CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-208

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 12/30/99, 3/7/2000, 4/28/2000

NDA:	21-208
Name of Drug:	Remeron (Mirtazapine) 15mg, 30mg and 45mg Orally Disintegrating Tablets
Indication of Drug:	Antidepressant
Sponsor:	Organon Inc., West Orange, NJ
Type of Submission:	Original NDA
Reviewer:	Hong Zhao, Ph.D.

Introduction

Remeron (mirtazapine) Tablets have been approved since June 1996 for use in depression. The sponsor has developed a new dosage form, orally disintegrating tablets (ODT, ——— ') of mirtazapine for ease of use by patients who are not able to swallow tablets, as this dosage form will disintegrate rapidly on the tongue and can be swallowed with saliva. This NDA contains a bioequivalence study comparing the 30 mg ODT with the 30 mg conventional Remeron Tablet. Based on the fact that the dosage strengths of the mirtazapine ODT are compositionally proportional (Appendix I) and that the drug follows linear kinetics, the sponsor has requested a waiver of in vivo bioequivalence study for the 15mg and 45mg tablets. In this NDA, the sponsor has also provided in vitro dissolution profiles (N=12 per strength) for supporting the approval of the 15mg and 45mg orally disintegrating tablets.

Pharmacokinetics of Mirtazapine

After oral administration of Remeron tablets, mirtazapine is rapidly absorbed with peak plasma concentrations reached at about 2 hours after dosing. The drug undergoes substantial first pass metabolism resulting in about 50% bioavailability. Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The elimination half-life is 20-40 hours in healthy volunteers. Short half-life (around 20 hours) is observed in young males, and longer half-life up to 65 hours is also observed, especially in older people where kidney or liver is damaged. Females generally show longer half-life and higher AUC values than males. Steady-state is reached within 3 to 5 days of once daily dosing. Food intake appears to have no clinically important influence on the pharmacokinetics of Remeron tablets. Mirtazapine is a racemic mixture and the (-) enantiomer has longer elimination half-life (twice long) and higher plasma levels (three times high) compared to that of (+) enantiomer. Mirtazapine plasma protein binding is around 85%.

Mirtazapine is extensively metabolized through demethylation and hydroxylation followed by glucuronide conjugation. CYP2D6 showed the highest enzymatic activity towards the formation of the 8-hydroxy metabolite of mirtazapine, followed by CYP1A2. CYP1A2 showed the highest activity towards the formation of N-demethyl mirtazapine and the N-oxide of mirtazapine, followed by CYP2D6 and CYP3A4. There are no indications that genetic polymorphisms affect the pharmacokinetics of mirtazapine since N-oxidation, 8-hydroxylation, N-demethylation and glucuronidation are different routes of

elimination, which can substitute each other. Mirtazapine is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels.

Bioequivalence Study Review

Study Design

The bioequivalence study (Protocol 22527) is entitled "A Single-dose, fasting, open, 2-way cross-over bioequivalence trial on Org 3770 30 mg orally disintegrating tablet (——) versus 30 mg Org 3770 marketed tablet in 40 healthy subjects". The study design is illustrated as follows:

	Single Dose	Water	Washout Period
Treatment 1	30 mg CT	200 ml	2 weeks
Treatment 2	30 mg ODT	No	2 weeks

N=40 (20 males and 20 females, crossover), blood sampling time: right before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours after dosing

CT= Remeron conventional tablet, Lot 207394; ODT=Remeron orally disintegrating tablet, Lot 990017.

Bioanalysis

Mirtazapine concentration in human plasma was analyzed using ——

—— The lowest limit of quantitation (LLOQ) The assay covered the range of —— mirtazapine when 1 ml plasma was used. Calibration curves were calculated using quadratic weighted (1/conc.) regression. The assay has been validated for use in human pharmacokinetic study.

Study Results

See Appendix II for mean plasma concentration vs. time profiles. The values for mirtazapine pharmacokinetic parameters (Mean±SD) generated from the bioequivalence study are listed below:

	C_{max} (ng/ml)	AUC_t (ng.h/ml)	$AUC_{0-\infty}$ (ng.h.ml)	T_{max} (h)	$t_{1/2}$ (h)
Reference Tablet	81.6±38.4	710±256	760±299	1.8±1.4	25.8±9.3
Test Tablet	86.9±38.9	778±267	830±316	2.3±1.3	26.9±8.5
Point Estimate	1.072	1.103	1.101		
90% C.I.	0.948-1.212	1.052-1.156	1.049-1.156		

Mean values represent arithmetic means.

