

NDA 20-415 SE5-011
Sponsor: Organon
Drug: Mirtazapine (Remeron)
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Medical Reviewer: Ann-Kathryn Maust, MD

Executive Summary

The data presented in this supplement do not support the efficacy of Remeron in the treatment of pediatric MDD. Some of the safety findings may be different from what occurred in adult studies and might need to be noted in the labeling. (For details, see safety results for Studies 003045 and 003047 and the Conclusions and Recommendations section at the end of this review.) Also, the safety data is limited to short term exposure. Additional safety and PK information may need to be submitted.

If labeling revisions will be made as a result of this submission, changes might need to be made to the sponsor's proposed labeling.

The sponsor requested pediatric exclusivity but cannot receive it because a long term study was not done.

Clinical Review

I. Introduction and Background

Organon submitted this NDA supplement after receiving a written request to conduct pediatric studies for Remeron (mirtazapine). The proposed indication is pediatric MDD and the proposed dose is 15-45 mg q day.

Andrew Mosholder, MD, provided mentoring during the writing of this review.

II. Clinical Data Sources

The two pediatric studies that were submitted and reviewed are #003-045 and #003-047. Study 003-045 consists of Studies 1 and 2 and is an efficacy and safety study that also includes some PK information. Study 003-047 is a PK study. The sponsor presented safety findings from Studies 003-045 and 003-047 separately.

III. Clinical Review Methods

A. Materials Consulted in Review

The study reports and raw data were reviewed.

B. Evaluation of Financial Disclosure

Mitchell J. Weinberger, Executive Director of Clinical Development at Organon, certified on Form 3454 that he did not enter into any financial arrangements with the investigators that might have influenced the outcome of the study. He also certified that he acted with due diligence to obtain from the listed investigators or from the sponsor the information required under 54.4 and that it was not possible to do so. The reasons given for not obtaining the information from some of the investigators were the following: (1) no longer employed by site and site unable to locate, (2) unable to obtain required certification. A list of investigators was provided.

IV. Review of Efficacy

A. Design of Protocol # 003-045 (Protocol for Studies 1 and 2)

This was a multicenter, randomized, double-blind, placebo-controlled, flexible/fixed dose efficacy and safety study of Remeron in outpatient children and adolescents with MDD. The primary objective was to compare the efficacy (separately for Study 1 and Study 2) and safety of Remeron to placebo. The planned sample consisted of 123 patients in each of the two studies. The patients in Study 1 were to be enrolled at 17 sites, and Study 2 patients were to be enrolled at 15 sites. A maximum of 18 sites could have been used in each study. In each study, 82 patients were to receive Remeron, and 41 patients were to receive placebo for 56 days. Visits occurred weekly, except Visits 5 and 7 (Days 35 and 49, respectively) were optional. Patients aged 7 to less than 18 years must have met DSM-IV criteria for MDD (non-psychotic, chronic or recurrent) on Kiddie-SADS P-L. In addition, patients had to meet the following criteria at baseline: score of ≥ 15 on first 17 items of the HAM-D 21; score of < 70 on C-GAS; raw score of ≥ 40 on CDRS-R; must have never taken Remeron. Patients were to be excluded if they had (1) a history of drug or alcohol abuse within 90 days before the first screening; (2) Bipolar I or II or a parent with Bipolar I; (3) ever been diagnosed with an eating disorder; (4) a concurrent diagnosis of OCD or schizophrenia; (5) made a serious suicide attempt during the current MDD episode or had ever made a suicide attempt that resulted in hospitalization; (6) failed > 2 adequate trials of antidepressants; and for other reasons noted on p. 9 of the protocol. Plasma samples were obtained on Days 28 and 56 (or the subject's final day of treatment) for the purpose of analyzing mirtazapine levels.

The active group received a starting dose of Remeron 15 mg qhs, with the option to increase the dose to 30-45 mg in 15 mg increments during the subsequent weeks (up to Day 28). On and after Day 28, patients were to remain on a fixed Remeron dose. The placebo group received placebo qhs. Concomitant use of any other psychotropic drug was not permitted.

