

**Rapporteur's
Public Assessment Report
for paediatric data in EU Worksharing procedure**

**Mirtazapine
(Remeron)**

UK/H/0016/pdWS/001

Marketing Authorisation Holder(s):

Rapporteur:	UK
Start of the procedure (day 0):	12 November 2009
PPdAR: (Day 70)	21 January 2010
Date re-start procedure:(Day 90)	14 May 2010
Date of Finalisation procedure: (Day 120)	18 June 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Remeron tablets 15, 30 and 45 mg Remeron orodispersible tablets 15, 30 and 45 mg Remeron oral solution 15 mg/ml
INN (or common name) of the active substance(s):	Mirtazapine
MAH (s):	
Pharmaco-therapeutic group (ATC Code):	other antidepressants, ATC code: N06AX11
Pharmaceutical form(s) and strength(s):	tablets 15, 30 and 45 mg orodispersible tablets 15, 30 and 45 mg oral solution 15 mg/ml

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1 EXECUTIVE SUMMARY AND RECOMMENDATION

Three completed paediatric study reports for mirtazapine were submitted in accordance with Article 45 EC Regulation No 1901/2006 as amended: one single-dose PK trial in children aged ≥ 7 years and adolescents, one open-label uncontrolled pilot trial and one randomized (R), double-blind (DB), placebo-controlled (PC) efficacy and safety trial adolescents with major depressive disorder (MDD). A clinical overview, a copy of the latest PSUR and referenced publications were also provided.

The MAH considered no changes to the product information are necessary.

The results of the two randomised placebo-controlled trials in major depressive disorder indicate that mirtazapine is not effective in the treatment of major depressive disorder in children and adolescents and causes significant weight gain in approximately half the paediatric patient population.

These results should be reflected in the product information in accordance with the SmPC guideline, Revision 2, September 2009:

4.2 Posology and method of administration

Children and adolescents under the age of 18 years

Remeron should not be used in children and adolescents under the age of 18 years as efficacy was not demonstrated in two short-term clinical trials (see section 5.1) and because of safety concerns (see sections 4.4, 4.8 and 5.1).

4.8 Undesirable effects

Paediatric population:

The following adverse events were observed commonly in clinical trials in children: weight gain, urticaria and hypertriglyceridaemia (see also section 5.1).

5.1 Pharmacodynamic properties

Paediatric population:

Two randomised, double-blind, placebo-controlled trials in children aged between 7 and 18 years with major depressive disorder (n=259) using a flexible dose for the first 4 weeks (15-45mg mirtazapine) followed by a fixed dose (15, 30 or 45 mg mirtazapine) for another 4 weeks failed to demonstrate significant differences between mirtazapine and placebo on the primary and all secondary endpoints. Significant weight gain ($\geq 7\%$) was observed in 48.8% of the Remeron treated subjects compared to 5.7% in the placebo arm. Urticaria (11.8% vs 6.8%) and hypertriglyceridaemia (2.9% vs 0%) were also commonly observed.

The following wording is recommended for the PL:

Before you take Remeron

Take special care with Remeron

Use in children and adolescents under 18 years of age Remeron should normally not be used for children and adolescents under 18 years because efficacy was not demonstrated. Also, you should know that patients under 18 have an increased risk of side effects such as suicide attempt; suicidal thoughts and hostility [...] have not yet been demonstrated. In addition, significant weight gain has been observed in this age category more often when treated with Remeron compared with adults.

Possible side effects

Common:

...

- sleeping problems

In children under 18 years the following adverse events were observed commonly in clinical trials: significant weight gain hives and increased blood triglycerides.

2 INTRODUCTION

MIRTAZAPINE

Mirtazapine is an antagonist at presynaptic α_2 -receptors, 5-HT₂ and 5-HT₃ receptors and histamine H₁ receptors. Antagonism at presynaptic α_2 -receptors results in central disinhibition of serotonin and noradrenalin release. When mirtazapine disinhibits serotonin release by the α_2 -antagonist mechanism, it causes serotonin to be released onto all serotonin receptors; however, mirtazapine simultaneously blocks the actions of serotonin at 5HT_{2A}, 5HT_{2C} and 5HT₃ receptors, leaving net stimulation of only 5HT_{1A} receptors. Mirtazapine is therefore sometimes called a noradrenergic and specific serotonergic antidepressant (NaSSA). It is licensed for the treatment of episodes of major depression in adults.

The combined 5HT_{2C} and histamine H₁ antagonist properties may result in weight gain. The H₁ antagonist properties may contribute to drowsiness and sedation. Mirtazapine is therefore administered in the evening.

Section 5.1 of the SPC states that at therapeutic doses, has practically no effect on the cardiovascular system.

Mirtazapine is extensively metabolized and eliminated via the urine and faeces. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data indicate that CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites.

