Clinical Pharmacology Studies:

4.2.8. Study # MLN-PK-02 (Effect of Renal Impairment)

Objective:

The primary objective of this study was to evaluate the PK of milnacipran in patients with renal impairment after a single oral dose.

Study Design:

This was a single oral dose of 50 mg in parallel in four groups of 28 subjects with various degrees of renal functions as follows:

Group I (n=8): Normal (Clcr = >80 mL/min)

Group II (n=8): Mild (Clcr = 50-80 mL/min)

Group III (n=8): Moderate (Clcr = 30-49 mL/min)

Group IV (n=4): Severs (Clcr = 5-29 mL/min)

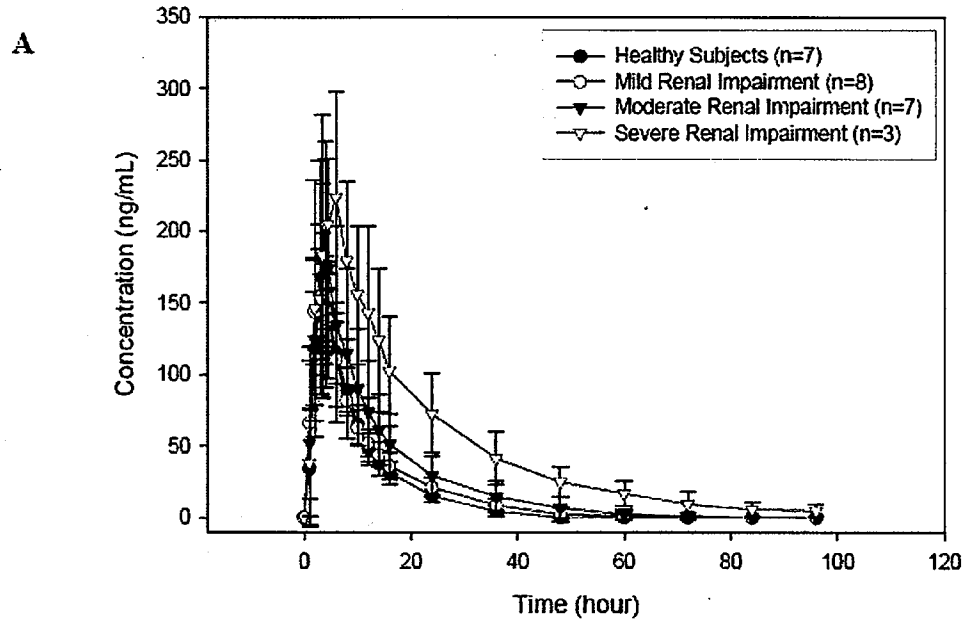Each subject received 50 mg oral dose of milnacipran with 240 ml water **with breakfast.**

Blood and urine samples were collected at appropriate time points over 96 hours for PK analysis of milnacipran.

Results:

- The plasma concentration-time profiles of milnacipran were progressively increasing by the severity of the renal function compared to healthy subjects (**Figures 4.2.8.1 A & B**). Correspondingly, the same trend was observed for the cumulative urinary excretion of milnacipran showed opposite trend (**Figures 4.2.8.2**).

- There were significant differences in exposure and half life of milnacipran in patients with severe renal impairment compared to healthy (**Tables 4.2.8.1. and 4.2.8.2**). The Cmax, AUC, and half life increased by 59%, 199%, and 122% in severe patients compared to healthy (**Table 4.2.8.2**).

Figure 4.2.8.1 A and B. Mean Plasma Concentration-Time Profiles of Milnacipran in Healthy Subjects and Patients With Renal Impairment (Study # MLN-PK-02).

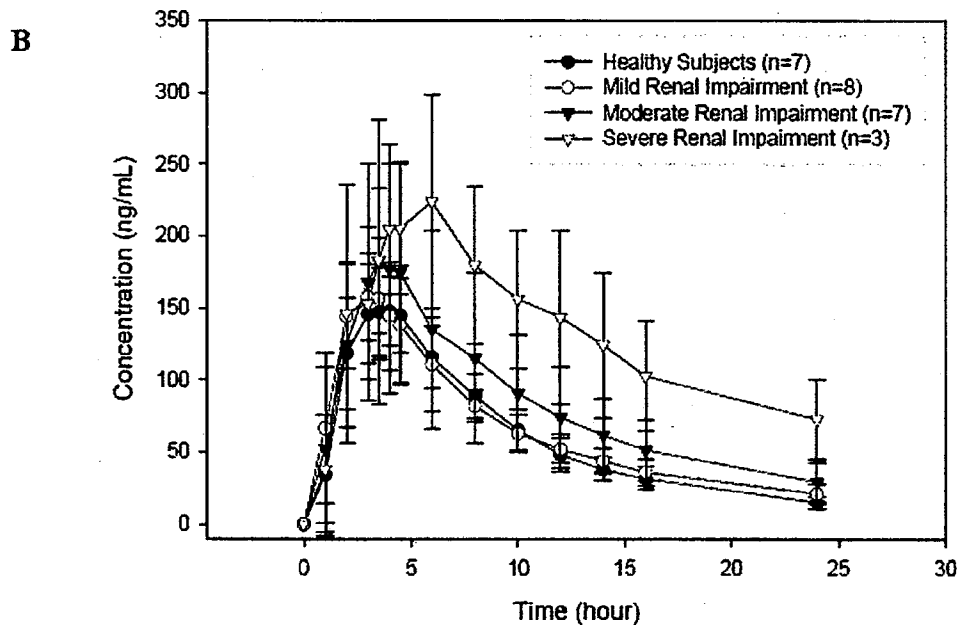A= Scale 0-96 hours

B= Scale 0-24 h

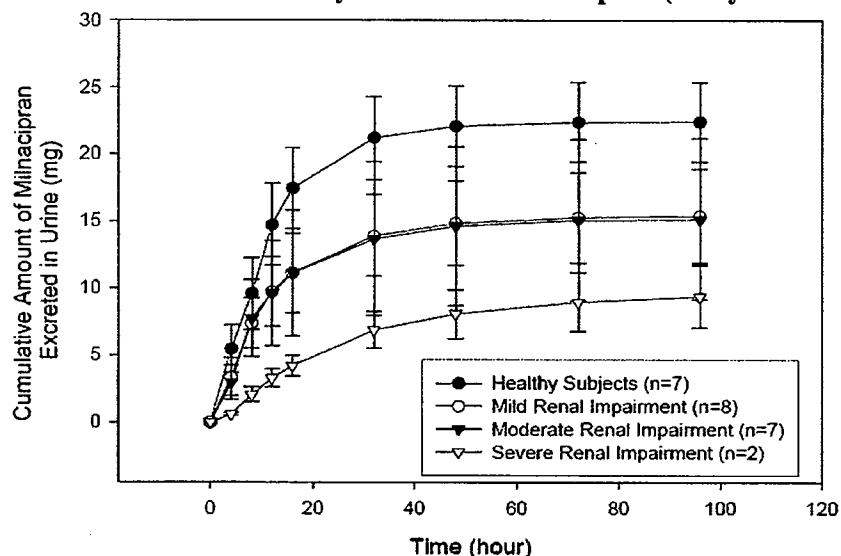# Figure 4.2.8.2. Cumulative Urinary excretion of Milnacipran (Study # MLN-PK-02).

Figure 4.2.8.2. Cumulative Urinary excretion of Milnacipran (Study # MLN-PK-02).

Table 4.2.8. Mean PK Parameters in Healthy and Renal Impairment Patients (Study # MLN-PK-02).

PK Parameter	Healthy Subjects (n=7)	Renal Function Impairment Group			Ratios of means, % (90% CI)[a]		
		Mild (n=8)	Moderate (n=7)	Severe (n=3)	Mild/ Healthy	Moderate/ Healthy	Severe/ Healthy
CL_{cr}, mL/min	98.4 ± 9.7	57.1 ± 6.0	44.7 ± 3.9	19.7 ± 8.5	58.0	45.4	20.0
C_{max}, ng/mL	154.8 ± 29.0	173.8 ± 35.7	195.6 ± 87.3	246.4 ± 63.7	112.2 (84.4–149.2)	116.3 (86.6–156.1)	158.0[*] (108.0–231.0)
AUC_{0-t}, ng·h/mL	1543.1 ± 371.6	1787.3 ± 412.0	2374.0 ± 1060.2	4733.9 ± 1552.4	116.3 (88.7–152.5)	145.9[e] (110.3–192.9)	303.6[f] (211.6–435.6)
$AUC_{0-\infty}$, ng·hr/mL	1645.5 ± 358.7	1911.7 ± 431.5	2500.9 ± 1054.1	4914.8 ± 1552.7	116.3 (90.5–149.4)	145.0[g] (111.9–187.8)	294.9[h] (211.1–411.9)
T_{max}, h	3.8 ± 0.6	2.4 ± 0.9 (0.0113)[c]	4.2 ± 1.9 (1.0000)[c]	4.7 ± 2.3 (0.4888)[c]	63.2	110.5	123.7
$T_{1/2}$, h	7.9 ± 1.7	10.9 ± 4.5 (0.1034)[b]	11.1 ± 3.5 (0.1014)[b]	17.5 ±3.2 (0.0006)[b]	138.0	140.5	221.5
CL/F, L/h	27.5 ± 5.8	23.6 ± 4.3	19.8 ± 7.2	9.5 ± 2.9	85.8	72.0	34.5

a   Data presented are percent ratios of geometric mean (90% CI) for AUC and C_{max}, and arithmetic means for T_{max}, $T_{1/2}$, and CL/F.

b   p value of ANOVA test with healthy subject group as the reference group.

c   p value of nonparametric Wilcoxon Rank Sum Test, with healthy subject group as the reference group.

d   p = 0.051.

e   p = 0.03, ANOVA test with healthy subject group as the reference group.

f   p < 0.0001 ANOVA test with healthy subject group as the reference group.

g   p = 0.0222, ANOVA test with healthy subject group as the reference group

h   p < 0.0001. ANOVA test with healthy subject group as the reference group.

ANOVA = analysis of variance; AUC_{0-t} = AUC up to the time corresponding to the last measurable concentration; $AUC_{0-\infty}$ = AUC vs time curve up to infinity; CI = confidence interval; CL_{cr} = creatinine clearance; CL/F = oral clearance; C_{max} = maximum plasma drug concentration; PK = pharmacokinetic; $T_{1/2}$ = elimination half-life; T_{max} = .time to maximum drug concentration.

Table 4.2.8.2. Changes in Mean Milnacipran PK Parameters Relative to Renal Function (Study # MLN-PK-02).

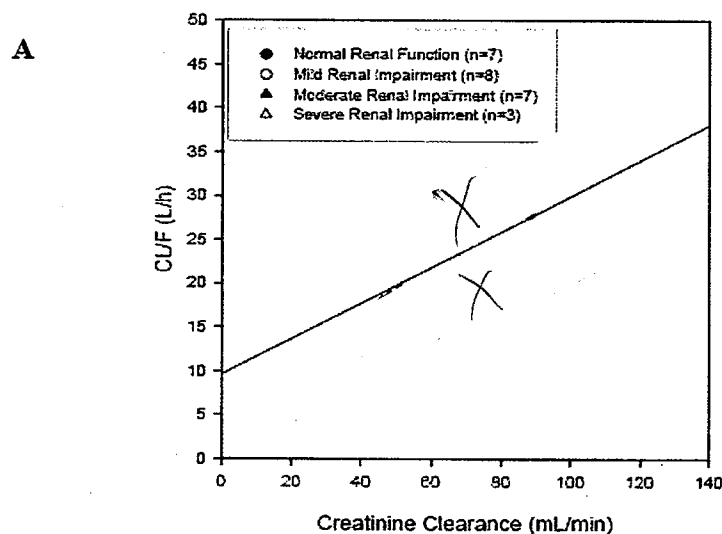| Renal Impairment Group	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$T_{\frac{1}{2}}$ (h)	CL/F (L/h)
Mild	12%	16%	38%	−14%
Moderate	26%	52%	41%	−28%
Severe	59%	199%	122%	−65%

a   Subjects without vomiting

C_{max} = maximum plasma drug concentration; $AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{\frac{1}{2}}$ = terminal elimination half-life; CL/F = apparent total clearance of drug from plasma after oral administration.

- There was relatively good correlation between oral (apparent) clearance (CL/F) and creatinine clearance (CLcr) (**Figures 4.2.8.3 A**). A similar correlation was observed between milnacipran renal clearance (CLr) and CLcr (**Figures 4.2.8.3 B**)

Figure 4.2.8.3. Relationship Between Oral (Apparent) Clearance (CL/F) of Minlacipran and Creatinine Clearance (CLcr) (A) and Between Renal Clearance (CLr) and CLcr (B) (Study # MLN-PK-02).
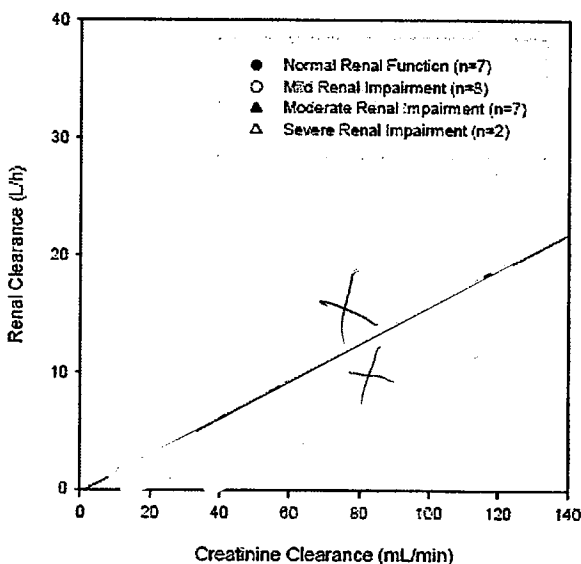
A= CL/F vs CLcr

A

Creatinine Clearance (mL/min)

b(4)

B= CLr vs CLr

B

- The PK data from the plasma levels was confirmed by urinary excretion data. The % of dose excreted in urine was reduced from 44.8% in healthy subjects to 18.7% in severe subjects (**Table 4.2.8.1 and 4.2.8.2 and Figure 4.2.8.3 A, B, C**). Compared to the single doses, the Cmax was approximately 1.6 higher than after multiple doses for all analyets.