In addition, subgroup analysis (by gender) reveals that the extent of exposure to mirtazapine for both conventional tablets and ODT is higher in female subjects as compared to that in male subjects as shown below:

	C_{max} (ng/ml)	AUC_t (ng.h/ml)	$AUC_{0-\infty}$ (ng.h.ml)
Reference Tablet (M/F)	67.2 / 81.2	541 / 825	555 / 901
Test Tablet (M/F)	72.4 / 86.6	630 / 862	647 / 937

Summary

- The 90% confidence intervals for the primary parameters C_{max}, AUC_t and $AUC_{0-\infty}$ are within the acceptance range 0.8-1.25, indicating that the 30 mg orally disintegrating tablet (——) is bioequivalent to the 30 mg marketed conventional tablet.
- Gender effect was found for the extent of exposure, being higher by 50% in female subjects than that in male subjects. This is similar to that seen for the conventional tablets in the NDA 20,415.

Safety

Both treatments were safe and tolerated. Adverse drug reactions were in line with the product labeling. No important clinically significant effects on laboratory tests, vital signs or ECG were observed.

Dissolution Study Review

Dissolution Method

The dissolution method and specification used for the orally disintegrating tablets are the same as approved for currently marketed conventional Remeron tablets.

Apparatus: USP Apparatus 2 (Paddle) at 50 rpm
Medium: 900 ml 0.1 N HCL at 37°C±0.5°C
Specification: (——) in 15 minutes

Dissolution Results

Dissolution data are provided in the NDA for 30mg biobatches of conventional Remeron tablet and Remeron ODT, and 15mg (2 batches) and 45mg (2 batches) of Remeron ODT at 7.5, 15, 30, 45 and 60 minutes. See Appendix III for individual tablet dissolution data up to 60 minutes. The mean data (% released) at 7.5 min and 15 min are shown below:

Lot#	30mg 207394*	30mg 990017**	15mg 990018	15mg 990019	45mg 990020	45mg 990021
7.5min	67±12.1	104±2.6	101±6.1	103±5.5	112±2.6	110±6.6
15min	98±2.6	105±2.0	102±6.0	104±5.0	112±2.2	111±6.5

*Biobatch of Remeron 30mg Conventional tablets. ** Biobatch of Remeron 30mg ODT.

Summary

- N (——), of the drug released in 7.5 minutes for all the ODT batches tested.
- The dissolution data for all the batches tested meet the specification for Remeron tablets (in 15 minutes).
- The 15mg and 45mg orally disintegrating tablets have comparable dissolution performance as the 30mg orally disintegrating tablets (biobatch).

Proposed Labeling

CLINICAL PHARMACOLOGY (Pharmacokinetics)

A pharmacokinetic study has shown REMERON® SolTab™ Orally Disintegrating Tablets are bioequivalent to REMERON® (mirtazapine) Tablets. *with respect to maximum concentration (C_{max}), the area under the curve from zero to the last measurable concentration ($AUC_{0-tlast}$), and the area under the cure from time zero to infinity ($AUC_{0-\infty}$).*

Comment 1

The results of the bioequivalence study show that the 30 mg orally disintegrating tablet ——— is bioequivalent to the 30 mg marketed conventional tablet with respective to C_{max}, AUC_t and $AUC_{0-\infty}$. From an OCPB perspective, the approval of the 30 mg ODT tablets can be granted.

Comment 2

Based on the following facts: (1) the dosage strengths of the mirtazapine orally disintegrating tablets are compositionally proportional, (2) the drug follows linear kinetics, and (3) dissolution data show that the 15mg and 45mg orally disintegrating tablets have comparable dissolution performance as the 30mg orally disintegrating tablets that were used in the bioequivalence study, the approval of 15mg and 45mg orally disintegrating tablets can be granted.

Comment 3

The proposed labeling in the pharmacokinetics subsection is modified and the sponsor should adapt the labeling as follows:

REMERON® SolTab™ Orally Disintegrating Tablets are bioequivalent to REMERON® (*mirtazapine*) Tablets.