The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.

SUBMISSION

On 12 November 2009, the MAHs submitted three completed paediatric study reports in accordance with Article 45 EC Regulation No 1901/2006, as amended on medicinal products for paediatric use: one single-dose PK trial in children aged ≥ 7 years and adolescents, one open-label uncontrolled pilot trial and one randomized (R), double-blind (DB), placebo-controlled (PC) efficacy and safety trial adolescents with major depressive disorder (MDD). A clinical overview, a copy of the latest PSUR and referenced publications were also provided.

Based on the available data and in view of the SPC wording adopted in the recently completed article 30 referral procedure (<http://www.emea.europa.eu/htms/human/referral/article30/remeron.htm>), the MAH considers no changes to the EU-SmPC are necessary. The relevant wording adopted in the article 30 referral (http://www.emea.europa.eu/pdfs/human/referral/remeron/remeron_annexI_III_en.pdf) is as follows:

4.2 Children and adolescents under the age of 18 years

Remeron should not be used in children and adolescents under the age of 18 years (see section 4.4).

4.4 Use in children and adolescents under 18 years of age

Remeron should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly

aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany therapy with antidepressants especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of Remeron orodispersible tablets should be given to the patient.

3 SCIENTIFIC DISCUSSION

3.1 NON-CLINICAL ASPECTS

Not applicable.

3.2 CLINICAL ASPECTS

3.2.1 Introduction

The MAH submitted two full clinical study reports (report number US0001102 for trial 3045 and report number US0001106 for trial 3047, both dated April 2001) and one trial publication (Haapasalo-Pesu K-M et al, Mirtazapine in the Treatment of Adolescents with Major Depression: An Open-Label, Multicenter Pilot Study, Journal Of Child And Adolescent Psychopharmacology, 14, 2, 2004, 175-184) plus the corresponding statistical report (Protocol number E-1737 dated 31 December 2004) and a Drug Safety Report on QT interval prolongation (No. 1031745, dated 25 November 2008). A clinical overview was also provided.

3.2.2 Information on the pharmaceutical formulation used in the clinical studies

Study medication in the PK trial and in the R, DB, PC efficacy and safety trial consisted 15 mg mirtazapine tablets. Mirtazapine 30mg tablets were used in the open-label pilot study.

3.2.3 Clinical studies

➤ Study Report 1

➤ **Title:**

A single dose, pharmacokinetic trial of Remeron (mirtazapine) in children and adolescents with major depression, 003047

➤ **Description**

This study was conducted at 2 centres in the United States from April to December 2000.

➤ **Methods**

Study Design: Single dose PK trial.

Study Objectives: To determine the pharmacokinetic parameters of mirtazapine and the major active metabolite (Org 3838, demethylmirtazapine) after a single dose of mirtazapine in both male and female children and adolescents with major depression.

Study population: 17 subjects with a primary diagnosis of major depressive episode (DSM-IV, non-psychotic, chronic or recurrent). Nine subjects aged 7-11; eight subjects aged 12-17)

Study Treatment: Mirtazapine 15 mg tablets, single dose, oral administration, Batch No. CP098164.

Safety Evaluations: Adverse events, incidence of adverse events, laboratory assessments and vital signs

Statistical Methods: Descriptive statistics. Several linear models were explored with \log_e -transform of C_{\max} , AUC_{last} , $AUC_{0-\infty}$ and $t_{1/2}$ and rank of t_{\max} as response variable and age, body weight and gender as explanatory variables. Variable gender was included as class variable, body weight as continuous variable and age either as continuous variable or as class variable (7-11 years or 12-17 years).

➤ **Results**

PK results:

Both C_{\max} and $AUC_{0-\infty}$ of mirtazapine (Org 3770) decrease with increasing age in subjects aged between 7 and 17 years. Per year increase of age the decrease is 9.5% in C_{\max} and 6.2% in $AUC_{0-\infty}$. The decreasing tendency with increasing age is also observed when comparing the $AUC_{0-\infty}$ values in adolescents with those found in young adults receiving 15 mg of mirtazapine. The elimination half-life is longer in adolescents than in children. The elimination half-life increases 0.81% per kg increase of body weight. No differences were seen for t_{\max} .

For demethylmirtazapine (Org 3868) there is a decrease of 15% in C_{\max} per year increase of age. $AUC_{0-\infty}$ decreases 0.92% per kg of increase in body weight. The mean half-life of demethylmirtazapine for females is 55% longer than the mean half-life for males.