Figure 4.2.8.3. Mean Plasma Concentration-Time Profiles of Milnacipran and its Enantiomers Following Single (Day 1) Multiple Doses (BID X 3 Days) (Study # MLN-PK-02).

PK Parameter	Healthy Subjects (n=7)	Renal Function Impairment Group		
		Mild (n=8)	Moderate (n=7)	Severe (n=2)
Ae₀-ₜ, mg	22.41 ± 2.92	15.38 ± 3.46	15.13 ± 6.01	9.36 ± 2.33
CLᵣ, mL/min	15.04 ± 2.98	8.83 ± 2.28	7.12 ± 2.96	1.85 ± 0.92
Ae, %dose	44.83 ± 5.85	30.76 ± 6.93	30.26 ± 12.01	18.72 ± 4.65

Ae_{0-t} = amount of drug excreted over all collection intervals; CL_r = renal clearance; PK = pharmacokinetic.

PK Parameter	p-Value for Group Comparison		
	Mild vs Healthy	Moderate vs Healthy	Severe vs Healthy
Ae₀-ₜ	0.0043	0.004	0.0010
CLᵣ	0.0002	< 0.0001	< 0.0001

p-value of analysis of variance test with healthy subject group as the reference group.
Ae_{0-t} = amount of drug excreted over all collection intervals; CL_r = renal clearance; PK = pharmacokinetic.

Reviewer's Comments:

It is apparent that the PK of milnacipran is dramatically affected in patients with renal impairment. This is not a surprising observation as the drug and its metabolites are excreted in urine. In this study only the parent drug, milnacipran, was measured.

Conclusions:

The main conclusion from this study is that milnacipran exposure is dramatically increased in patients with renal impairment. Dose adjustment is necessary, possibly in all stages of renal impairment. Special caution should also be taken in elderly patients since milnacipran exposure generally appears to be greater compared to young adults.

4.2.9. Study # M045/M117 (Effect of Renal Impairment)

Objective:

The primary objective of this study was to evaluate the PK of milnacipran in patients with renal impairment (Chronic Renal Failure-CRF) after a single oral dose.

Study Design:

This is small study after a single oral dose of 50 mg in subjects with various degrees of renal functions as follows:

Group I (n=7): Normal (Clcr = >80 mL/min)

Group II (n=1): Mild (Clcr = 50-80 mL/min)

Group III (n=1): Moderate (Clcr = 30-49 mL/min)

Group IV (n=5): Severs (Clcr = 5-29 mL/min)

Each subject received 50 mg oral dose of milnacipran with 150 ml water on Day 1 **under fasting condition.**

Blood and urine samples were collected at appropriate time points over 96 hours for PK analysis of milnacipran.

Results:

- The plasma concentration-time profiles of unchanged milnacipran (**Figure 4.2.9.1**) and total (unchanged and conjugates, **Figure 4.2.9.2**) were higher in patients with renal insufficiency compared to healthy subjects. As expected, the reverse trend was observed for the cumulative urinary excretion of milnacipran (**Figures 4.2.8.3 and 4.2.8.4**).

- There was some correlation between oral (apparent) clearance (CL/F) and creatinine clearance (CLcr) (**Figures 4.2.8.5 A**). A similar correlation was observed between milnacipran, the free fraction excreted in urine (fe) and CLcr (**Figures 4.2.8.5 B**).

- The individual PK data in healthy subjects and patients with renal impairment are in **Tables 4.2.8.2 A-F.**

Figure 4.2.9.1 Mean Plasma Concentration-Time Profiles of Milnacipran in Healthy Subjects and Patients With Chronic Renal Failure-CRF (Study # MO45/M117).

Conc.
(ng/ml)
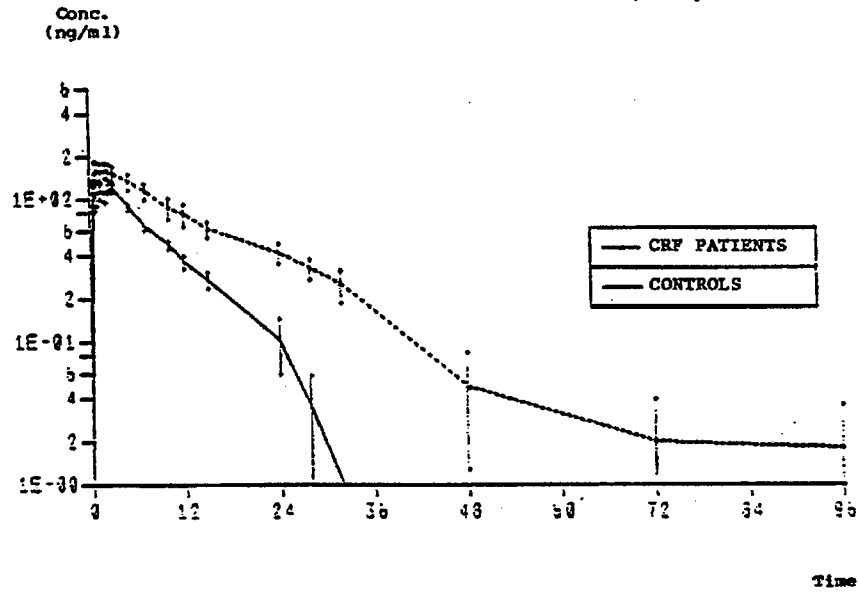
CRF PATIENTS
CONTROLS

Time (h)

Figure 4.2.9.2. Mean Plasma Concentration-Time Profiles of Total Milnacipran (Unchanged and conjugates) in Healthy Subjects and Patients With Chronic Renal Failure (Study # MO45/M117).

Mean ± s.e.m.
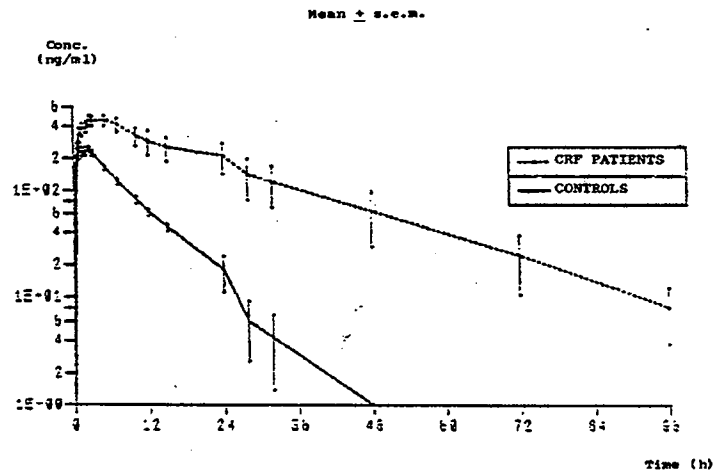
Conc.
(ng/ml)

CRF PATIENTS
CONTROLS

Time (h)

Figure 4.2.9.3. Cumulative Urinary Excretion of Unchanged Milnacipran (Study # M045/M117).

Figure 4.2.9.4. Cumulative Urinary Excretion of Total (Changed and Unchanged) Milnacipran (Study # M045/M117) (Note the difference in the y scale with the previous figure for changed)
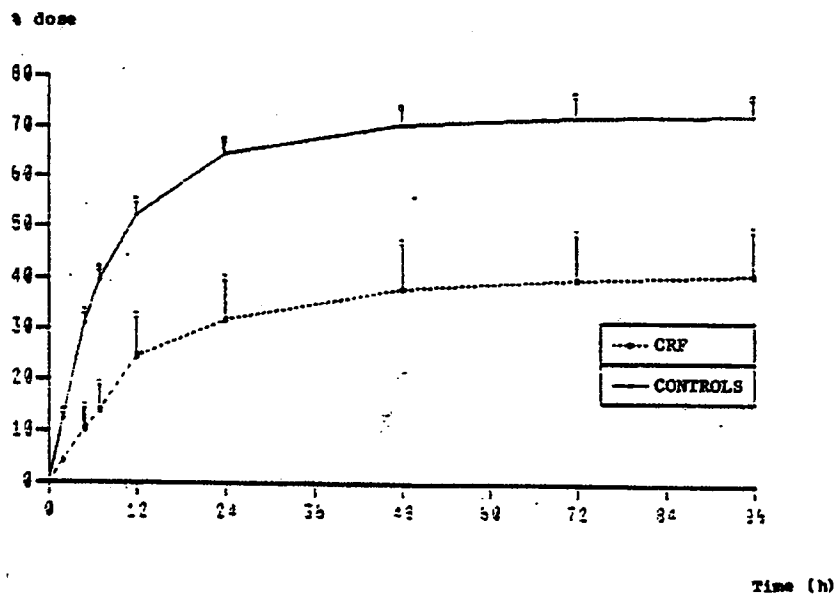
Figure 4.2.8.5. Relationship Between Oral (Apparent) Clearance (CL/F) of Minlacipran and Creatinine Clearance (CLcr) (A) and Between Free Fraction Excreted in Urine (Fe) and CLcr (B) (Study # M045/M117).
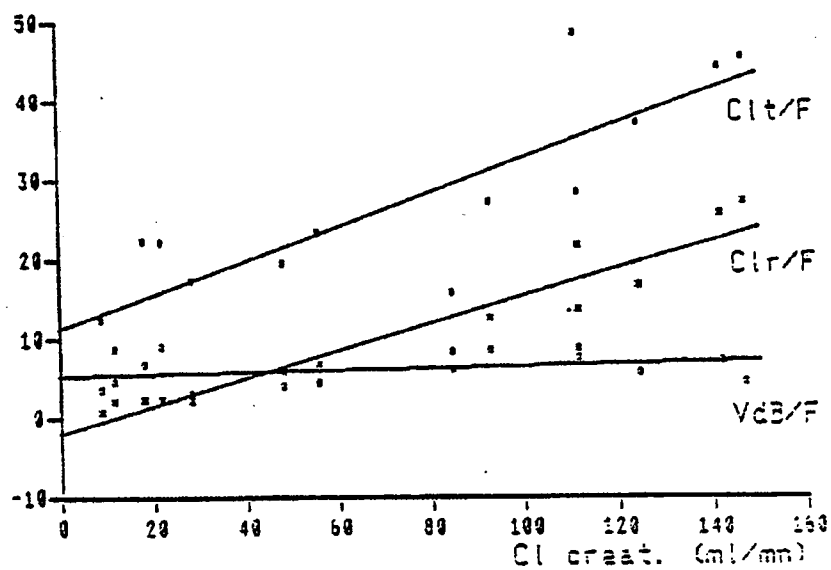
Figure 4.2.8.5. A= CL/F vs CLcr

Figure 4.2.8.5. B= Fe vs CLr

Table 4.2.8.2. A: Mean Milnacipran PK Parameters in Healthy and Patients with Renal Impairment (Study # M045/M117).