Recommendation

From an OCPB perspective, the approval of the 15mg, 30mg and 45mg Remeron Orally Disintegrating Tablets can be granted. The sponsor is requested to adopt the following dissolution method and specification for all strengths of Remeron Orally Disintegrating Tablets:

Apparatus:	USP Apparatus 2 (Paddle) at 50 rpm
Medium:	900 mL 0.1 N HCL at 37°C±0.5°C
Specification:	——— in 15 minutes

Also, the sponsor should adapt the following labeling in the Pharmacokinetics subsection: ——— ...s are bioequivalent to REMERON® (mirtazapine) Tablets."

Please convey the above Recommendation to the sponsor.

Hong Zhao, Ph.D. /S/ 9/18/2000

RD/FT Initialed by Raman Baweja, Ph.D. /S/ 9/18/00.

cc: NDA 21-208 (———), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

Complete Composition

Table 1: REMERON® ORALLY DISINTEGRATING TABLETS - 15 mg

Names of Ingredients	Quantity/Unit	% w/w	Function	Reference to Standards
Active Ingredients				
Mirtazapine (as coated Mirtazapine containing 24% active ingredient)*	g		Active drug	Organon - raw Mirtazapine
				Mirtazapine
Other Ingredients				
Mannitol	ng		Diluent	Ph. Eur., USP
Granular Mannitol	ng		Diluent	Ph. Eur., USP
Crospovidone	ng		Disintegrant	Ph. Eur., NF
Sodium Bicarbonate,	ng		Effervescent Couple	Ph. Eur., USP
Citric Acid, Anhydrous Fine Granular	ng		Effervescent Couple	Ph. Eur., USP
Microcrystalline Cellulose	ng		Compression Aid	Ph. Eur., NF
Aspartame	ng		Sweetner	Ph. Eur., NF
Magnesium Stearate	ng		Lubricant	Ph. Eur., NF
Natural & Artificial Orange Flavor	ng		Flavor	GRAS (Generally Recognized as Safe)

* Actual amount to be added is calculated from the assay of a coated Mirtazapine batch. The amount of mannitol and granular mannitol is adjusted accordingly.

Qualitative and Quantitative Composition

Remeron® (mirtazapine) Tablets -

INGREDIENTS	15 mg Tablet
Tablet Core:	
Mirtazapine (100%)	15.0 mg
Starch, NF (Corn	mg
Hydroxypropyl Cellulose, NF	ng
Magnesium Stearate, NF	5 mg**
Colloidal Silicon Dioxide, NF	mg
Lactose, NF qs to	0 mg
Coating Layer:	
Hydroxypropyl Methylcellulose, USP	mg
Polyethylene Glycol 8000, NF	mg
Titanium Dioxide, USP	mg
Ferric Oxide, NF (Yellow)	mg
Ferric Oxide, NF (Red)	-

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Complete Composition

Table 2: REMERON® ORALLY DISINTEGRATING TABLETS - 30 mg

Names of Ingredients	Quantity/Unit	% w/w	Function	Reference to Standards
Active Ingredients				
Mirtazapine (as coated Mirtazapine containing 24% active ingredient)*	mg		Active drug	Organon - raw Mirtazapine Mirtazapine
Other Ingredients				
Mannitol	mg		Diluent	Ph. Eur., USP
Granular Mannitol	mg		Diluent	Ph. Eur., USP
Crospovidone	mg		Disintegrant	Ph. Eur., NF
Sodium Bicarbonate,	mg		Effervescent Couple	Ph. Eur., USP
Citric Acid, Anhydrous Fine Granular	mg		Effervescent Couple	Ph. Eur., USP
Microcrystalline Cellulose	mg		Compression Aid	Ph. Eur., NF
Aspartame	mg		Sweetner	Ph. Eur., NF
Magnesium Stearate	mg		Lubricant	Ph. Eur., NF
Natural & Artificial Orange Flavor	mg		Flavor	GRAS (Generally Recognized as Safe)

* Actual amount to be added is calculated from the assay of a coated Mirtazapine batch. The amount of mannitol and granular mannitol is adjusted accordingly.