Table 1: PK results for mirtazapine

Arithmetic means and ranges (min-max) of the PK parameters for Org 3770

PK parameter	Females Children (n=3)	Females Adolescents (n=4)	Males Children (n=5)	Males Adolescents (n=4)
C _{max} (ng/mL)	51.8 37.2 - 64.9	28.1 18.2 - 51.8	62.5 40.9 - 94.2	41.1 23.4 - 71.0
t _{max} (h)	1.55 1.00 - 2.00	1.65 1.00 - 3.00	1.50 1.00 - 2.00	2.39 1.50 - 4.00
AUC _{0t-last} (ng*h/mL)	483 382 - 645	362 286 - 497	454 354 - 656	414 287 - 650
AUC _{10-∞} (ng*h/mL)	529 411 - 714	466 341 - 685	493 372 - 750	491 303 - 770
t _{1/2} (h)	23.7 22.0 - 25.0	35.3 29.1 - 42.4	22.7 17.8 - 26.6	31.7 18.4 - 48.4
wn-CL _{app} (L/h/kg)	0.719 0.648 - 0.786	0.470 0.187 - 0.746	0.858 0.400 - 1.34	0.608 0.324 - 0.896
wn-V _{z,app} (L/kg)	24.6 22.5 - 28.4	22.5 11.4 - 31.4	27.9 15.4 - 47.0	24.3 22.6 - 28.5

Table 2: PK results for demethylmirtazapine

Arithmetic means and ranges (min-max) of the PK parameters for Org 3838

PK parameter	Females Children (n=3)	Females Adolescents (n=4)	Males Children (n=5)	Males Adolescents (n=4)
C _{max} (ng/mL)	12.8 9.73 - 14.7	4.01 2.69 - 6.62	10.2 7.49 - 13.0	7.97 5.26 - 10.4
t _{max} (h)	6.50 1.50 - 12.0	3.25 2.00 - 4.00	1.70 1.48 - 2.00	2.50 1.50 - 4.00
AUC _{0t-last} (ng*h/mL)	299 272 - 335	102 65.9 - 148	187 127 - 246	181 117 - 316
AUC _{10-∞} (ng*h/mL)	335 312 - 377	159 125 - 202	209 141 - 283	213 137 - 385
t _{1/2} (h)	22.9 19.6 - 24.8	43.5 23.4 - 62.7	18.6 15.0 - 24.7	19.0 10.7 - 29.6
wn-CL _{app} (L/h/kg)	1.13 0.951 - 1.49	1.17 0.907 - 1.38	1.92 1.19 - 2.60	1.40 0.935 - 1.98
wn-V _{z,app} (L/kg)	37.6 26.9 - 52.0	71.8 46.6 - 114	50.2 34.5 - 73.6	37.0 17.0 - 47.0

Rapporteur's comments

The report does not contain a formal comparison of PK data in children and adolescents versus adults.

Given the negative results of the DB, R, PC trial and the lack of a comparison of paediatric versus adult PK data it is considered that PK data do not merit being reflected in the SmPC.

Safety Results:

Sixteen subjects (94.1%) had adverse events. No deaths, serious adverse events, unexpected adverse events or discontinuations due to adverse events were reported. One subject (5.8%) had at least one unresolved adverse events on the final day of the trial. Two subjects in the 11-17 age group had slightly elevated cholesterol values.

Rapporteur's comments

The appendix with the safety data listings is missing from the submitted documentation. There is no information regarding the nature and severity of the unresolved adverse event. In the response to the Request for Supplementary Information (RSI) the applicant stated that information regarding the nature and severity of the unresolved adverse event from trial 003-047 (subject 0003) is not available.

➤ **Study Report 2**

➤ **Study Title:**

Mirtazapine in the Treatment of Adolescents with Major Depression: An Open-Label, Multicenter Pilot Study.

Rapporteur's comments

A full study report for this trial has not been made available, only the trial publication (Haapasalo-Pesu K-M et al, Journal Of Child And Adolescent Psychopharmacology, 14, 2, **2004**, 175-184) plus corresponding statistical report (Protocol number E-1737 dated 31 December 2004). In the response to the RSI the applicant notes that they do not have a clinical study report or appendices. This trial was not performed by the sponsor.

The assessor notes that the positive results of this pilot trial appear to have been published when the (negative) trial results from the 2 randomised double-blind placebo-controlled trials discussed below were already available. The negative trials were not published.

➤ **Description**

This study was conducted at 6 centres in Finland from May 2000 to August 2001.

➤ **Methods**

Study Design: open-label uncontrolled trial with 85 days treatment duration.

Study Objectives: This open-label pilot study was aimed at evaluating the effectiveness and safety of mirtazapine in the treatment of adolescents with major depressive disorder.

Primary efficacy measures: Hamilton Depression Rating Scale (HAM-D-17), Beck Depression Inventory (BDI), Clinical Global Impression (CGI) scale.