Table 4.2.8.2. A: Cmax and Tmax

Group	Subject no.	Unchanged F2207		Total F2207	
		Tmax (h)	Cmax (ng/ml)	Tmax (h)	Cmax (ng/ml)
CONTROLS	T1	0.5	180	2	268
	T2	2.5	138	2.5	289
	T3	1	178	0.75	295
	T4	1.5	141	1	305
	T5	3	122	1.5	265
	T6	3	121	2.5	191
Mean		1.9	146.7	1.7	268.8
s.e.m.		0.4	10.7	0.3	16.8
CRF PATIENTS	P1	5	160	12	668
	P2	0.5	216	2.5	700
	P3	2	195	2	523
	P4	3	182	5	515
	P5	2.5	239	7	646
	P6	0.75	296	2.5	577
	P7	0.75	101	3	297
	P8	0.75	131	5	315
Mean		1.9	190.0	4.9	530.1
s.e.m.		0.6	21.8	1.2	54.2

Table 4.2.8.2. B: AUC

| Group | Subject no. | AUC unchanged F2207 | | AUC total F2207 |
		0–N	0–00	0–N
CONTROLS	T1	1507	1825	2133
	T2	981	1345	2092
	T3	1443	1755	1968
	T4	1064	1127	2327
	T5	822	1027	2146
	T6	1061	1098	2184
Mean		1146	1363	2142
s.e.m.		110	142	48
CRF PATIENTS	P1	2607	2879	18287
	P2	2227	2531	7534
	P3	2052	3149	3897
	P4	1931	2131	5454
	P5	3201	3988	28198
	P6	5330	5689	21829
	P7	1715	2209	6949
	P8	1905	2239	9229
Mean		2621	3102	12672
s.e.m.		422	430	3117

Table 4.2.8.2. C: Oral (Apparent) Clearance and Volume of Distribution

Group	Subject no.	Cl$_T$/F 1.h^{-1}	Cl$_T$/F 1.h^{-1}/1.73m^2	Vdβ/F 1	Vdβ/F 1.kg^{-1}
CONTROLS	T1	27.4	28.7	494	8.6
	T2	37.2	32.8	424	5.6
	T3	28.5	33.8	415	8.8
	T4	44.3	40.1	524	7.2
	T5	48.7	50.1	478	7.5
	T6	45.5	43.5	302	4.5
Mean		38.6	38.2	439	7.0
s.e.m.		3.7	3.2	32	0.7
CRF PATIENTS	P1	17.4	19.4	218	3.1
	P2	19.7	18.7	298	4.1
	P3	15.9	15.9	555	8.4
	P4	23.5	23.5	292	4.5
	P5	12.5	15.7	180	3.6
	P6	8.8	8.8	312	4.7
	P7	22.6	21.1	476	6.8
	P8	22.3	23.5	598	9.1
Mean		17.8	18.3	366	5.5
s.e.m.		1.8	1.7	55	0.8

Table 4.2.8.2. D: Excreted Renal Fraction

Group	Subject no.	fe (unchanged)	fe (total)	fe (conjugated)
CONTROLS	T1	0.46	0.60	0.14
	T2	0.45	0.76	0.31
	T3	0.48	0.62	0.14
	T4	0.58	0.78	0.20
	T5	0.45	0.78	0.33
	T6	0.60	0.82	0.22
Mean		0.50	0.73	0.22
s.e.m.		0.03	0.04	0.03
CRF PATIENTS	P1	0.13	0.33	0.20
	P2	0.31	0.57	0.26
	P3	0.39	0.87	0.48
	P4	0.30	0.62	0.32
	P5	0.07	0.15	0.08
	P6	0.25	0.35	0.10
	P7	0.11	0.22	0.11
	P8	0.11	0.20	0.09
Mean		0.21	0.41	0.21
s.e.m.		0.04	0.09	0.05

Table 4.2.8.2. E: Renal and Non-Renal Clearance

Group	Subject no.	Cl_R/F		Cl_{NR}/F	
		1/h	1/h /1.73m^2	1/h	1/h /1.73m^2
CONTROLS	T1	12.6	13.2	14.8	15.5
	T2	16.7	14.7	20.5	18.1
	T3	13.7	16.2	14.8	17.6
	T4	25.7	23.3	18.6	16.8
	T5	21.9	22.5	26.8	27.6
	T6	27.3	26.1	18.2	17.4
Mean		19.6	19.3	18.9	18.8
s.e.m.		2.5	2.2	1.8	1.8
CRF PATIENTS	P1	2.3	2.6	15.1	16.8
	P2	5.9	5.6	13.8	13.1
	P3	6.2	6.2	9.7	9.7
	P4	6.8	6.8	16.7	16.7
	P5	0.9	1.1	11.6	14.6
	P6	2.2	2.2	6.6	6.6
	P7	2.5	2.3	20.1	18.8
	P8	2.5	2.6	19.8	20.9
Mean		3.7	3.7	14.2	14.6
s.e.m.		0.8	0.8	1.7	1.7

Table 4.2.8.2. F: Half Life and Mean Resident Time (MRT)

Group	Subject n°	$T1/2_\beta$ (h)	MRT (h)
CONTROLS	T1	12.5	15.3
	T2	7.9	11.6
	T3	10.1	13.4
	T4	8.2	10.4
	T5	6.8	9.5
	T6	4.6	8.5
Mean		8.3	11.4
s.e.m.		0.9	1.0
CRF PATIENTS	P1	8.7	14.8
	P2	10.5	14.6
	P3	24.2	30.9
	P4	8.6	11.6
	P5	10.0	14.2
	P6	24.6	31.3
	P7	14.6	21.4
	P8	18.6	24.7
Mean		15.0	20.4
s.e.m.		2.4	2.8

Reviewer's Comments:

This is a confirmatory study to the previous study # MLN-PK-02. The data appears to be identical. However, the present study is too small to be used to adequately describe the PK characteristics based on the severity of renal failure. For instance, there was only one subject in each mild and moderate group. Therefore, the emphasis of this study is on comparing the data from patients with severe renal impairment to healthy subjects.

Conclusions:

As in the previous study (#MLN-PK-02), the main conclusion from this study is that milnacipran exposure is dramatically increased in patients with renal impairment. Dose adjustment is necessary, possibly in all stages of renal impairment.

APPEARS THIS WAY
ON ORIGINAL

4.2.10. Study # MLN-PK-11 (Effect of Hepatic Impairment After <u>Oral Administration</u> Only)

Objective:

The primary objective of this study was to evaluate the PK of milnacipran in patients with hepatic impairment after a **single oral dose.**

Study Design:

This was a single 50 mg oral dose in parallel-group of 21 subjects with various degrees of liver functions as follows:

Group I (n=8): Normal

Group II (n=8): Mild (Child-Pugh A)

Group III (n=8): Moderate (Child-Pugh B)

Group IV (n=5): Severs (Child Pugh C)

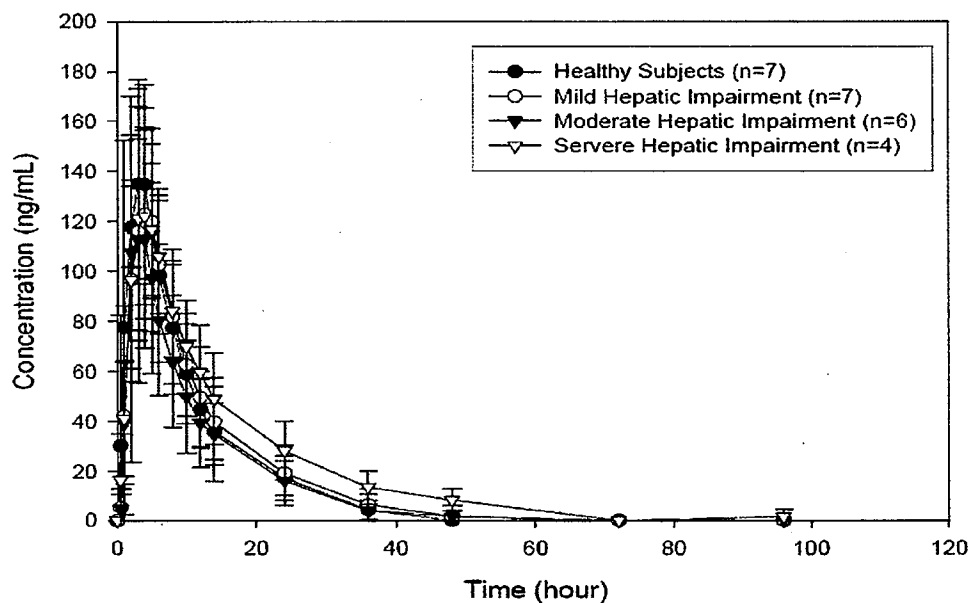Each subject received 50 mg oral dose of milnacipran with 240 ml water **with food.**

Blood and urine samples were collected at appropriate time points over 96 hours for PK analysis of milnacipran.

Results:

- The plasma concentration-time profiles of milnacipran were slightly lower in patients with hepatic function compared to healthy subjects (**Figures 4.2.10.1 A & B**). It is also noted that there was a wide variability in the data. The reverse trend was observed for the cumulative urinary excretion of milnacipran (**Figures 4.2.10.2**).

- The Cmax was lower in all hepatic impairment patients than healthy subjects. However, the AUC in mild and moderate patients was comparable to healthy subjects, but was slightly higher in severe patients (**Table 4.2.10.1**)

Figure 4.2.10.1 A and B. Mean Plasma Concentration-Time Profiles of Milnacipran in Healthy Subjects and Patients With Hepatic Impairment (Study # MLN-PK-11).
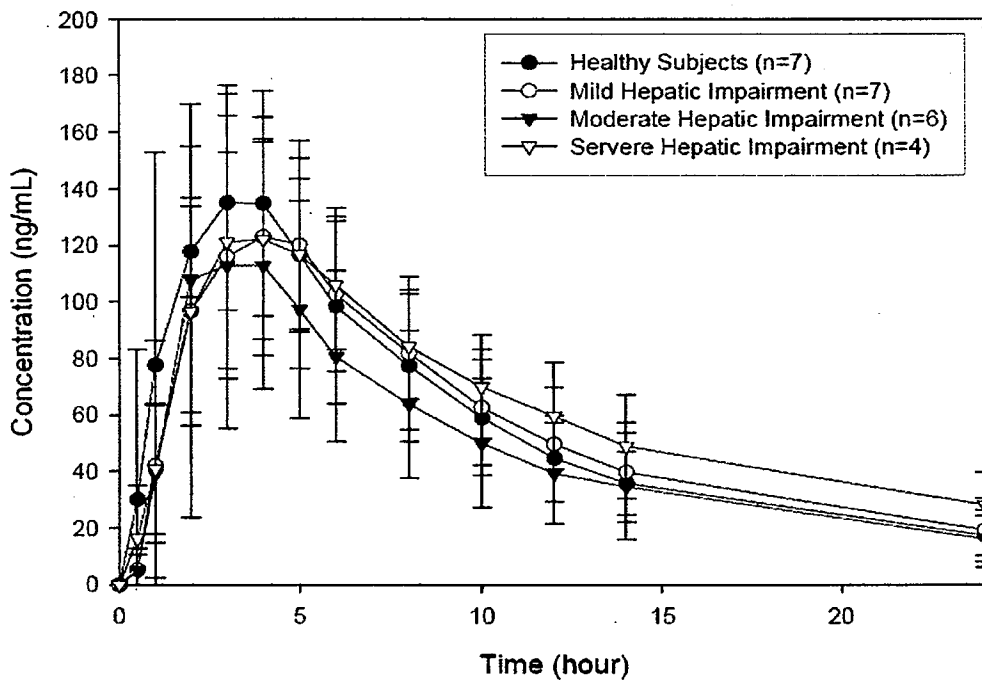
A: Scale (0-120)

B: Scale (0-24 h)

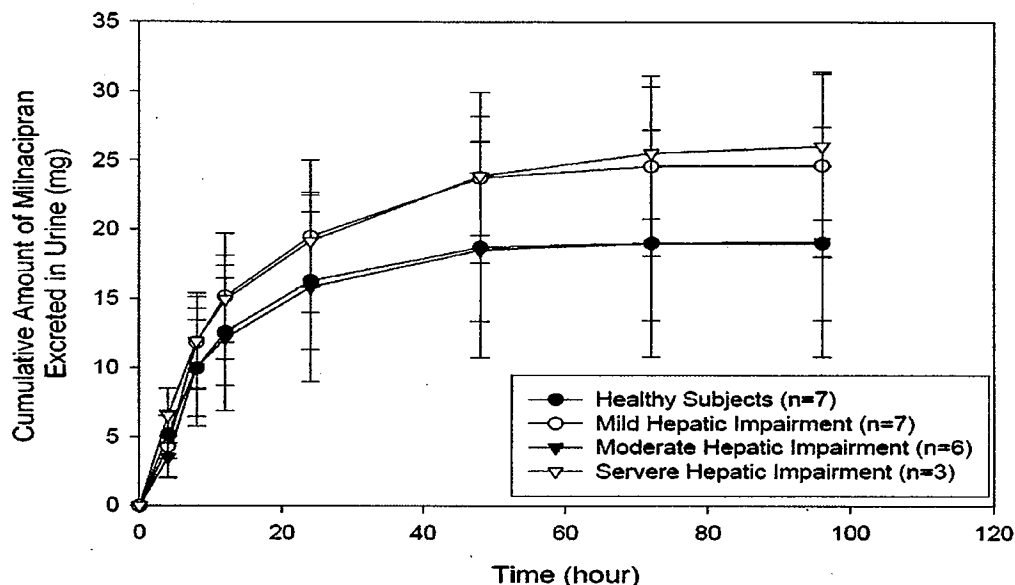**Figure 4.2.10.2. Cumulative Urinary excretion of Milnacipran (Study # MLN-PK-11).**

Table 4.2.10.1. Mean PK Parameters in Healthy and Hepatic Impairment Patients (Study # MLN-PK-11).

Parameter	Healthy (n=7)	Hepatic Impaired Group[b]			P-value[d]	Ratios of means (90% CI)[c]		
		Mild (n=7)	Moderate (n=6)	Severe (n=4)		Mild/ Healthy	Moderate /Healthy	Severe/Healthy
C_{max} (ng/mL)	157.26±30.1	136.17±51.33	130.48±43.43	132.78±37.57	0.5934	83.9 (61-115)	78.1 (57-108)	83.4 (60-120)
AUC_{0-t} (ng·hr/mL)	1488±467	1528±729	1280±621	1955±573	0.3327	99.6 (68-145)	80.6 (54-119)	133.3 (86-208)
$AUC_{0-\infty}$ (ng·hr/mL)	1591±455	1635±762	1403±655	2062±588	0.3780	99.3 (69-143)	82.6 (57-121)	130.8 (85-200)
T_{max} (h)	2.6±1.4	4.0±1.2 (0.0998)[e]	2.5±0.8 (0.6693)[e]	3.8±1.0 (0.2966)[e]	NA	153.8	96.2	146.2
$T_{1/2}$ (h)	8±1.4	8.7±1.7 (0.4111)[f]	8.4±2.1 (0.6706)[f]	12.4±1.1 (0.0004)[f]	0.0024	108.8	105.0	155.0
CL/F (L/h)	29.7±9.6	30.3±9.7	39.1±24.2	22.4±6.2	0.3613	102.0	131.6	75.4
Milnacipran Renal Excretion Parameter								
Ae_{0-t} (mg)	19.02±5.55	24.65±6.59	19.1±8.3	26.05±5.33[g]	0.2337	129.6	100.4	137.0
CLr (L/h)	13.6±5.7	17.8±7.6	14.3±5.2	14.7±0.5[g]	0.5697	130.9	105.1	108.1

a Five subjects vomited within 2 times T_{max} during the study and were therefore excluded from the PK analysis.

b Mild = total Child-Pugh score of 5-6 (Grade A); moderate = total Child-Pugh score of 7-9 (Grade B); severe = total Child-Pugh score of 10-15 (Grade C).

c Data presented are percent ratios of geometric means (90% CI) for Cmax and AUC values and arithmetic means for T_{max}, $T_{1/2}$, CL/F, Ae_{0-t}, and CLr.

d One-way analysis of variance (ANOVA) model with study group as a factor.

e p-value of nonparametric Wilcoxon rank sum test. Healthy subject group was the reference group.

f p-value of pair wise comparisons. Healthy subject group was the reference group.

g N=3; one subject (Subject 0021) was not included because the subject had an unusually high Ae_{0-t} value.