Qualitative and Quantitative Composition

Remeron® (mirtazapine) Tablets -

INGREDIENTS	30 mg Tablet
Tablet Core:	
Mirtazapine (100%)	mg
Starch, NF (Corn	mg
Hydroxypropyl Cellulose, NF	ıg
Magnesium Stearate, NF	mg**
Colloidal Silicon Dioxide, NF	mg
Lactose, NF qs to	) mg
Coating Layer:	
Hydroxypropyl Methylcellulose, USP	mg
Polyethylene Glycol 8000, NF	mg
Titanium Dioxide, USP	mg
Ferric Oxide, NF (Yellow)	mg
Ferric Oxide, NF (Red)	mg

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Complete Composition

Table 3: REMERON® ORALLY DISINTEGRATING TABLETS - 45 mg

Names of Ingredients	Quantity/Unit	% w/w	Function	Reference to Standards
Active Ingredients				
Mirtazapine (as coated Mirtazapine containing 24% active ingredient)*	) mg		Active drug	Organon - raw Mirtazapine Mirtazapine
Other Ingredients				
Mannitol	) mg		Diluent	Ph. Eur., USP
Granular Mannitol	) mg		Diluent	Ph. Eur., USP
Crospovidone	) mg		Disintegrant	Ph. Eur., NF
Sodium Bicarbonate	mg		Effervescent Couple	Ph. Eur., USP
Citric Acid, Anhydrous Fine Granular	mg		Effervescent Couple	Ph. Eur., USP
Microcrystalline Cellulose	mg		Compression Aid	Ph. Eur., NF
Aspartame	mg		Sweetner	Ph. Eur., NF
Magnesium Stearate	mg		Lubricant	Ph. Eur., NF
Natural & Artificial Orange Flavor	mg		Flavor	GRAS (Generally Recognized as Safe)

* Actual amount to be added is calculated from the assay of a coated Mirtazapine batch. The amount of mannitol and granular mannitol is adjusted accordingly.

Qualitative and Quantitative Composition

Remeron® (mirtazapine) Tablets -

INGREDIENTS	45 mg Tablet
Tablet Core:	
Mirtazapine (100%)	45.0 mg
Starch, NF (Corn	mg
Hydroxypropyl Cellulose, NF	ng
Magnesium Stearate, NF	ng
Colloidal Silicon Dioxide, NF	ng
Lactose, NF qs to	) mg
Coating Layer:	
Hydroxypropyl Methylcellulose, USP	ng
Polyethylene Glycol 8000, NF	ng
Titanium Dioxide, USP	ng
Ferric Oxide, NF (Yellow)	
Ferric Oxide, NF (Red)	-

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Table 1-1 Descriptive statistics of pharmacokinetic parameters by treatment (n=40).

TREATMENT	PARAMETER	Arithmetic mean	Geometric mean	SD	CV (%)
Ref	Cmax (ng/mL)	81.6	73.9	38.4	47.0
	Tmax (h)	1.81	-	1.42	78.5
	Thalf (h)	25.8	-	9.32	36.1
	AUC0-tlast (ng.h/mL)	710	668	256	36.0
	AUC0-inf (ng.h/mL)	760	707	299	39.3
Test	Cmax (ng/mL)	86.9	79.2	38.9	44.7
	Tmax (h)	2.27	-	1.25	55.2
	Thalf (h)	26.9	-	8.51	31.7
	AUC0-tlast (ng.h/mL)	778	737	267	34.4
	AUC0-inf (ng.h/mL)	830	779	316	38.1

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- : not applicable

Compound: [redacted] (P22527), SAS program: TAB_PARMEAN.SAS /Date:26APR00 11:56

9600 26APR00

Table 1-2 Point Estimates of the Ratio of the (Least-Squares) Geometric Means of the Test Treatment over the Ref Treatment with Corresponding 90 % Confidence Intervals.