Secondary efficacy measures:

Those included response (defined as a reduction of $\geq 50\%$ in the HAM-D-17 total score from baseline to last visit and/or CGI ≤ 2), remission (defined as a HAM-D-17 total score of ≤ 7), anxiety as rated on the Hamilton Anxiety Rating Scale (HAM-A) and suicidal ideation using the HAM-D-17 item 11, dichotomized to no suicidal ideation (scores 0 and 1) and suicidal ideation (scores 2–4).

Study population: 24 subjects aged ≥ 12 and ≤ 18 years nonpsychotic major depressive disorder (DSM-IV), single or recurrent, with a total score of ≥ 18 on the HAM-D-17 rating scale at screening and baseline. Patients with a decrease of $\geq 25\%$ of the HAM-D-17 total score after the run-in period were excluded as were those with lack of response to two adequate antidepressant therapies in the present episode of depression; actual risk of committing suicide, or a serious suicide attempt during the current major depressive episode; and history of or current bipolar I or II disorder, etc.

Study Treatment: 30-mg mirtazapine tablets in a daily dose range of 30–45 mg. Dose levels could be changed on visit days by steps of 15 mg/day from day 8 onwards.

Safety Evaluations: Adverse events.

Statistical Methods: Descriptive statistics using the Intention-To-Treat (ITT) sample with the Last Observation Carried Forward (LOCF).

➤ Results

24 subjects were enrolled. 1 subject did not fulfill the inclusion criteria, 2 subjects stopped the trial because of protocol violations and 1 subject discontinued treatment for lack of efficacy.

The mean daily dose was 32.9 mg of mirtazapine. Fifteen (15) subjects received mirtazapine at a dosage of 30 mg/day, and 8 subjects received a dosage of 45 mg/day.

Efficacy Results:

Results for primary efficacy endpoints are summarized in the Table below. The response rate was 78.3%, the remission rate was 60.9%.

Table 3: Primary outcome measure results of the open-label uncontrolled pilot study

TABLE 2. CHANGES IN OUTCOME MEASURES							
Scale	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12
Hamilton Rating Scale for Depression baseline (SD) 23.0 (2.70) change from baseline (SD) % change	-7.1(4.90)* 30.9	-9.2(5.84)* 40.0	-11.9(4.81)* 51.7	-13.2(4.84)* 57.4	-14.6(4.09)* 63.5	-15.0(4.54)* 65.2	-15.7(5.73)* 68.3
Beck Depression Inventory baseline (SD) 25.3 (12.77) change from baseline (SD) % change	-7(7.13) 27.7	-6.2(7.17) 24.5	-8.5(7.02)* 33.6	-11.4(9.64)* 45.0	-13.3(10.25)* 52.6	-12.4(11.48)* 49.0	-11.8(11.60)* 46.6
Hamilton Anxiety Rating Scale baseline (SD) 18.0 (6.46) change from baseline (SD) % change	-4.1(6.25)* 22.8	-5.3(5.63)* 29.4	-7.7(4.91)* 42.8	-9.2(4.82)* 51.1	-10.9(6.22)* 60.6	-10.0(7.14)* 55.6	-10.8(6.10)* 60.0

*Statistically significant at 0.05 significant level.

Safety Results:

Three serious adverse events were reported in one 14-year old girl (hospitalisation for tonsillar abscess, prolonged hospitalisation as depression continued despite mirtazapine, tonsillectomy).

Eight patients reported eleven treatment-related adverse effects. The most frequent adverse events were tiredness (4 patients), increased appetite (2 patients), and dizziness (2 patients). One patient reported increased dreaming, one nervousness, and one edema in hands. Two of the patients reported tiredness twice; in one case tiredness was assessed as severe.

Assessor's comment

As an open-label uncontrolled trial in a small number of subjects, this study does not contribute any data that would merit being included in the SmPC.

➤ Study Report 3 (Studies 3 and 4)

➤ Study Title:

A multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron® in outpatient children and adolescents with major depressive disorder. Protocol no. 003045

Rapporteur's comments

These were in fact 2 separate trials which were amalgamated by protocol amendment a few months after trial initiation. It would appear that both trials had identical design, but this is not specifically stated in the report. The relevant protocol amendment was not submitted.

➤ Description

The studies were conducted at 35 centres in the USA from February 1999 to November 2000. In September 1999 the 2 trials were combined per protocol amendment.

➤ Methods

Study Design: Multicentre, double-blind, placebo-controlled. Flexible dose for the first 4 weeks (15-45mg) then fixed dose (15 mg, 30 mg or 45 mg) for another 4 weeks (total treatment duration 56 days). No placebo run-in. Follow-up interview 30 days after treatment discontinuation.

Study Objectives: To compare the efficacy (separately for Study 1 and Study 2) and safety of Remeron® to placebo in the treatment of outpatient children and adolescents with major depression (per Amendment 1, September 14, 1999).

Primary efficacy measures: Total CDRS-R raw score.