CI = confidence interval; NA = not applicable.

Reviewer's Comments:

Based on this study, the effect of hepatic impairment is not as dramatic as that observed in patients with renal failure. The dramatic effect observed in renal failure is not expected to be repeated in this patient's population as the drug does not undergo extensive metabolism by the liver. However, the renal route is the primary elimination mechanism for milnacipran, its isomers and glucuronidated metabolites.

Conclusions:

The main conclusion from this study is that the Cmax of milnacipran was unexpectedly decreased instead of increasing in patients with hepatic impairment compared to control. In addition, the AUC in mild and moderate hepatic impairment was comparable to that of the healthy but increased by 33% in severe patients. Furthermore, there was wide variability in the data.

APPEARS THIS WAY
ON ORIGINAL

4.2.10B. Study # M046 (Effect of Hepatic Impairment after <u>Intravenous and Oral</u> Administration)

Objective:

The primary objective of this study was to evaluate the PK of milnacipran in patients with hepatic impairment after a single IV and oral doses.

Study Design:

This was a single 50 mg IV or oral dose in 17 subjects with various degrees of liver functions as follows:

Group I (n=6): Normal

Group II (n=1): Mild (Child-Pugh A)

Group III (n=6): Moderate (Child-Pugh B)

Group IV (n=4): Severs (Child Pugh C)

The study was conducted in crossover design with a washout period of 3 days as follows:

Group A: 50 mg oral single dose capsule
Group B: 50 mg single IV injection

Blood and urine samples were collected at appropriate time points over 60 hours for PK analysis of milnacipran.

Results:

- After IV administration, the AUC increased by approximately 13% and 31% in moderate and severe, respectively (**Table 4.2.10B.1**).

- Following oral administration, the AUC increased by approximately 46% and 60% in moderate and severe, respectively. The Cmax increased slightly by approximately 23% and 17% for moderate and severe, respectively.

Table 4.2.10B.1. Mean PK Parameters in Healthy and Hepatic Impairment Patients (Study # M046).

Pharmacokinetic Parameter	Control Subjects (N = 6)	Group B (N = 6)	Group C (N = 4)
Intravenous Administration			
$AUC_{t-\infty}$ (ng·h/mL) (HCl salt)	1522 ± 370	1720 ± 595	1990 ± 668
$AUC_{t-\infty}$ (ng·h/mL) (freebase)[a]	1324 ± 322	1496 ± 517	1732 ± 581
$T_{\frac{1}{2}}$ (h)	8.3 ± 2.1	10.2 ± 2.6	10.5 ± 3.6
fe (%)	50.2 ± 18.6	53.8 ± 18.4[b]	49.4 ± 11.8
CL_r (L/h)	20.2 ± 6.7	16.8 ± 6.9	14.2 ± 5.4
CL (L/h)	34.3 ± 7.5	32.0 ± 10.8	27.5 ± 10.0
V_d (L)	396 ± 54	442 ± 88.0	393 ± 115
Oral Administration			
C_{max} (ng/mL) (HCl salt)	134 ± 16	165 ± 63	158 ± 64
C_{max} (ng/mL)[a] (freebase)	117 ± 14	144 ± 55	137 ± 56
T_{max} (h)	2.2 ± 0.8	2.3 ± 1.2	3.8 ± 2.9
$AUC_{t-\infty}$ (ng·h/mL) (HCl salt)	1367 ± 299	1992 ± 1382	2193 ± 628
$AUC_{t-\infty}$ (ng·h/mL) (freebase)[a]	1189 ± 257	1733 ± 1202	1908 ± 547
$T_{\frac{1}{2}}$ (h)	8.3 ± 1.7	9.9 ± 2.8	10.5 ± 4.3
fe (%)	50.1 ± 16.7	57.1 ± 11.0	61.9 ± 8.8[d]
CL_r (L/h)	20.2 ± 6.7	16.1 ± 8.4[c]	13.3 ± 2.6[d]
CL/F (L/h)	38.0 ± 7.5	31.4 ± 11.4	24.6 ± 8.5
V_d/F (L)	446 ± 87	424 ± 164	353 ± 122
F (%)	90 ± 3	110 ± 36	111 ± 12[d]

a   Conversion factor of 0.87 from HCl salt to freebase.

c   N = 5;

c   N = 4;

d   N = 3

$AUC_{t-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{\frac{1}{2}}$ = terminal elimination half-life; fe = fraction of dose excreted as unchanged drug in urine; CL_r = renal clearance; CL = plasma clearance after intravenous administration; Vd = apparent volume of distribution; C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; CL/F = apparent total clearance of drug from plasma after oral administration; V_d/F = apparent volume of distribution after oral administration; F = absolute bioavailability.

Reviewer's Comments:

Overall, the data from this study appears to be more consistent than the previous study (MLN-PK-11). However, the effect of hepatic impairment is still not as dramatic as was seen in renal impairment studies. Nevertheless, considering the wide variability in the data and the small number of subjects, the study shows some trend for higher exposure in patients with moderate and severe hepatic impairment compared to healthy subjects.

Conclusions:

Unlike the previous study, this study shows a trend for higher exposure in patients with hepatic impairment compared to healthy subjects.

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4.2.11. Study # MLN-PK-05 (^{14}C-Mass Balance)

Objective:

This study was conducted in two parts:

Part A: The primary objective of this part of the study was to determine the tolerability of 100 mg milnacipran oral solution in healthy subjects.

Part B: The primary objective of this part of the study was to evaluate the metabolic and radioactivity profiles and mass balance of ^{14}C-milnacipran oral solution in healthy subjects.

Study Design:

Part A: This was a single oral 100 mg dose in 20 healthy subjects administered as oral solution of 20 mg/mL strengths after standard breakfast.

Washout period: All subjects in part A had a washout period of 7 days before starting Part B. Selection of subjects for part B was based on GI tolerability of the 100 mg dose.

Part B: This was a single oral 100 mg dose of ^{14}C-milnacipran oral solution (20 mg/mL) with 100 μCi in six healthy male subjects selected **from Part A**. As in Part A, the drug was administered after standard breakfast.

Blood samples were collected at appropriate time points over 120 hours for PK analysis of milnacipran in part B. In addition, urine and fecal samples were collected at appropriate intervals over 120 hours.

Results:

- The plasma concentration-time profiles of milnacipran and radioactivity is shown in **(Figures 4.2.11.1)**.

- The Cmax and AUC of the total radioactivity consisted of approximately 35% to 60% of the parent drug **(Table 4.2.11.1 and Figure 4.2.11.1)**.

- There was almost complete recovery (~97%) of the radioactivity in urine and feces **(Table 4.2.11.2)**. More than 90% of the dose was excreted in urine and small percentage in feces (<5%).

- Based on urine data, approximately 55% of the dose was recovered unchanged in urine **(Table 4.2.11.3)**. For *d* and *l* isomers, the percent of dose was approximately 24 and 31%, respectively.

Figure 4.2.11.1. Mean Urine Concentration-Time Profiles of Radioactivity and Milnacipran in Healthy Subjects (Study # MLN-PK-05).
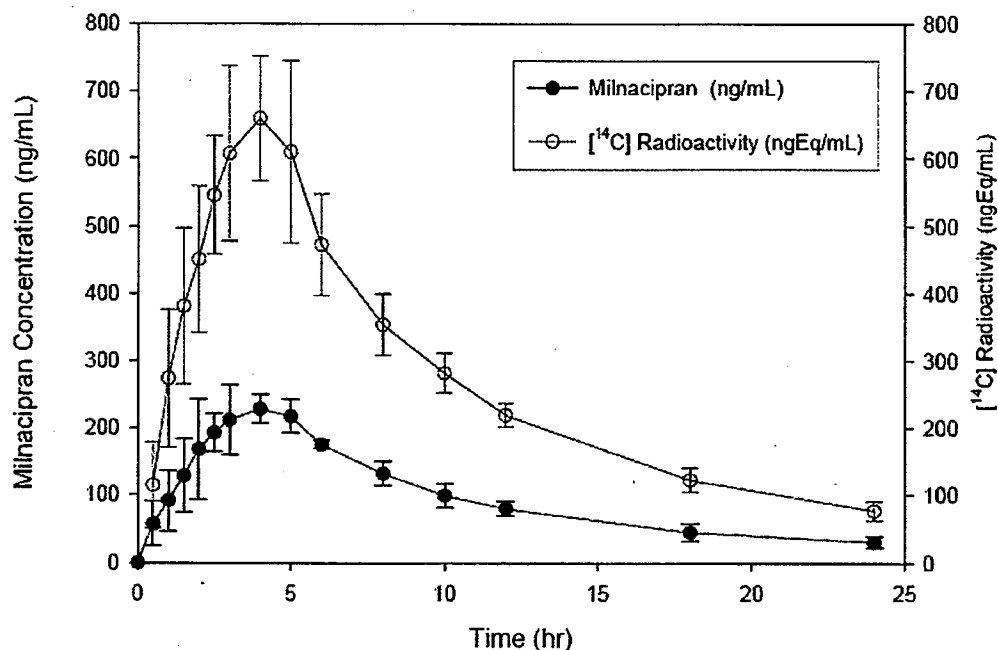

Figure 4.2.11.2. Mean Plasma PK Parameters of Milnacipran and Radioactivity (Study # MLN-PK-05).

PK Parameters	[^{14}C]- Radioactivity[a]	Milnacipran	Ratio % Milnacipran: [^{14}C]- Radioactivity
C_{max} (ng/mL)	679.0± 112.6	239.6± 33.2	35.3
AUC_{0-t} (hr• ng /mL)	6446.3± 666.3	2342.6± 252.0	36.3
$AUC_{0-\infty}$ (hr• ng /mL)	7325.3± 622.1	2766.5±413.2	37.8
T_{max} (hr)	4.3± 0.5	3.5± 1.0	
$T_{1/2}$ (hr)	7.7± 1.0	8.9± 3.2	

[a] Units for C_{max} = ngEq/mL; AUC_{0-t} and $AUC_{0-\infty}$ = hr•ngEq/mL

Table 4.2.11.1. Mass Balance Data. Mean Excretion of Radioactivity in Urine and Feces in Healthy Subjects (Study # MLN-PK-05).

Subject #	Excretion (%Dose)		
	Urine	Feces	Total
0008	91.3	5.29	96.6
0011	94.3	2.8	97.1
0013	93.2	3.16	96.4
0017	94.2	3.34	97.5
Mean	93.3	3.65	96.9
SD	1.4	1.1	0.5
%CV	1.5	30.6	0.6

Table 4.2.11.1. % Excreted of in Urine for Unchanged, *d*-, and *l*-, milnacipran (Study # MLN-PK-05).

Urine pool (0-96 h)	Excretion (% dose)		
	l-Milnacipran	*d*-Milnacipran	Unchanged* milnacipran
Subject 1	22.1	33.6	55.7
Subject 2	24.4	28.6	53.0
Subject 3	23.8	32.4	56.2
Subject 4	23.6	30.4	54.0
Mean	23.5	31.2	54.7

Reviewer's Comments:

Although the number of subjects is relatively small in this study, the data is very convincing to show almost complete recovery of the radioactivity. In addition, by comparing the exposure of the total radioactivity (Cmax and AUC) to the cold parent drug indicates substantial metabolism of the drug following oral administration. However, this metabolism does not appear to be CYP450 mediated, but related to the conversion of milnacipran to its *d* and *l* isomers and glucuronadation.

Urine is the primary route of elimination of milnacipran. The percent of unchanged milnacipran excreted in urine is approximately 55%, including 24% for *d* and 31% for *l* isomers, respectively.

Conclusions:

A mass balance of approximately 97% of radioactivity was achieved in this study. The ratio of exposure for the parent (unchanged) milnacipran and the total radioactivity indicates substantial metabolism of the drug to its *d* and *l* isomers and glucuronadation following oral administration. The AUC was approximately 38% (parent to radioactivity).

4.2.12. Study # M036 (Dose Proportionality)

Objective:

The primary objective of this study was to determine the PK of milnacipran in relation to dose.

Study Design:

Part I: Placebo controlled, crossover with three day washout between the two treatment groups of healthy subjects:

Group 1 (n=6): Received **two** milnacipran doses (25, 100, **or** 300 mg) or placebo
Group 2 (n=6): Received **two** milnacipran doses (50, 200, **or** 400 mg) or placebo

Blood samples were collected at appropriate time intervals over 24 hours post dose.

