not pool all the data first and then determine one correction factor for the pooled data. The tables below summarize the findings.

Percentage of patients with treatment emergent QTc > 450 msec

Correction method	Mirtazapine (n=338)	Placebo (n=261)	p-value
Bazett's	7.4%	4.6%	0.17
Exponent	2.4%	1.9%	0.78
Linear model	1.8%	1.5%	1.00
Fridericia	2.1%	1.5%	0.76

Percentage of patients with treatment emergent QTc ≥ 500 msec

Correction method	Mirtazapine (n=338)	Placebo (n=261)	p-value
Bazett's	0.3%	0.4%	1.00
Exponent	0	0.4%	0.44
Linear model	0	0	-
Fridericia	0	0.4%	0.44

Mean change from baseline in QTc, msec

Correction method	Mirtazapine (n=338)	Placebo (n=261)	p-value
Bazett's	4.9	-3.8	0.002
Exponent	1.3	-2.8	0.063
Linear model	1.1	-2.6	0.070
Fridericia	1.6	-3.1	0.058

For completeness, here are the descriptive statistics for the active control amitriptyline:

Mean change from baseline in QTc, msec

Correction method	Amitriptyline (n=168)	Placebo (n=261)
Bazett's	17.0	-3.8
Exponent	3.9	-2.8
Linear model	2.2	-2.6
Fridericia	4.5	-3.1

Percentage of patients with treatment emergent QTc \geq 500 msec

Correction method	Amitriptyline (n=168)	Placebo (n=261)
Bazett's	1.2%	0.4%
Exponent	0.6%	0.4%
Linear model	0.6%	0
Fridericia	0.6%	0.4%

Of possible significance is the observation that mean QTc decreased in the placebo group, by all three correction methods. This suggests that subjects may have received medications prior to the trial that lengthened the QT interval. Although I agree with Organon that the new p-values are greater than 0.05, they are still rather small. On balance, mirtazapine appears to have a slight effect on repolarization when compared to placebo, but the magnitude of the effect appears smaller with the new analyses.

Torsades de pointes

The sponsor conducted another search for postmarketing cases of Torsades de Pointes (TdeP), using their own safety database and also the FDA's postmarketing database through the Freedom of Information Act. The search disclosed the two cases previously reviewed along with two additional cases. One of the new cases was a 23 year old man who survived an episode of TdeP and subsequently had a defibrillator implanted. However, this patient was also taking cisapride, which is associated with cardiac repolarization abnormalities and ventricular arrhythmias. The second new case was a 79 year old female who already had undergone implantation of a defibrillator. She experienced three new episodes of TdeP, but the reporting physician felt this was more closely linked to use of concomitant gatifloxacin, a quinolone antibiotic associated with QT prolongation. Organon argues that none of these four cases are worth noting in labeling, and that TdeP has been reported for other drugs such as Prozac, Serzone and Effexor.

Conclusions and recommendations

With respect to the new analyses of the QT data, these show that the effect is much smaller than previously indicated by the square root correction. However, there are some doubts about the method the sponsor used; i.e., applying separate correction factors to each trial separately before pooling the data in a meta-analysis. With the cube root correction, the magnitude of QT increase is smaller (1.6 msec), but the mirtazapine-placebo mean difference is still 4.7 msec ($p=0.058$). Organon interprets the p-value as meaning there is essentially no finding, but in my opinion this approach represents over-reliance on a cutoff of 0.05. Furthermore, it is my understanding that Fridericia's correction over-compensates for an increase in heart rate.

On balance, it appears that mirtazapine is associated with a slight effect on cardiac repolarization. Although the degree of QT prolongation in question is modest, recall that the labeling for Avelox (moxifloxacin) notes a 6 msec increase in mean QTc in a bolded Warning. I recommend retaining all our labeling from the approvable letter (see above), but I would not object to replacing Bazett's correction with Fridericia's, as in the following: " ———"

With respect to the labeling regarding postmarketing cases of Torsades de Pointes, there are now the two new cases, although Organon does not consider them any more worthy of reporting in labeling than the first two. Probably the least confounded case is the earlier one that occurred after one initial dose of mirtazapine (please refer to my previous clinical review). Overall I do not feel the sponsor has made a persuasive case for omitting these reports from the labeling; by tradition, causality does not have to be certain for presenting events in the Postintroduction Reports subsection. Even if TdeP is labeled, I think we should ask Organon to process any future TdeP postmarketing cases as 15 day reports.

Please note that these are my own opinions, and that HFD-110 has not been re-consulted.

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 21-208
Div file
HFD-120 Laughren, David, Racoosin, Mosholder

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Andy Mosholder
12/11/00 05:08:21 PM
MEDICAL OFFICER

Thomas Laughren
12/23/00 11:53:20 AM
MEDICAL OFFICER

We have reached final agreement with the sponsor on final labeling [as of 12-21-00] and I recommend proceeding with approval. See memo to file for more detailed comments.--TPL

**APPEARS THIS WAY
ON ORIGINAL**