Secondary efficacy measures:

Clinical Global Impressions Scale CGI, Children's Global Assessment Scale CGAS, 21-item Hamilton Scale for Depression HAM-D, Self-Report for Childhood Anxiety Related Disorder (SCARED), Conners' Global Index –Parent and Teacher Versions.

Assessor's comment

Rater-training was provided and inter-rater reliability was evaluated, although results of this evaluation are not contained in the report. In the response document, the applicant states that inter-rater reliability evaluation was not available from the archives.

Pharmacokinetic assessments:

Plasma samples were collected on Study Days 28 and 56 for comparison with historical data on file from adult males and the influence of demographic variables age, weight and gender were to be explored.

Study population: 259 children and adolescents aged ≥ 7 and ≤ 18 years with nonpsychotic major depressive disorder (DSM-IV), chronic or recurrent, were randomised (Study 1 n=126, Study 2 n= 133). For inclusion, subjects had to have a total score of ≥ 15 on the first 17 items of the HAM-D-21 rating scale, a CGAS score of <70 , and a CDRS-R score ≥ 40 . Psychotherapy could not be started during the trial, but 'supportive care' as defined in the protocol was permitted.

Patients with bipolar disorder or a family history of bipolar disorder, drug/and or alcohol abuse, eating disorders, OCD, schizophrenia, cognitive deficiencies, lack of response to two adequate antidepressant trials; a serious suicide attempt during the current major depressive episode or history of suicide attempt with hospitalization were excluded.

Patients with a history of seizures and with SGOT or SGPT values on screening labs which were equal to or more than 1.25 times the upper limit of normal were also excluded.

Study Treatment: 15-mg mirtazapine tablets in a daily dose range of 30–45 mg. Dose levels could be changed in steps of 15 mg/day from day 8 onwards until day 28, after which the dose had to remain unchanged. Total treatment duration: 56 days.

Safety Evaluations: Adverse events, laboratory evaluations, vital signs, ECG.

Statistics: Based on a two-sample t-test at the $\alpha=0.05$ significance level, there was at least 80% power to detect a treatment difference of 8.7 on the total CDRS-R raw score when the total sample size per study was 123, using a 2:1 ratio in treatment group allocation (mirtazapine to placebo).

➤ Results

259 subjects were randomized (Study n=126, Study 2 n= 133). One subject was randomized to placebo, but was not treated.

The table below gives a break-down of all treated patients per age-group.

Table 4: Number of patients per age group

	Active		Placebo	
	7-11 years	12-17 years	7-11 years	12-17 years
Study 1	30	52	19	25
Study 2	41	47	18	26

All 8 subjects from one study site were excluded as reported data and CRF records were not in compliance with GCP.

32 subjects discontinued treatment. Number (%) of subjects who discontinued per treatment group, and reason for discontinuation (all-subjects-treated population) are summarized in the table below.

Table 5: Reasons for discontinuation

Reason for Discontinuation	Combine Study 1 and Study 2					
	Remeron (N=170)		Placebo (N=88)		Total (N=258)	
	n	%	n	%	n	%
Adverse Event	9	5.3	3	3.4	12	4.7
Lack of Efficacy	8	4.7	6	6.8	14	5.4
Other	15	8.8	8	9.1	23	8.9

Efficacy Results:

Each of the 2 studies failed to meet any of the endpoints, primary and/or secondary.

For study 1, the results of the analyses of all subjects in the mirtazapine-treated group were 35.08±1.58 (SE) mean total raw scores at endpoint versus 37.24±2.16 (SE) in the placebo-treated group. The results for Study 2 were similar: 35.39±3.31 (SE) versus 38.76±2.09 (SE).

A subgroup analysis with respect to the primary endpoint (CDRS-R scores) failed to demonstrate statistically significant effects for either children or adolescents.

Table6: Primary endpoint results

	Total CDRS-R LS mean score at week 8				p-value	
	Active		Placebo		7-11 years	12-17 years
	7-11 years	12-17 years	7-11 years	12-17 years		
Study 1	34.63	35.4	36.01	38.06	0.733	0.469
Study 2	32.64	37.44	35.95	41.38	0.416	0.217

Assessor’s comment

The LS mean scores at *week 1* were as follows:

	Total CDRS-R LS mean score at week 1			
	Active		Placebo	
	7-11 years	12-17 years	7-11 years	12-17 years
Study 1	47.22	52.99	52.25	51.64
Study 2	46.94	50.6	43.88	50.6

Baseline CDRS-R scores were provided for each individual patient, but mean baseline scores were not provided in the study report.

No statistically significant difference was observed between treatment groups at any time point for any of the secondary endpoints (CGI –I responders i.e.” much improved “ or “very much improved”, CGI –S mean change from baseline, HAM-D 21 change from baseline, SCARED total scores or any of the factors of the SCARED, Conners’ Global Index Scale scores, parent- and teacher-versions).