Washout period: 3 days washout between the two groups.

Part II: Multiple dose in two groups of subjects:

Group 1 (n= 5): Received milnacipran at 25-50 mg BID or placebo X 14 days as follows:
- 2 subjects 25 mg BID X 14 days
- 2 subjects 25 mg BID on Days 1-7 and 50 mg BID on Days 8-14
- 1 subject placebo

Group 2 (n=5): Received milnacipran at 75-200 mg BID or placebo X 14 days as follows:
- 2 subjects 75 mg BID on Days 1-7 and 100 mg BID on Days 8-14
- 2 subjects 100 mg BID on Days 1-7 and 200 mg BID on Days 8-14
- 1 subject placebo

Blood samples were collected at appropriate time intervals on Days 1, 2, and 3

Results:

- All four subjects who receive the 400 mg dose vomited. Therefore, the data show low exposure (**Figure 4.2.12.1 and Table 4.2.12.1**).
- By excluding all the four subjects who vomited following the 400 mg dose the the plasma concentration-time profiles increased with increase in dose up to 300 mg (**Figure 4.2.12.1**). Therefore, Cmax and AUC increased proportionally with dose up to 300 mg (**Figure 4.2.12.1 and Table 4.2.12.1**).

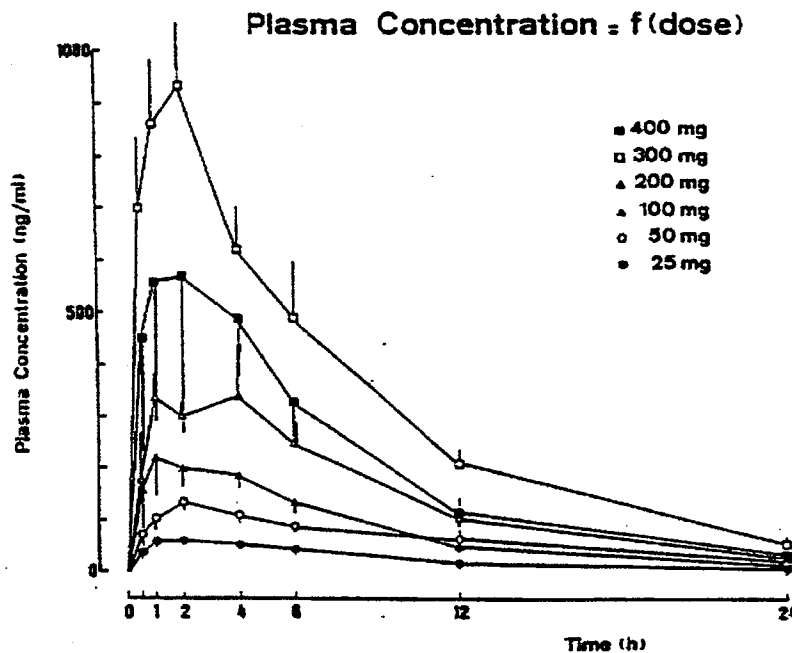**Figure 4.2.12.1. Mean Plasma Concentration-Time Profiles (Study # MO36).**

Figure 4.2.12.2. Cmax and AUC in relation to Dose (Study # MO36).
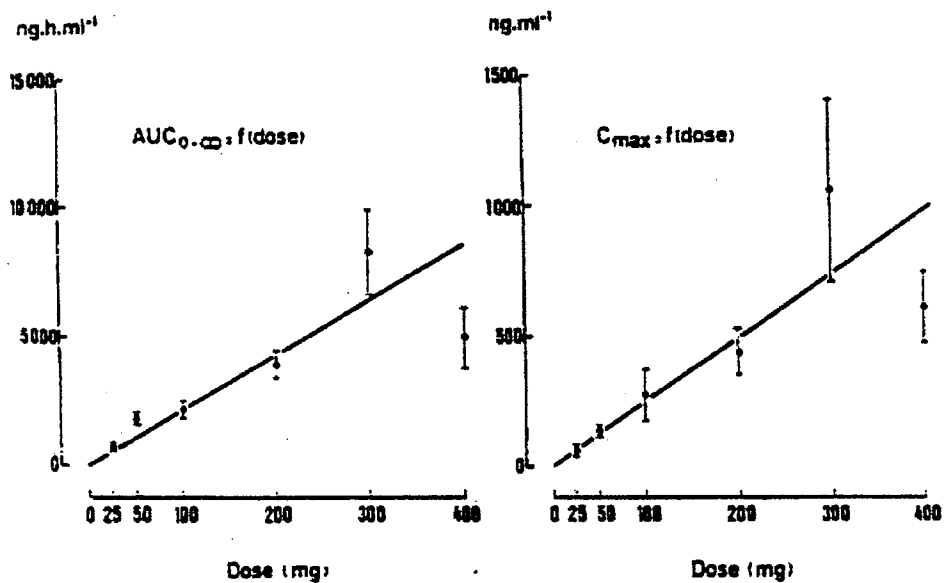
Table 4.2.12.1. Mean PK Parameters (Study # M036).

Pharmacokinetic Parameters (Mean ± SD) of Milnacipran Following Single Oral Increasing Doses of Milnacipran HCl						
Pharmacokinetic Parameter	25 mg (N=4)	50 mg (N=4)	100 mg (N=4)	200 mg (N=4)	300 mg (N=4)	400 mg (N=4)
C_{max} (ng/mL) (HCl salt)	64.1 ± 10.9	134 ± 33	236 ± 128	435 ± 147	1026 ± 589	606 ± 237
C_{max} (ng/mL) (freebase)[a]	56 ± 10	117 ± 28	205 ± 111	378 ± 127	893 ± 513	527 ± 206
T_{max} (h)	1.8 ± 1.5	1.8 ± 0.5	2.0 ± 1.4	1.9 ± 1.5	1.8 ± 1.7	1.8 ± 1.5
$AUC_{0-\infty}$ (ng·h/L) (HCl salt)	731 ± 199	1833 ± 368	2150 ± 599	3895 ± 962	8272±2891	4945±2050
$AUC_{0-\infty}$ (ng·h/mL) (freebase)[a]	636 ± 173	1595 ± 320	1870 ± 521	3388 ± 837	7196±2515	4302±1784
$T_{\frac{1}{2}}$ (h)	7.2 ± 1.0	8.2 ± 2.0	5.8 ± 0.8	6.3 ± 0.9	5.9 ± 0.6	6.2 ± 2.1

a   Conversion factor of 0.87 from HCl salt to freebase.

C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; AUC_{0-t} = area under the plasma concentration vs time curve from time 0 to t; $AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{\frac{1}{2}}$ = terminal elimination half-life.

Reviewer's Comments:

Although the number of subjects is relatively small with high variability especially at the higher dose, the data shows dose linearity for both Cmax and AUC up to a dose of 300 mg.

Conclusions:

It can be concluded that milnacipran exhibits dose linearity up to 300 mg.

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4.2.13. Study # M040 (Dose Proportionality)

Objective:

The primary objective of this study was to determine the PK of milnacipran in relation to dose.

Study Design:

This study was conducted in 6 healthy subjects with successive administration of 4 increasing doses of 25, 50, 100, and 200 mg.

Blood and urine samples were collected at appropriate time intervals over 48 hours post dose.

Results:

- The plasma concentration-time profiles increased with increase in dose up to 100 mg (Figure 4.2.13.1).
- The increase in Cmax and AUC was directly proportional to dose up to 100 mg (Figures 4.2.13.1-3 and Table 4.2.13.1). Although, the Cmax and AUC increased with dose at 200 mg dose there was wide variability in the data at this dose level.

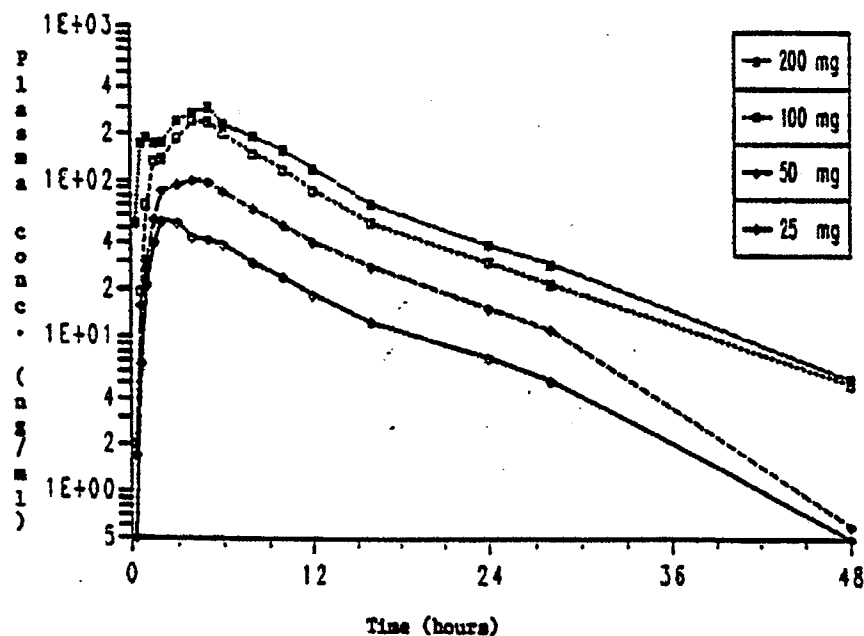**Figure 4.2.13.1. Mean Plasma Concentration-Time Profiles (Study # MO40).**

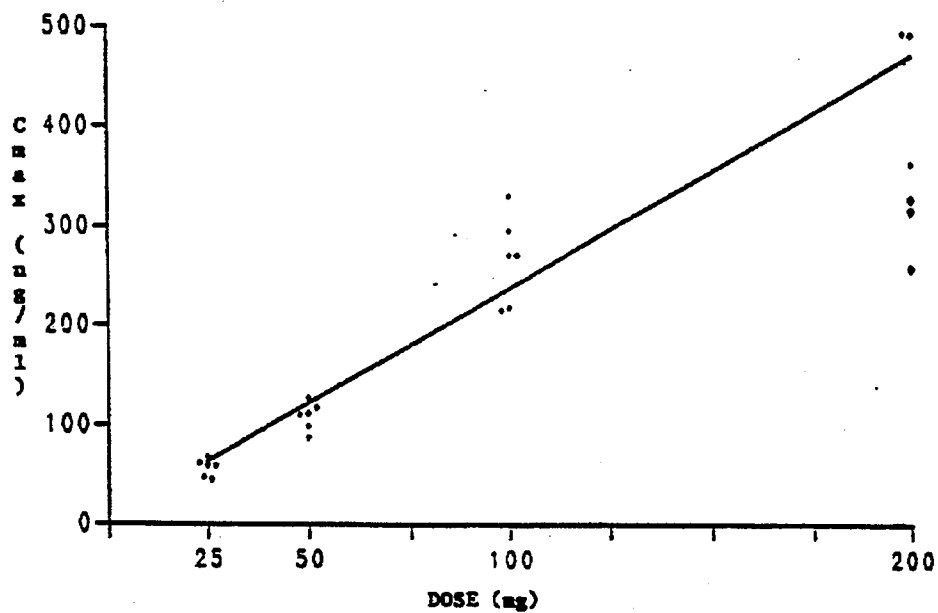**Figure 4.2.13.2. Cmax in Relation to Dose (Study # MO40).**

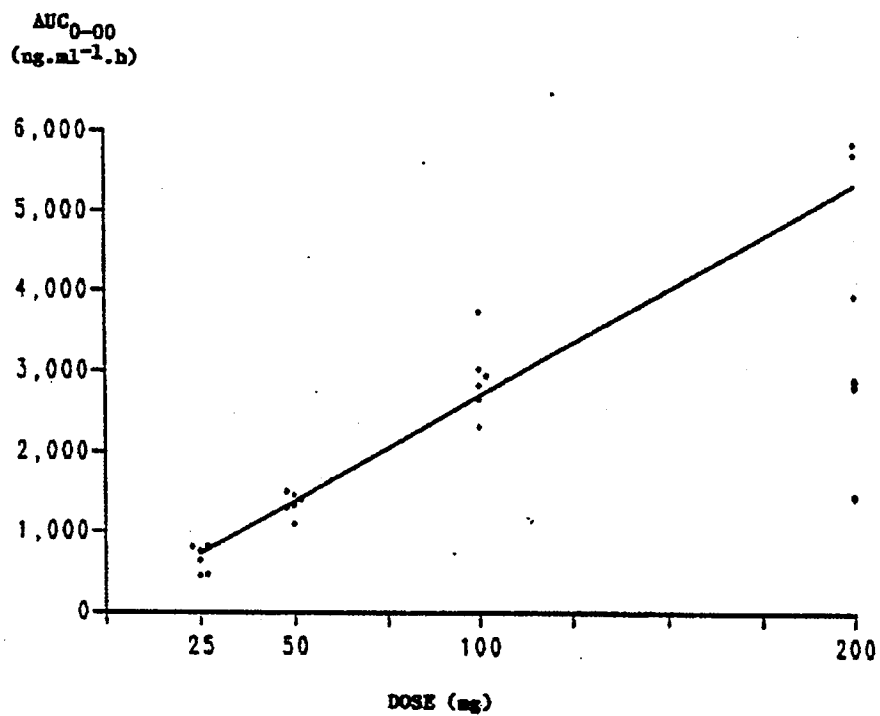**Figure 4.2.13.3. AUC in Relation to Dose (Study # M040).**

Table 4.2.13.1. AUC in Relation to Dose (Study # M040).