Parameter	Point Estimate (Test/Ref)	Lower 90% Confidence Limit	Upper 90% Confidence Limit
AUC0-inf (ng.h/mL)	1.101	1.049	1.156
AUC0-tlast (ng.h/mL)	1.103	1.052	1.156
Cmax (ng/mL)	1.072	0.948	1.212

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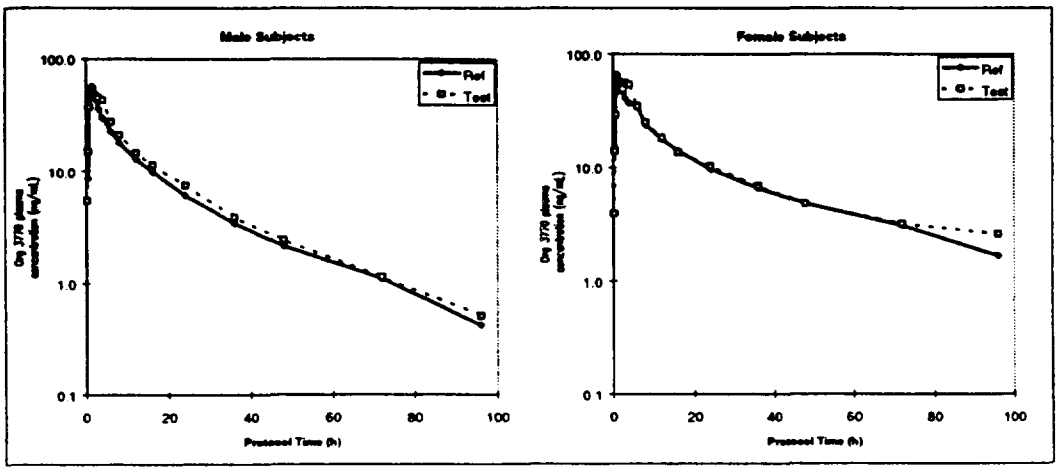
The individual and mean Org 3770 plasma concentrations are given in Appendix B: Pharmacokinetics, Section B.2. No concentrations were excluded from the calculation of the mean concentrations. Deviations from the protocol time are presented in Appendix B: Pharmacokinetics, Section B.2. Individual and mean plasma concentrations are graphically presented in Appendix B: Pharmacokinetics, Section B.3 and B.5. In addition, the mean C-t curves per gender and treatment are presented in Figure 1.

Figure 1 Mean Concentration Versus Time Curves per Gender and Treatment



Data taken from Appendix B: Pharmacokinetics, Section B.2.

Two samples were missing. From subject 24 (Treatment T) 2 h after dosing and from subject 40 (Treatment R) 2.5 h after dosing, no concentration was reported.

8.7.3 Pharmacokinetic Parameters

Individual and mean pharmacokinetic parameters are tabulated in Appendix B: Pharmacokinetics, Section B.6. Mean values of the parameters are also given in Table 4.

Table 4 Mean Pharmacokinetic Parameters per Gender and Treatment

Parameter	Gender	R Tablet	T tablet
C_{max}	M	67.2	72.4
(ng/mL)	F	81.2	86.6
AUC_{0-last}	M	541	630
(ng h/mL)	F	825	862
$AUC_{0-\infty}$	M	555	647

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Report 22527 (FR 99.052.2 CP/99/1212), Final version: 01-Nov-1999

(ng.h/mL)	F	901	937
t_{max}	M	1.50	1.50
(h)	F	1.25	2.00

Data taken from Appendix B: Pharmacokinetics, Section B.6.
Geometric mean (median for t_{max}) for all parameters (females n=20, males n=20)

The data points selected for calculation of the elimination half-life are graphically presented in Appendix B: Pharmacokinetics, Section B.4.

For subject No. 7 (Treatment R), 11 (Treatment R) and 32 (Treatment T), it was decided to not use the last measurable concentration of each plasma concentration versus time curve for the calculation of the elimination half-life and the $AUC_{0-\infty}$ because these concentrations were obviously too high. Nevertheless for the calculation of the $AUC_{0-tlast}$ these data points were included because it was to be based merely on all concentrations measured.

8.7.4 Statistical Analysis

The statistical analysis of the pharmacokinetic parameters is given in Appendix B: Pharmacokinetics, Section B.7.

Before discussing the results of bioequivalence testing, sequence, period and gender effects as well as gender by treatment interaction effect were investigated. As can be found in Appendix B: Pharmacokinetics, Section B.7, Analysis 7-1 to 7-4, no statistically significant sequence and period effects were seen. A statistically significant gender effect was found for both $AUC_{0-\infty}$ and $AUC_{0-tlast}$, being higher in female subjects. Also no statistically significant gender by treatment effect was found.