Assessor’s comment

In the assessor’s opinion these results merit reflection in the SmPC.

Pharmacokinetics Results:

An age related effect on the pharmacokinetics of mirtazapine was reported. Plasma concentrations increased significantly ($p \leq 0.05$) by decreasing age. When reaching the age of 14 (male) or 15 (female), plasma concentrations became similar to those of an adult. No significant effects of gender or body weight were found.

Assessor’s comment

The Appendix relating to PK results has not been submitted. An assessment of PK results is therefore not possible.

Safety Results:

There were no deaths. Three serious adverse events were reported on study medication

Subject 0404, a 15-year old male, took mirtazapine 15 mg/day for 7 days. On Day 8 the subject reported worsening of depression with suicidal ideations and was hospitalized. The outcome of the event was unknown. In the opinion of the investigator this SAE was unlikely related to the study drug.

Subject 0801, a 9-year old male, took mirtazapine 15mg/day for 7 days, 30 mg/day for 14 days and 45 mg/day for 31 days. On Day 53 the subject was found difficult to awaken and was taken to the emergency room. Upon awakening, the subject reported he had ingested 4 of his brother’s divalproex sodium tablets ‘on a dare’. The diagnosis was divalproex sodium overdose and the subject was treated and recovered from the event. In the opinion of the investigator this SAE was unlikely related to study drug.

Subject 3001, an 8-year old female, received placebo for 20 days. On Day 10 the subject was hospitalized for elevated temperature of 100.9 degrees F. The fever was presumed to be viral and not due to the drug. The subject was treated with antibiotics and recovered. In the opinion of the investigator this SAE was not related to the study drug.

12 subjects discontinued due to adverse events: 6 subjects in Study 1 (4.8%; 5 mirtazapine; 1 placebo) and 6 subjects in Study 2 (4.5%; 4 mirtazapine; 2 placebo).

The body system with the highest incidence of reported adverse events was psychiatric disorders in 81 (47.6%) subjects in the mirtazapine-treated group including increased appetite in 8.8% and somnolence in 38.8%, compared to 6 (9.1%) subjects on placebo;

Clinically significant weight gain (increase of $\geq 7\%$) was reported in 48.8% of mirtazapine treated subjects as compared to 5.7% in the placebo-treated group.

Heart rate increase was reported for 19 subjects (11.2%) on mirtazapine and 8 (9.1%) on placebo. Decreased heart rate was reported for 5 subjects (2.9%) on mirtazapine and 8 (9.1%) on placebo.

On the ECG, in the mirtazapine-treated group axis deviations were reported in 1 (0.6%) subject, hypertrophy in 3 (1.8%) subjects and ST/T wave abnormalities in 5 (2.9%) subjects. In the placebo-treated group, axis deviations were reported in 1 (1.1%) subject and ST/T wave abnormalities in 3 (3.4%) subjects.

Individual cases of abnormal haematology values were reported for mirtazapine and placebo.

Assessor's comment

The case of suicidal ideation is noted.

Haematological adverse reactions (granulocytopenia, agranulocytosis, aplastic anemia, thrombocytopenia and eosinophilia) are listed reactions.

In the response document, the applicant has supplied adverse event (AE) listings for each individual patient with an adverse event. Summary tables on a SOC basis have not been provided. A review of the AE listings does not add new information over and above the one previously published by the CSM <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf> and quoted by the applicant below – please refer to section 6.2 below.

It is noted that section 5.1 of the SPC states that at therapeutic doses, has practically no effect on the cardiovascular system. However, orthostatic hypotension is listed as a commonly occurring adverse reaction in the present SPC. These appear to be contradictory statements.

In the response document, the applicant states the following:

The phrase that mirtazapine “has practically no effects on the cardiovascular system” refers to cardiovascular effects in general, while orthostatic hypotension is only one effect in this spectrum. In the past the MAH has performed a cumulative analysis of life-threatening arrhythmias on Remeron covering approximately 10 years of post-marketing data and a clinical evaluation (data on file). Based on a meta-analysis of more than 150 clinical studies with Remeron, it was concluded that “[...] there are no sudden death cases associated with Remeron, nor are there any cases of life-threatening arrhythmias reported in association with Remeron. Moreover it is demonstrated that the risk of an arrhythmia-related event is not statistically different from active control or placebo. In addition, ECG analyses in a subset of clinical trials showed that Remeron does not induce clinically relevant QTc interval changes compared to placebo. Furthermore, the extensive post-marketing data of Remeron indicate that an association of Remeron with sudden death, fatal arrhythmias (not reported as sudden death) and life-threatening arrhythmias appears to be coincidental. It is known, however, that Remeron blocks α_2 adrenoceptors and has a relatively low affinity for α_1 -adrenergic receptors. As α_2 and α_1 adrenoceptors mediate peripheral vasoconstriction, this is thought to account for the reported cases of (orthostatic) hypotension. In addition, the meta-analysis of clinical trials data underlying Section 4.8 of the EU-SmPC, shows that orthostatic hypotension occurs “Common” (1.3% versus 1.1% in placebo, $p=0.70$). Therefore, orthostatic hypotension is listed for Remeron. In view of the above, the MAH does not consider the current EU-SmPC wording contradictory.