Parameter	25 mg	50 mg	100 mg	200 mg
Unchanged F2207				
Cmax	57.2 ± 3.5	109.5 ± 6.0	268.8 ± 18.2	377.1 ± 39.8 (451.8 ± 43.2)
Tmax	2.6 ± 0.4	3.8 ± 0.6	4.2 ± 0.2	3.1 ± 0.8 5 ± 0
AUC_{0-N}	562.2 ± 47.7	1221.3 ± 69.9	2746.0 ± 181.7	3693.8 ± 685.8 (5048.4 ± 562.9)
AUC_{0-oo}	665.1 ± 67.9	1357.5 ± 59.7	2891.5 ± 169.9	3785.4 ± 709.3 (5174.4 ± 608.3)
$T_{1/2.a}$	0.53 ± 0.09	0.93 ± 0.16	0.64 ± 0.04	0.81 ± 0.33 (1.26 ± 0.33)
$T_{1/2}\,\alpha$	2.38 ± 0.36	0.13 ± 0.04	0.28 ± 0.03	—
$T_{1/2}\,\beta$	10.5 ± 1.6	8.9 ± 1.1	10.2 ± 1.6	7.2 ± 1.1 (8.2 ± 1.7)
Cl_T/F	39.9 ± 4.5	37.2 ± 1.8	34.9 ± 2.2	66.0 ± 15.5 (39.9 ± 5.3)
Vd_β/F	567 ± 58	464 ± 42	509 ± 71	615 ± 92 (455 ± 69)
MRT	14.1 ± 1.5	13.5 ± 1.2	13.3 ± 1.0	11.3 ± 1.4 (13.3 ± 1.8)
fe	0.46 ± 0.12	0.41 ± 0.06	0.54 ± 0.08	0.40 ± 0.11 (0.51 ± 0.16)

*( ): Mean calculated without subject nos.3, 5, and 6

Table 4.2.13.1 Continued)

Parameter	25 mg	50 mg	100 mg	200 mg
Unchanged F2207				
Cl_R/F	19.7 ± 6.9	15.2 ± 2.4	18.5 ± 2.9	20.5 ± 4.2 (18.7 ± 4.6)
Cl_{NR}/F	20.1 ± 5.3	22.0 ± 2.1	16.4 ± 3.3	45.4 ± 17.0 (21.2 ± 9.9)
Total F2207				
Cmax	133.9 ± 11.8	222.3 ± 16.9	596.8 ± 81.2	861.8 ± 104.6 (1039.2 ± 67.6)
AUC_{0-N}	1207.5 ± 158.3	2135.7 ± 171.4	5419.5 ± 480.0	7970.4 ± 1438.6 (10987.3 ± 731.9)
AUC F2207 unch / AUC F2207 tot.	0.51 ± 0.06	0.63 ± 0.08	0.54 ± 0.05	0.47 ± 0.04 (0.47 ± 0.08)
Cmax F2207 unch / Cmax F2207 tot	0.44 ± 0.04	0.50 ± 0.04	0.49 ± 0.07	0.45 ± 0.04 (0.44 ± 0.04)

Reviewer's Comments:

There was high variability in the data at the 200 mg dose. However, there was increase in exposure at this dose level. Overall, the study confirms dose proportionality up 100 mg dose but less proportional (due to the high variability) at the 200 mg level.

Conclusions:

Based on this study, it can be concluded that milnacipran is dose proportional up to 100 mg and possibly up to 200 mg.

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4.2.14. Study # M0120 (Dose Proportionality, Multiple Dose X 56 Days)

Objective:

The primary objective of this study was to determine the PK of milnacipran in relation to dose in a subgroup of patients with depressive illness.

Study Design:

This was a sub-study of a large clinical trial conducted in 74 depressed patients. It was designed as double blind in four parallel groups as follows:

Treatment A (n=18): 25 mg BID X 56 days
Treatment B (n=18): 50 mg BID X 56 days
Treatment C (n=19): 200 mg BID X 56 days
Treatment D (n=19): Placebo BID X 56 days

On the first day (Day 1) and the last day (Day 56) patients received only the morning doses.

Blood samples were collected at appropriate time intervals over 24 hour on Day 1 and 48 hours on the last day (Day 56). Urine was collected over 12 hours on the last dose (Day 56).

Overdosed Patient:

- Based on the sponsor report, one patient inadvertently received an over dose of approximately 600 mg of milnacipran (Patient # 5423). The patient was shortly hospitalized in an unresponsive state with shallow respiration. PK blood samples were collected from 3 hours to 56 hours post ingestion.
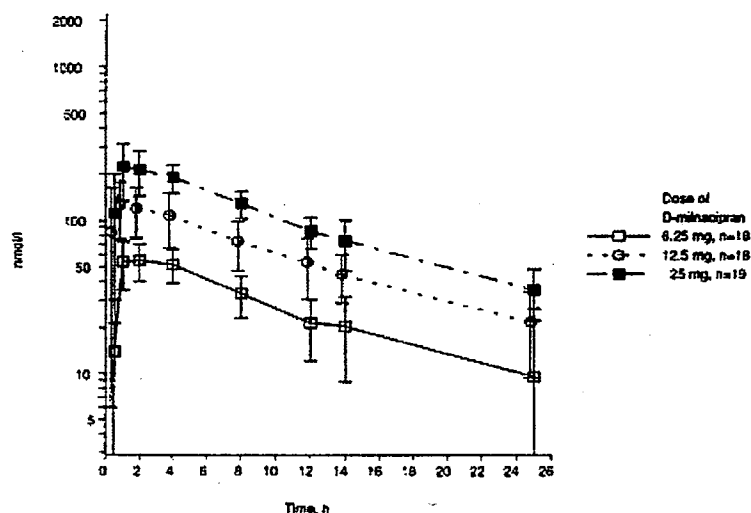
Results:

- The plasma concentration-time profiles increased with increase dose following single and multiple doses for both d-(**Figure 4.2.14.1 A & B**) and l-isomers (**Figure 4.2.14.1 A & B**).

- The increase in Cmax and AUC was directly proportional to dose up to 200 mg for both d- and l-isomers following a single dose (**Table 4.2.14.1**) and multiple doses (**Table 4.2.14.2**).

- The urinary recover for both isomers ranged from approximately 35% to 57% at all doses (**Table 4.2.14.3**). This tends to be higher at the highest dose compared to the lower dose for both d-and l- isomers.

- No change in renal clearance was found at all doses for either *d-* or *l-* isomers (**Table 4.2.14.4**). However, the renal clearance for *l-*isomer was higher (mean 302 m/min) than for *d-*isomer (mean 195 mL/min).

- The plasma profile for overdosed patient with approximately 600 mg shows clear separation in the exposure to d and l isomers (**Figure 4.2.14.3**). This further confirms that the exposure to *d-*isomer is always higher than the *l-* isomer.

Figure 4.2.14.1. Mean Plasma Concentration-Time Profiles (Study # M120).

A: *d-***Isomer (Single Dose)**

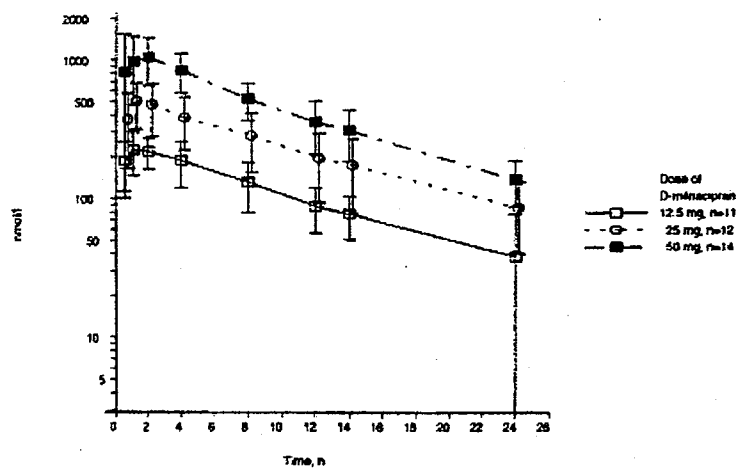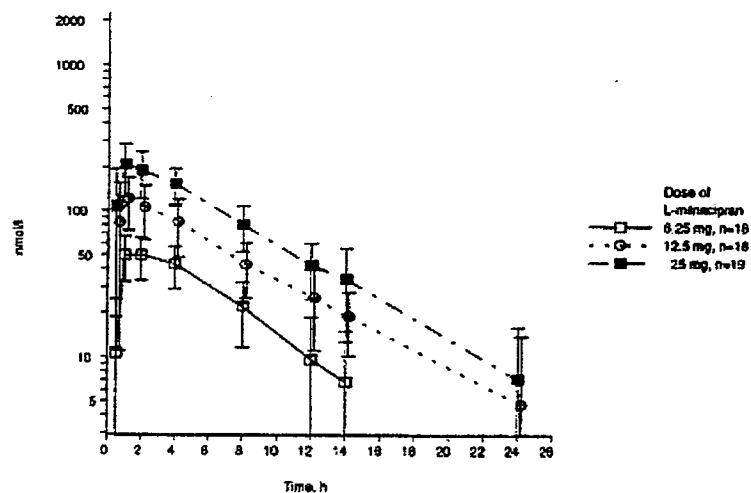**B:** *d-***Isomer (Multiple Dose)**

Figure 4.2.14.2. Mean Plasma Concentration-Time Profiles (Study # M120).

A: *l*-Isomer (Single Dose)
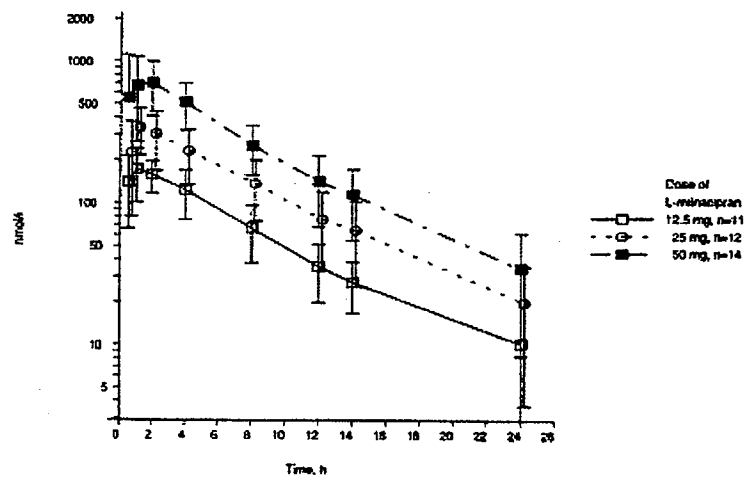

B: *l*-Isomer (Multiple Dose)

Table 4.2.14.1. Mean PK Parameters for *d*- and *l*-isomers in 55 Patients after Single Dose of Milnacipran (Day 1) (Study # MO120).

		D-Milnacipran			L-Milnacipran		
	Dose group	50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
	Enantiomer dose #	6.25 mg	12.5 mg	25 mg	6.25 mg	12.5 mg	25 mg
Cmax (nmol/l)	Mean	61.0	145.5	245.4	55.5	131.7	217.6
	SD	15.0	47.3	62.5	14.5	48.2	65.4
	Max	93.0	269.0	365.0	93.0	260.0	352.0
	Min	40.0	86.0	137.0	36.0	68.0	105.0
	Max/Min	2.3	3.1	2.7	2.6	3.8	3.4
	n	18	18	19	18	18	19
Tmax (h)	Mean	2.1	2.2	2.2	1.8	2.0	1.8
	SD	1.2	2.7	1.8	1.2	2.7	1.7
	Max	4.1	12.0	8.0	4.0	12.0	8.0
	Min	0.5	0.5	1.0	0.5	0.5	0.5
	Max/Min	8.2	24.0	8.0	8.0	24.0	16.0
	n	18	18	19	18	18	19
AUC 0-inf (nmol·h/l)	Mean	822.0	1785.6	2975.6	453.6	933.6	1678.1
	SD	338.4	568.7	650.2	141.0	307.5	547.3
	Max	1701.8	2934.8	4338.1	786.8	1573.8	2827.4
	Min	466.8	851.4	1899.5	259.8	351.7	988.0
	Max/Min	3.6	3.4	2.3	3.0	4.5	2.9
	n	18	18	19	18	18	19
t1/2 (h)	Mean	10.5	9.4	9.2	5.0	4.8	5.1
	SD	7.7	2.3	2.2	1.2	1.1	1.5
	Max	33.7	15.7	14.3	7.0	6.6	8.3
	Min	3.8	6.5	4.9	2.6	3.1	2.8
	Max/Min	8.9	2.4	2.9	2.8	2.1	2.9
	n	18	18	19	18	18	19

Half dose day 1 (cf. Table 2 section 4.4.2)
*p<0.05

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Table 4.2.14.2. Mean PK Parameters for *d*- and *l*-isomers in 37 Patients after Multiple Dose of Milnacipran (Day 56) (Study # MO120).