Because no statistically significant gender by treatment interactions were found, differences between the treatments were not significantly different for male and female subjects. As a consequence bioequivalence testing was done pooled for both males and females.

Point estimates of and their 90 % confidence intervals for the ratio of geometric means (T/R) for the primary parameters are presented in Table 5.

Table 5 Results of Bioequivalence Testing

Parameter	Point estimate	90 % C.I.	Conclusion
C_{max}	1.072	0.948 - 1.212	Bioequivalent

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Report 22527 (FR 99.052.2 CP/99/1212), Final version: 01-Nov-1999

$AUC_{0-tlast}$	1.103	1.052 - 1.156	Bioequivalent
$AUC_{0-\infty}$	1.101	1.049 - 1.156	Bioequivalent

Data taken from Appendix B: Pharmacokinetics, Section B.7.
For all parameters n=40
Point estimate : Point estimate of parameter ratio (least-squares geometric means of treatment T over treatment R);
90% C.I. : 90% confidence interval for ratio.

The 90 % confidence limits for the primary parameters C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ fitted well within the acceptance range 0.8 - 1.25, indicating that the formulations were bioequivalent with respect to these primary parameters.

For t_{max}, which was not tested on bioequivalence, a statistically significant treatment effect was found. When looking closer into the data it is observed that particularly in female subjects (although no gender by treatment interaction was found) the maximum concentration is reached later after treatment with the T formulation compared to treatment with the R formulation.

8.7.5 Summary of Pharmacokinetics

No statistically significant gender by treatment interactions were found, differences between the treatments were not significantly different for male and female subjects. As a consequence bioequivalence testing was done pooled for both males and females. Bioequivalence was proven for the two formulations based on C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$. For t_{max}, which was not tested on bioequivalence, a statistically significant treatment effect was found, t_{max} was reached earlier for treatment R.

8.8 PHARMACODYNAMICS

Not applicable.

8.9 POST-TREATMENT EVALUATIONS

The individual results for blood biochemistry, hematology and urinalysis for the post-trial measurements are given in Appendix G, Tables 26 up to and including 29.
The individual results for BP/HR and ECG for the post-trial measurements are given in Appendix G, Table 21 and Table 5, respectively. See 8.6.2, 8.6.4 and 8.6.5 for description of results.

1. Principle

This dissolution method utilizes automated dissolution and sampling apparatus with 0.1 N HCl as the media to determine the rate of mirtazapine released in Remeron® Orally Disintegrating Tablets - 15 mg. The amount of mirtazapine released is quantitated using ——— The target absorbance for the mirtazapine reference standard is approximately ———

2. Remarks

When stored at room temperature, the working reference standards are stable for 7 days. When refrigerated, the stock reference standards are stable for 7 days.

3. Reagents

1.	Purified water, USP
2.	Hydrochloric acid (12N), reagent grade
3.	Mirtazapine, reference standard

4. Dissolution Parameters

An automated dissolution apparatus including all necessary pumps, valves, sippers, UV spectrophotometers and software is required. Alternatively, manual sample pulling and measurement can be performed.

Apparatus	Paddles (USP 2)
Paddle Speed	50 rpm
Bath Temperature	37°C ± 0.5°C
Media Type	0.1 N HCl
Media Volume	900 mL
Analytical Wavelength	———
Sampling Time	15 minutes for single time point
UV Cell Path Length	1.0 cm

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Subsection (iii): Investigational Formulations

Investigational Formulations

In-Vitro Dissolution

Dissolution Comparison of Remeron® 15 mg, 30 mg, and 45 mg Orally Disintegrating Tablets and Remeron® 30 mg Conventional Tablets

Medium: 900 mL 0.1N HCl

Table 1: Release - 7.5 Minutes

Release- 7.5 min	30mg	15 mg	15 mg	45 mg	45 mg	30mg
replicate	Lot 990017	Lot 990018	Lot 990019	Lot 990020	Lot 990021	Conventional
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
mean	**104**	**101**	**103**	**112**	**110**	**67**
SD	2.59	6.10	5.53	2.56	6.64	12.12
%RSD	2.5	6.0	5.4	2.3	6.0	18.1

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Subsection (iii): Investigational Formulations