The Rapporteur maintains that the wording with respect to effects on the cardiovascular system in SPC section 5.1 would benefit from being phrased clearly and unambiguously. We recommend that this be addressed separately from the current procedure.

3.2.4 Periodic Safety Update Report

In the PSUR dated 18 October 2007, covering the period of 01 September 2004 up to 01 September 2007, an analysis of adverse events in different age groups (<12 years, 12 – 17 years, 18 – 64 years, ≥ 65 years) was reported. The MAH concluded that no obvious differences in adverse event reporting pattern were found between the various age groups.

Assessor's comment

In the response document, the applicant clarified that adverse events reported from the submitted trials had not been included in the submitted PSUR analysis of adverse events in different age groups. For the PSUR analysis N.V. Organon's pharmacovigilance database for Remeron containing all spontaneous case reports (incl. those of unsponsored studies) received between 01 September 1994 (international birth date) and 31 August 2007 was used.

Since the analysis of adverse events in different age groups was based on spontaneously reported cases, a true comparison of incidence of adverse events across different age groups cannot be made.

3.2.5 Evidence from paediatric patients included in adult trials

2 patients are identified in the Clinical overview, a 17-year old girl and a 17-year old boy. The boy received 30mg mirtazapine and experienced 'dizziness', 'more hungry' and 'tiredness' (investigator terms). The girl was treated with mirtazapine in the flexible dose regimen of 30 to 45 mg/day and reported 'scabies' (noted when trial was completed), 'asthma (exacerbation)', 'flu', 'painful left foot', 'chest infection', 'injury right hand' (observed after treatment was stopped), 'inflammation of windpipe', 'chest infection'.

Assessor's comment

These cases do not contribute information that would merit being included in the SPC.

3.2.6 Evidence from literature

The following publications were referenced in the Clinical Overview:

1. Bronstein et al., Annual report of the American Association of Poison Control Centers' national poison data system. *Clinical Toxicology* 2007;45:815-917
2. Anttila SAK, et al. Fluvoxamine augmentation increases serum mirtazapine concentrations three- to four fold. *Ann of Pharmacotherapy* 2001; 35 (Oct):1221-3.
3. Turkel SB et al. Possible serotonin syndrome in association with 5-HT3 antagonist agents. *Psychosomatic s* 2001;42:258-60.
4. Bremner JD, et al. Safety of mirtazapine in overdose. *J Clin Psychiatry* 1998;59:233-235.
5. Brkanac Z, et al. Prazosin in PTSD. *J Am Acad Child Adolesc Psychiatry* 2003;42(4):384-385
6. Ayton A. Selective resolution of bulimic symptoms and increased suicidal behaviour in an adolescent during fluoxetine treatment. *Int J Psych Clin Pract* 2003; 7: 213-216
7. Gail Griffith. *Will's choice: a suicidal teen, a desperate mother and a chronicle of recovery.* HarperCollins 2005
8. Montanas-Rada et al. Choking phobia: clinical presentation of nine cases. *An Psiquiatr* 2005;21(6):289-296
9. Albertini G, et al. Compulsive masturbation in infantile autism treated by mirtazapine. *Pediatr Neurol* 2006;34:417-418.

10. Savva D et al. Manualised Cognitive-Behavioural Therapy in the intensive treatment of Adolescent Obsessive Compulsive-Disorder, Behaviour Change 2006;23-3;200-220.
11. Posey DJ et al. A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. J Child Adolescent Psychopharmacol 2001;11:267-277.
12. Personne et al., Toxicity at overdose with new antidepressants. Lakartidningen 2008;105:125-127
13. Goyal et al., Mirtazapine-induced manic switch in adolescent unipolar depression. Australian and New Zealand Journal of Psychiatry 2008;42:1068-1069

The MAH states that do not point to significant safety concerns that would be specific to this age category or requiring warnings other than the ones currently present in the labeling of mirtazapine, but does not discuss any of the publications.

Assessor's comment

In the response document, the applicant clarified that the search criteria used for identifying published case reports data from the pharmacovigilance database included: 'suspect drug: Remeron/mirtazapine' and 'source: literature' and 'age <18 years' or age group 'neonate', 'infant', 'child' or 'adolescent'. With respect to the published data, the following search criteria were used: 'Remeron/mirtazapine', 'indication: (major)depression/depressive disorder' and age group: child(ren)/adolescents/p(a)ediatric/age <18 years; the following databases have been searched: Medline, Embase, Biosis and Derwent Drug File.