		D-Milnacipran			L-Milnacipran		
	Dose group	50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
	Enantiomer dose	12.5 mg	25 mg	50 mg	12.5 mg	25 mg	50 mg
Cmax (nmol/l)	Mean	253.6	552.1	1160.1	191.7	379.3	839.0
	SD	68.1	158.6	479.3	54.2	105.0	380.7
	Max	370.0	746.0	2356.0	282.0	526.0	1746.0
	Min	141.0	264.0	533.0	126.0	238.0	259.0
	Max/Min	2.6	2.8	4.4	2.2	2.2	6.7
	n	11	12	14	11	12	14
Tmax (h)	Mean	1.5	1.5	1.5	1.4	1.3	1.5
	SD	1.0	1.2	1.0	1.0	1.0	1.0
	Max	4.1	4.1	4.0	4.1	4.0	4.0
	Min	0.5	0.5	0.3	0.5	0.5	0.3
	Max/Min	8.2	8.1	12.1	8.2	8.0	12.1
	n	11	12	14	11	12	14
AUC 0-12h (nmol·h/l)	Mean	1842.5	3949.5	7830.4	1130.4	2190.2	4449.6
	SD	555.6	1582.3	2844.7	359.3	806.1	1939.3
	Max	3050.3	6653.9	13875.9	1719.0	3215.7	8546.7
	Min	1065.4	1576.5	4769.1	643.7	889.0	1901.0
	Max/Min	2.9	4.2	2.9	2.7	3.6	4.5
	n	11	12	14	11	12	14
AUC 0-12h (nmol·h/l) Corrected	Mean	1836.0	3857.2	7520.5	1081.6	2111.1	4255.5
	SD	512.9	1609.6	2437.6	363.5	855.7	1691.6
	Max	3002.4	6696.0	12827.3	1687.7	3289.4	7861.6
	Min	1310.6	1576.5	4693.1	594.2	889.0	1878.0
	Max/Min	2.3	4.2	2.7	2.8	3.7	4.2
	n	10*	12	14	10*	11**	14
t1/2 (h)	Mean	8.9	9.9	8.5	4.9	5.5	5.6
	SD	2.1	2.6	1.3	1.0	1.9	1.3
	Max	12.5	17.1	10.5	6.2	10.1	8.2
	Min	6.8	7.5	5.6	3.8	3.1	3.4
	Max/Min	1.8	2.3	1.9	1.6	3.3	2.4
	n	11	12	14	11	12	14

* Data is unavailable for patient 5416.
**Data is unavailable for patient 5705.

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Table 4.2.14.3. Urinary Recovery (% of Dose) of *d*- and *l*-isomers at Steady State (Study # MO120).

Dose group	Urinary recovery, % of dose					
	D-milnacipran			L-milnacipran		
	50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
Median	42.1	42.1	55.7	43.6	31.2	43.4
Mean	46.8	41.0	57.5	43.3	35.9	49.5
SD	19.5	9.3	15.8	17.8	11.2	18.7
Max	95.0	56.0	87.6	85.5	55.1	88.5
Min	24.9	24.0	35.7	25.0	21.4	31.0
Max/Min	3.8	2.3	2.5	3.4	2.6	2.9
n	9	9	11	9	9	11

* $p<0.05$

Table 4.2.14.4. Renal Clearance of *d*- and *I*-isomers at Steady State (Study # M0120)

Dose group	Renal clearance (Cl_R), ml/min					
	D-milnacipran			L-milnacipran		
	50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
Median	191	154	181	263	254	296
Mean	186	189	212	285	293	329
SD	30	70	61	55	122	89
Max	229	322	342	366	517	518
Min	144	101	123	230	122	191
Max/Min	1.6	3.2	3.8	1.6	4.2	2.7
n	9	9	11	9	9	11

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Figure 4.2.14.3. Plasma Concentration-Time Profiles of *d-* and *l-*isomers in One Patient with Overdosed with Approximately 600 mg.

b(4)

Reviewer's Comments:

This is another confirmatory study to demonstrate the dose proportionality of milnacipran, specifically for *d-* and *l-* isomers based on both plasma and urine data. The data is conclusive to state that the exposure to *d-*isomer is consistently higher than that of *l-*isomer. In addition, the half life for *l-*isomer is shorter than that of the *d-*isomer.

Conclusions:

It can be concluded that milnacipran exhibits dose linearity up to 200 mg.

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4.2.15 Study # M146/C241 (Dose Proportionality and Cardiovascular Effect of 50, 100, and 200 mg/day)

Objective:

The primary objective of this study was to evaluate the cardiovascular tolerability of milnacipran at different doses vs placebo. In addition, the study attempted to establish the dose proportionality and the relationship between exposure and cardiovascular effects such as blood pressure and pulse rate.

Study Design:

This was a double-blind, 4 x 4 Latin-square design with 4-7 days washout period in 16 healthy subjects as follows:

Treatment A: 25 mg BID x 3 days (total daily dose = 50 mg)

Treatment B: 50 mg BID x 3 days (total daily dose = 100 mg)

Treatment C: 100 mg BID x 3 days (total daily dose = 200 mg)

Treatment D: Placebo x 3 days (total daily dose = 0 mg)

Schedule of Administration:

TREATMENT	MORNING	EVENING	
MILNACIPRAN 50 mg/day	1 capsule 25 mg + 3 capsules placebo	1 capsule 25 mg + 3 capsules placebo	M1
MILNACIPRAN 100 mg/day	2 capsules 25 mg + 2 capsules placebo	2 capsules 25 mg + 2 capsules placebo	M2
MILNACIPRAN 200 mg/day	4 capsules 25 mg	4 capsules 25 mg	M3
PLACEBO	4 capsules placebo	4 capsules placebo	M4

MI = Milnacipran 50 mg/day, M2 = Milnacipran 100 mg/day, M3 = Milnacipran 200 mg/day, and M4 = Placebo

Blood samples were collected at appropriate time points on Day 1 and Day 3 for PK analysis of milnacipran and its enantiomers.

Pharmacodynamic measurements:

Heart rate (HR), blood pressure (BP), and ECG were monitored at the following time points:

Supine:

0, 30, 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 14 hours.

Standing:

0, 30, 45 min, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 14 hours.

ECG:

0, 1, 2, 3, 4, 6, 8, and 12 hours.

Results:

Pharmacokinetics:

The sponsor submitted two reports from this study, one is for the PK data and the other is for pharmacodynamic (PD) data. The PK report is coded as Study # M146 and the PD report is coded as Study # C241. It should be noted that this study was also reviewed by the Division of the cardio-renal to specifically evaluate the effect of milnacipran on the cardio-vascular parameters (Review dated June 22, 2008 and e-mail dated June 26, 2008).

- There was a dose linear increase in both Camx and AUC for the parent and d-and l- enantiomers (**Figures 4.2.15.1 and 4.2.15.2**).

Figure 4.2.15.1. Dose-Exposure response for Milnacipran and its Enantiomers Following Single Doses-Day 1 (Study # M146).
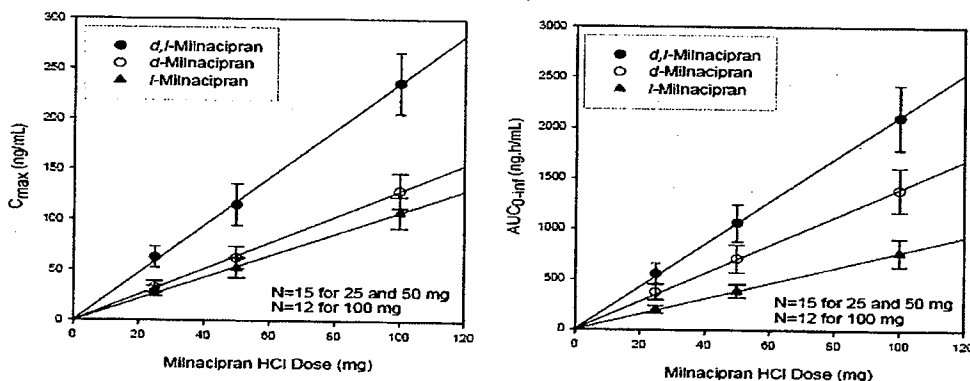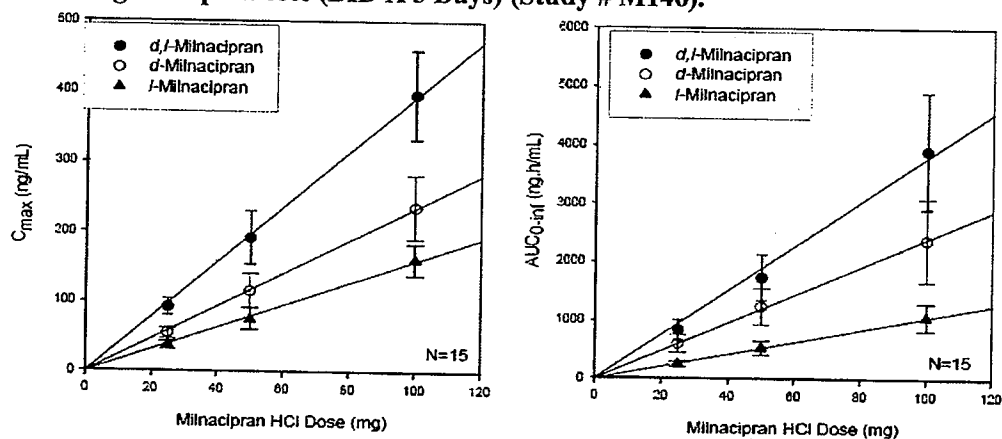
Figure 4.2.15.2. Dose-Exposure response for Milnacipran and its Enantiomers Following Multiple Doses (BID X 3 Days) (Study # M146).

- Overall the level of exposure following the *d*-isomer was consistently higher than *l*. isomer due to its slow elimination process (**Table 4.2.15.1 and Figure 4.2.15.3 A, B, C**). Compared to the single doses, the Cmax was approximately 1.6 higher than after multiple doses for all analytes.

Table 4.2.15.1. Mean PK Parameters for Single and Multiple Doses (Study # M146).

Pharmacokinetic Parameter[b]	Single Dose—Day 1			Multiple Dose—Day 3		
	25 mg (N = 15)	50 mg (N = 15)	100 mg (N = 12)	25 mg BID (N = 15)	50 mg BID (N = 15)	100 mg BID (N = 15)
	d,l-Milnacipran					
C_{max} (ng/mL)	63.2 ± 10.4	115.3 ± 20.2	236.5 ± 30.2	92.7 ± 12.1	191.7 ± 37.6	396.0 ± 63.7
T_{max} (h)	2.1 ± 0.6	3.1 ± 1.0	2.8 ± 1.2	2.3 ± 0.7	2.5 ± 0.7	2.3 ± 0.7
AUC_{0-t} (ng·h/mL)	402 ± 62	787 ± 116	1608 ± 225	–	–	–
$AUC_{0-\infty}$ (ng·h/mL)	556 ± 101	1061 ± 183	2107 ± 319	609 ± 85[c]	1292 ± 225[c]	2613 ± 515[c]
$T_{1/2}$ (h)	5.9 ± 1.1	5.4 ± 0.8	5.0 ± 0.5	6.0 ± 1.2	5.8 ± 1.1	5.3 ± 1.0
CL/F (L/h)	40.3 ± 6.9	42.2 ± 7.4	42.3 ± 7.1	36.4 ± 5.2	34.7 ± 6.3	34.5 ± 6.8
V_d/F (L)	339 ± 56	322 ± 45	299 ± 37	310 ± 40	287 ± 51	261 ± 51
	d-Milnacipran					
C_{max} (ng/mL)	33.6 ± 5.7	62.8 ± 10.8	129.7 ± 17.1	55.1 ± 7.5	116.0 ± 24.3	236.0 ± 45.5
T_{max} (h)	2.1 ± 0.6	3.1 ± 1.0	3.1 ± 1.2	2.3 ± 0.7	2.5 ± 0.7	2.3 ± 0.7
AUC_{0-t} (ng·h/mL)	237 ± 38	464 ± 71	952 ± 129	–	–	–
$AUC_{0-\infty}$ (ng·h/mL)	374 ± 77	706 ± 137	1387 ± 218	399 ± 63[c]	848 ± 158[c]	1697 ± 362[c]
$T_{1/2}$ (h)	8.0 ± 1.8	6.8 ± 1.3	6.1 ± 0.8	7.2 ± 1.6	6.9 ± 1.4	6.2 ± 1.4
CL/F (L/h)	30.2 ± 5.8	31.9 ± 6.3	32.2 ± 5.8	27.9 ± 4.2	26.5 ± 4.9	26.8 ± 5.9
V_d/F (L)	319 ± 54	304 ± 43	281 ± 33	283 ± 42	258 ± 46.6	234 ± 56

Pharmacokinetic Parameter[b]	Single Dose—Day 1			Multiple Dose—Day 3		
	25 mg (N = 15)	50 mg (N = 15)	100 mg (N = 12)	25 mg BID (N = 15)	50 mg BID (N = 15)	100 mg BID (N = 15)
	l-Milnacipran					
C_{max} (ng/mL)	29.6 ± 5.0	52.6 ± 10.0	108 ± 15.7	37.7 ± 5.8	75.7 ± 16.2	161.0 ± 22.0
T_{max} (h)	2.1 ± 0.6	2.9 ± 1.1	2.8 ± 1.2	2.3 ± 0.7	2.3 ± 0.8	2.3 ± 0.7
AUC_{0-t} (ng·h/mL)	165 ± 28	323 ± 54	656 ± 112	–	–	–
$AUC_{0-\infty}$ (ng·h/mL)	200 ± 40	384 ± 70	768 ± 140	210 ± 34[c]	443 ± 92[c]	916 ± 195[c]
$T_{1/2}$ (h)	4.3 ± 0.8	4.0 ± 0.5	3.7 ± 0.4	4.4 ± 0.7	4.4 ± 0.8	4.0 ± 0.5
CL/F (L/h)	56.4 ± 10.6	58.4 ± 10.5	58.4 ± 10.7	53 ± 8.5	51.0 ± 10.7	49.3 ± 9.7
V_d/F (L)	344 ± 56	330 ± 54	310 ± 48	333 ± 47	314 ± 58	279 ± 49

a   Data are presented for subjects who did not experience emesis during treatment.
b C_{max} and AUC values reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).
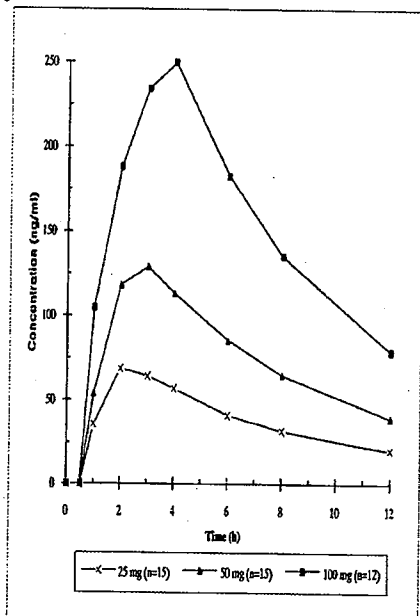c $AUC_{0-\tau}$

C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; AUC_{0-t} = area under the plasma concentration vs time curve from time 0 to t; $AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{1/2}$= terminal elimination half-life; CL/F = apparent total clearance of drug from plasma after oral administration; V_d/F = apparent volume of distribution after oral administration; $AUC_{0-\tau}$ = area under the plasma concentration versus time curve over the dosing interval at steady state.
Cross-reference: Study M146, Tables 8, 9, 10, 12, 13, and 14.