The primary efficacy measure was the total CDRS-R (Children’s Depression Rating Scale-Revised) raw score. Other assessments that were done are noted in the tables on pages 41-42 of volume 6.

Safety evaluations included the following. At screening: VS, weight, height, PE, ECG, hematology, chemistry, UA, urine drug test, pregnancy test. Throughout the study: AE monitoring, VS, weight. At study end or on final treatment day: VS, weight, height, PE, ECG, hematology, chemistry, UA. The last three tests mentioned were also done on Day 28. Approximately 1 month after the end of treatment, a follow-up interview occurred to evaluate any after effects of treatment.

B. Results of Studies 1 and 2

1. Study 1

Sample characteristics of all subjects treated or AST (which means all subjects who were randomized and received at least one dose of study medication): 44 patients were randomized to placebo and 82 to Remeron. The mean age was 12.3 years for the Remeron group and 12.4 years for the placebo group. In the Remeron group, the male to female distribution was 52.4 % to 47.6%. In the placebo group, the distribution was 43.2% to 56.8%. The percentages of Caucasian and African American patients in the study were 83.3% and 11.9%, respectively. The table below shows the distribution of patients by treatment group.

	Remeron	Placebo
Randomized	82	44
All-Subjects-Treated	82	44
Intent-to-Treat*	82	44
Total Discontinued	13	9
Completed Treatment	69	35

* All patients from the AST group who had at least one post-baseline assessment of the primary efficacy variable

In the Remeron group, 5 patients discontinued due to an AE, 2 discontinued due to lack of efficacy, and 6 discontinued due to other reasons. In the placebo group, 1 patient discontinued due to an AE, 3 discontinued due to lack of efficacy, and 5 discontinued due to other reasons.

The table below shows the mean and median doses for the Remeron AST group.

Mean daily dose range	N	Mean	SD	Median
15-30 mg	26	24.2	5.1	25.6
30-45 mg	56	36.6	2.8	37.5

Analyses of efficacy parameters were based on the ITT group using the LOCF approach. See table below for results for the primary efficacy measure. A statistically significant difference was not observed.

Mean Total Raw CDRS-R Scores in Study 1 (p-value = 0.421)

Remeron (N=82)	35.08
Placebo (N=44)	37.24

Analyses of secondary efficacy parameters revealed no statistically significant differences between the Remeron and placebo treatment groups. (CGAS scores were not compared statistically.)

Conclusion: This trial provides no evidence that Remeron is effective for the treatment child and adolescent MDD.

2. Study 2

Sample characteristics of AST: 44 patients were randomized to placebo and 88 to Remeron. The mean age was 11.9 years for the Remeron group and 12.3 years for the placebo group. In the Remeron group, the male to female distribution was approximately 48% to 52%. The distribution in the placebo group was ~ 46% to 55%. The percentages of Caucasian and African American patients in the study were ~ 78% and 13%, respectively. The table below shows the distribution of patients by treatment group.

	Remeron	Placebo
Randomized	88	45
All-Subjects-Treated	88	44
Intent-to-Treat	83	41
Total Discontinued	19	8
Completed Treatment	69	36

In the Remeron group, 4 patients discontinued due to an AE, 6 discontinued due to lack of efficacy, and 9 discontinued due to other reasons. In the placebo group, 2 patient discontinued due to an AE, 3 discontinued due to lack of efficacy, and 3 discontinued due to other reasons.

The table below shows the mean and median doses for the Remeron AST group.

Mean daily dose range	n	Mean	SD	Median
15-30 mg	44	22.2	5.2	24.4
30-45 mg	44	36.4	3.2	37.3

Analyses of efficacy parameters were based on the ITT group using the LOCF approach. See table below for results for the primary efficacy measure. A statistically significant difference was not observed.

Mean Total Raw CDRS-R Scores in Study 2 (p-value = 0.19)

Remeron (N=82)	35.39
Placebo (N=41)	38.76

Analyses of secondary efficacy parameters revealed no statistically significant differences between the Remeron and placebo treatment groups. (CGAS scores were not compared statistically.)

Conclusion: This trial provides no evidence that Remeron is effective for the treatment child and adolescent MDD.