The data reported from literature are generally either individual case reports or open-label naturalistic studies and do not warrant being included in the product information. The SmPC already contains a warning statement regarding concomitant use of other serotonergic active substances (pharmacodynamic interactions – serotonin syndrome).

The pharmacokinetic interaction with fluvoxamine, a potent inhibitor of CYP1A2 and to a lesser extent of CYP2C and CYP3A4, is not addressed in the SmPC. The information related to drug-drug interactions with Remeron (mirtazapine) has been assessed as part of an article 30 referral in 2007/2008 (procedure No. EMEA/H/A-30/877), which did not result in the inclusion of a warning statement.

In the response to the RSI the MAH agreed that the cited publications may be indicative of an interaction of mirtazapine with fluvoxamine/SSRIs but noted that there are methodological uncertainties (about e.g. sampling time, comedication, assay reliability/remeasurement, missing doses, controls) that would need to be addressed before proceeding to include such findings in the product information. In addition, mechanistically, fluvoxamine may be a strong inhibitor of CYP1A2 and weak inhibitor of CYP3A4, but that still leaves the paths of CYP2D6 and the major part of CYP3A4 free for metabolism. This may suggest that a significant pharmacokinetic effect of fluvoxamine requiring dose adjustment of mirtazapine is unlikely. Of note, the Periodic Safety Update Reports on Remeron includes a section on Interactions. Relevant (new) data is thus periodically discussed in this section and necessary actions will follow, if deemed necessary. Discussion on clinical aspects

3.3 DISCUSSION ON CLINICAL ASPECTS

Two randomized placebo-controlled trials in major depressive disorder provide evidence of a lack of efficacy of mirtazapine in the treatment of major depressive disorder in children and adolescents. Neither of the trials included an active comparator for assay sensitivity. The fact that the negative results were replicated in 2 trials conducted at different sites provides reassurance that this is not a spurious finding.

Significant weight gain was observed in approximately half the paediatric patient population. This is of clinical concern and should therefore be stated in the product information. In addition, two currently unlisted adverse events (urticaria and hypertriglyceridaemia) were observed commonly in the paediatric clinical trials – these should also be included in the product information. Other adverse events such as somnolence are already included in section 4.8 of the SmPC.

On the basis of the submitted evidence, the ratio of benefits to risks for mirtazapine in the paediatric population is considered negative. The submitted efficacy and safety data warrant inclusion in the product information.

4 OVERALL CONCLUSIONS AND RECOMMENDATIONS

The results of the two randomised placebo-controlled trials in major depressive disorder indicate that mirtazapine is not effective in the treatment of major depressive disorder in children and adolescents and causes significant weight gain in approximately half the paediatric patient population.

Given the negative results of the two trials and the lack of a comparison of paediatric versus adult PK data it is considered that PK data do not merit being reflected in the SmPC.

Following input of concerned European member states, the following final wording is recommended in accordance with the SmPC guideline, Revision 2, September 2009:

4.2 Posology and method of administration

Children and adolescents under the age of 18 years

Remeron should not be used in children and adolescents under the age of 18 years as efficacy was not demonstrated in two short-term clinical trials (see section 5.1) and because of safety concerns (see sections 4.4, 4.8 and 5.1).

4.8 Undesirable effects

Paediatric population:

The following adverse events were observed commonly in clinical trials in children: weight gain, urticaria and hypertriglyceridaemia (see also section 5.1).

5.1 Pharmacodynamic properties

Paediatric population:

Two randomised, double-blind, placebo-controlled trials in children aged between 7 and 18 years with major depressive disorder (n=259) using a flexible dose for the first 4 weeks (15-45mg mirtazapine) followed by a fixed dose (15, 30 or 45 mg mirtazapine) for another 4 weeks failed to demonstrate significant differences between mirtazapine and placebo on the primary and all secondary endpoints. Significant weight gain ($\geq 7\%$) was observed in 48.8% of the Remeron treated subjects compared to 5.7% in the placebo arm. Urticaria (11.8% vs 6.8%) and hypertriglyceridaemia (2.9% vs 0%) were also commonly observed.

The following wording is recommended for the PL:

Before you take Remeron

Take special care with Remeron

Use in children and adolescents under 18 years of age Remeron should normally not be used for children and adolescents under 18 years because efficacy was not demonstrated. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility [...] have not yet been demonstrated. In addition, significant weight gain has been observed in this age category more often when treated with Remeron compared with adults.

Possible side effects

Common:

...

- sleeping problems

In children under 18 years the following adverse events were observed commonly in clinical trials: significant weight gain, hives and increased blood triglycerides.