Investigational Formulations

In-Vitro Dissolution

Table 2: Release – 15 Minutes

Release- 15 min	30mg	15 mg	15 mg	45 mg	45 mg	30mg
replicate	Lot 990017	Lot 990018	Lot 990019	Lot 990020	Lot 990021	Conventional (IP699/0191, 207394)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
mean	**105**	**102**	**104**	**112**	**111**	**98**
SD	2.02	6.04	4.98	2.19	6.54	2.59
%RSD	1.9	5.9	4.8	2.0	5.9	2.6

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21 CFR 314.50 (d) (1)

Subsection (iii): Investigational Formulations

Investigational Formulations

In-Vitro Dissolution

Table 3: Release – 30 Minutes

Release- 30 min	30mg	15 mg	15 mg	45 mg	45 mg	30mg
replicate	Lot 990017	Lot 990018	Lot 990019	Lot 990020	Lot 990021	Conventional (IP699/0191, 207394)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
mean	**105**	**102**	**104**	**113**	**111**	**100**
SD	2.04	6.02	4.66	2.21	6.61	0.98
%RSD	1.9	5.9	4.5	2.0	6.0	1.0

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Subsection (iii): Investigational Formulations

Investigational Formulations

In-Vitro Dissolution

Table 4: Release – 45 Minutes

Release- 45 min	30mg	15 mg	15 mg	45 mg	45 mg	30mg
replicate	Lot 990017	Lot 990018	Lot 990019	Lot 990020	Lot 990021	Conventional (IP699/0191, 207394)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
mean	**105**	**102**	**105**	**113**	**111**	**100**
SD	1.90	5.96	5.13	2.59	6.58	1.06
%RSD	1.8	5.8	4.9	2.3	5.9	1.1

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Subsection (iii): Investigational Formulations

Investigational Formulations

In-Vitro Dissolution

Table 5: Release - 60 Minutes

Release- 60 min	30mg	15 mg	15 mg	45 mg	45 mg	30mg
replicate	Lot 990017	Lot 990018	Lot 990019	Lot 990020	Lot 990021	Conventional (IP699/0191, 207394)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
mean	**105**	**102**	**105**	**113**	**111**	**100**
SD	2.07	5.97	4.54	2.37	6.54	0.98
%RSD	2.0	5.9	4.3	2.1	5.9	1.0

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 12/30/99

NDA: 21-208
Name of Drug: ———
———

Indication of Drug: Antidepressant
Sponsor: Organon Inc., West Orange, NJ
Type of Submission: Original NDA, 45-Day Filing Meeting on 2/14/2000
Reviewer: Hong Zhao, Ph.D.

45-Day Filing Meeting

Introduction
This new dosage form for Remeron (mirtazapine) tablets is meant for ease of use by patients as a dosage form which can be taken without water.

This NDA contains a bioequivalence study in males and females comparing the 30mg Orally Disintegrating Tablet with the 30mg conventional Remeron (mirtazapine) Tablet. Based on the fact that the dosage strengths of the mirtazapine Orally Disintegrating Tablets are compositionally proportional and that the drug follows linear kinetics, the sponsor requested a waiver of in vivo bioequivalence study for the 15mg and 45mg tablets. In the NDA, the sponsor provided in vitro dissolution profiles (N=12 per strength) for supporting the approval of 15mg and 45mg tablets.

Bioequivalence Study and Dissolution Data
On its face, the biopharmaceutics section of the NDA is organized in a manner to allow substantive review to begin. No chromatograms of mirtazapine plasma concentration determinations in the bioequivalence study were provided.

Dissolution data are provided in the NDA for 15mg (2 batches), 45mg (2 batches), 30mg biobatch and 30mg conventional tablet (biobatch) at 7.5, 15, 30, 45 and 60 minutes. Dissolution medium was 900 mL 0.1 N HCl. Dissolution method was not described (What type of apparatus and rotated at what speed).

Comment 1
From OCPB perspective, this NDA is fileable. However, the sponsor is requested to provide representative chromatograms of mirtazapine plasma concentration determinations in the bioequivalence study. Also, a description of dissolution method used to generate the dissolution data should be provided.

Hong Zhao, Ph.D. /S/ 2/16/2000

RD/FT Initialed by Raman Baweja, Ph.D. /S/ 2/16/2000

cc: NDA 21-208 ——— Orally Disintegrating Tablets), HFD-110, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)