Figure 4.2.15.3. Mean Plasma Concentration-Time Profiles of Milnacipran and its Enantiomers Following Single (Day 1) Multiple Doses (BID X 3 Days) (Study # M146).
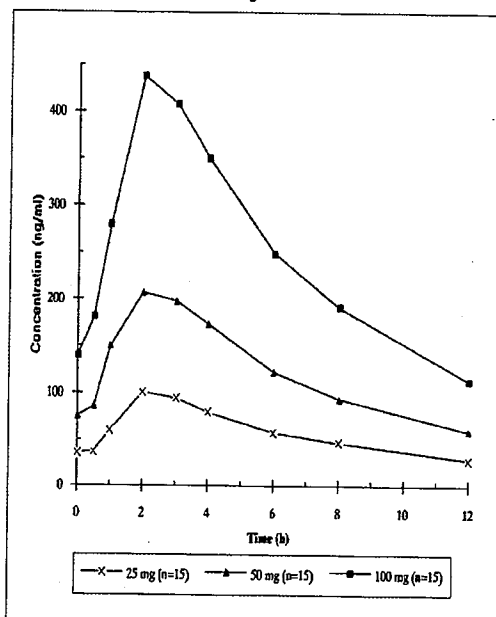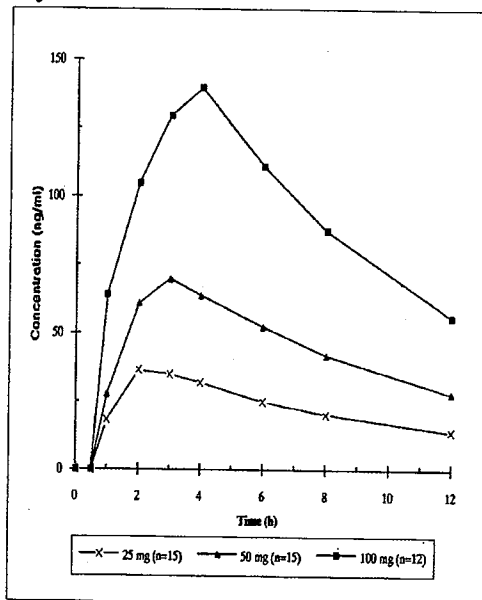
Figure 4.2.15.3 A: Milnacipran:
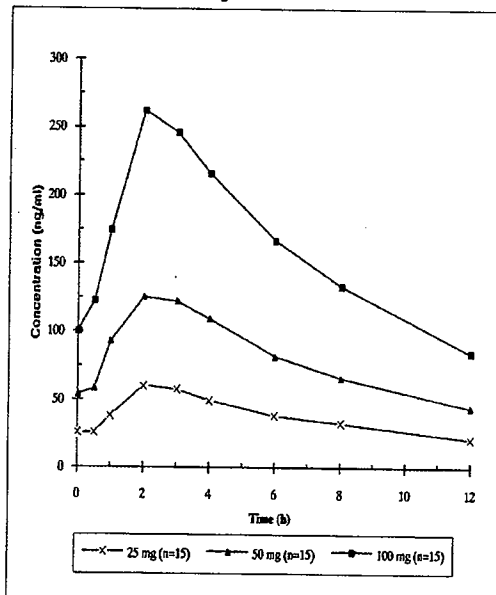
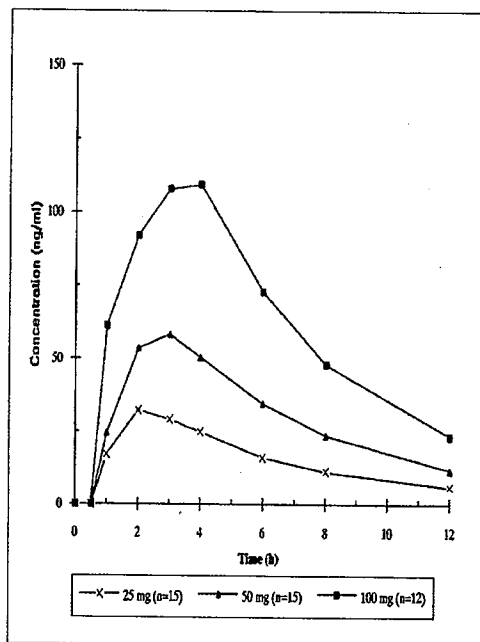Day 1

Day 3

Figure 4.2.15.3 B: d-Isomer
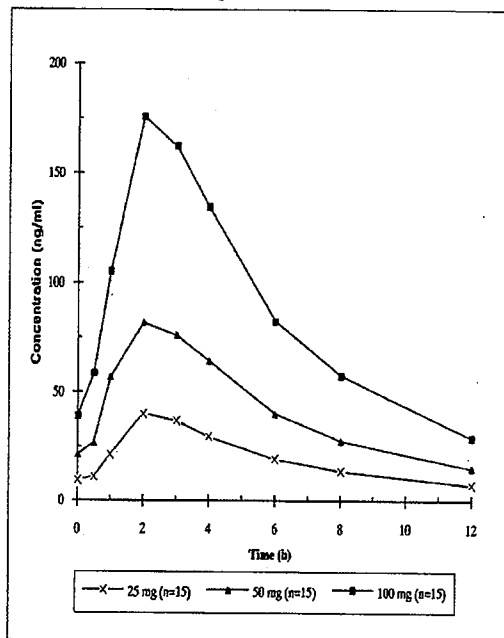
Day 1

Day 3

Figure 4.2.15.3 C: l-Isomer
Day 1   **Day 3**

Pharmacodynamics and Effect on Cardiovascular Parameters:

- From the pharmacodynamic's perspective, there was a trend for increase in pulse rate and heart rate over the three day dosing period compared to placebo (**Figures 4.2.15.4-6 and Tables 4.2.15.2-7**). As stated earlier that this section of the study was also reviewed by Dr. Gail Moreschi of the Division of cardio-renal (review dated June 22, 2008 and e-mail dated June 26).

- From the clinical pharmacology perspective, the drug appears to increase the blood pressure, heart rate and pulse rate in time dependent manner. From this study the data shows that the heart rate is higher on Day 3 compared to baseline on Day 0.

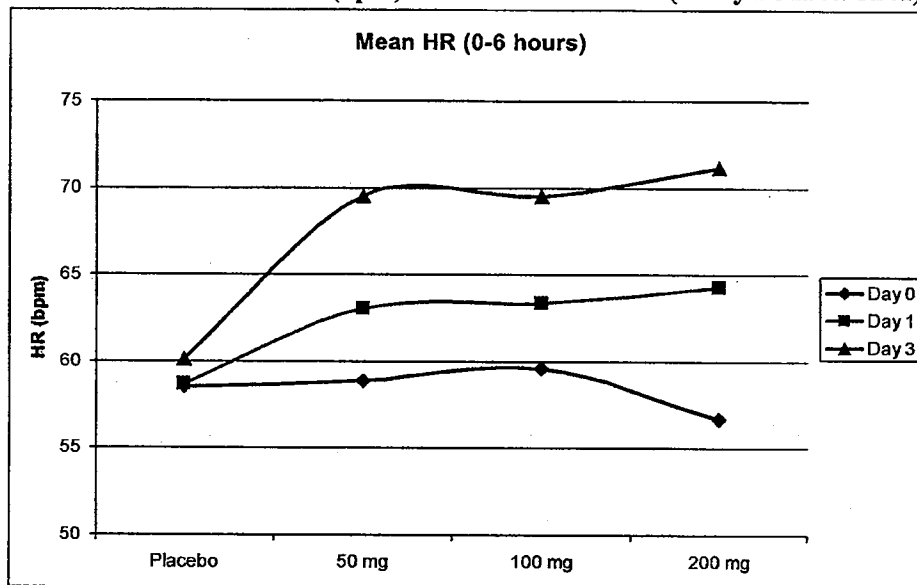**Figure 2.2.15.4. Mean Heart Rate (bpm) Holter From 0 to 6 h (Study # M146/C241)**

Table 2.2.15.2. Mean Heart Rate (bpm) Holter From 0 to 6 h (Study # M146/C241)
MEAN HEART RATE (bpm) Holter
from 0 h 00 to 6 h 00

	D0 mean ± SD	D1 mean ± SD	D3 mean ± SD
Placebo	58,50 ± 7,03	58,69 ± 6,58	60,13 ± 6,30
50 mg	58,88 ± 6,39	63,06 ± 5,81	69,53 ± 6,67
100 mg	59,56 ± 7,41	63,33 ± 7,00	69,50 ± 6,60
200 mg	56,69 ± 6,34	64,31 ± 9,18	71,19 ± 8,21

Table 2.2.15.3. Mean Variations of Heart Rate (bpm) Holter From 0 to 6 h (Study # M146/C241)

MEAN VARIATIONS OF HEART RATE (bpm) Holter
from 0 h 00 to 6 h 00

	D1 – D0 mean ± SD	D3 – D0 mean ± SD
Placebo	0,19 ± 3,54	1,75 ± 3,38
50 mg	4,19 ± 4,10	10,19 ± 6,82
100 mg	4,25 ± 3,96	9,94 ± 5,17
200 mg)	7,63 ± 5,07	14,50 ± 5,57

Figure 2.2.15.5. Mean Heart Rate (bpm) Holter From 0 to 24 h (Study # M146/C241)
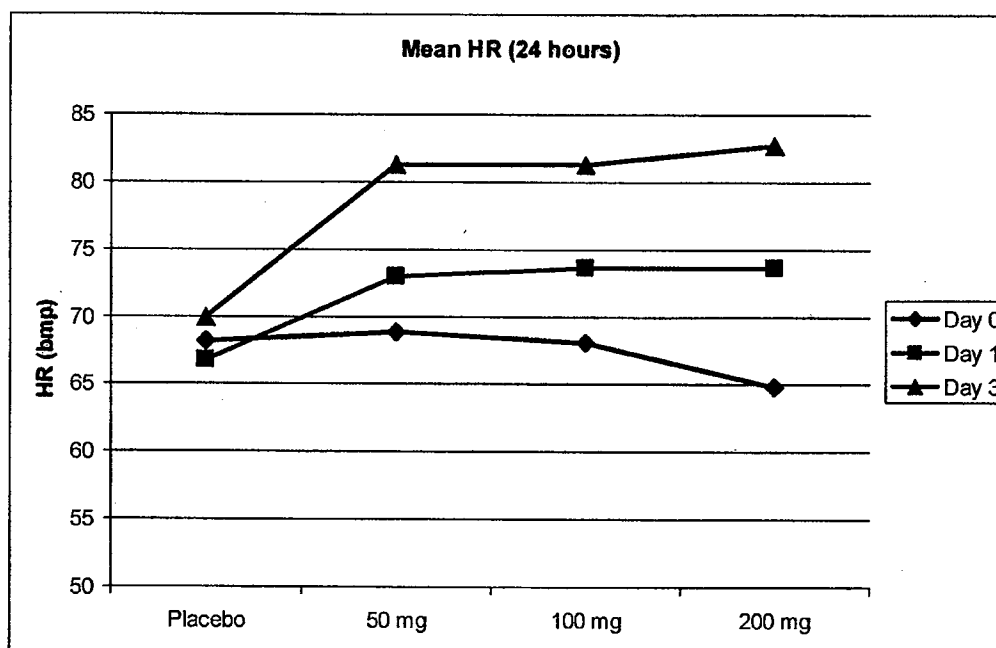
Table 2.2.15.4. Mean Heart Rate (bpm) Holter From 0 to 24 h (Study # M146/C241)

MEAN HEART RATE (bpm) : 24 hours at D0, D1, D3 (Holter)

	D0 mean ± SD	D1 mean ± SD	D3 mean ± SD
Placebo **50 mg** **100 mg** **200 mg**	68,25 ± 6,09 68,81 ± 6,65 68,13 ± 6,56 64,81 ± 6,84	66,81 ± 5,69 73,06 ± 6,93 73,69 ± 8,61 73,69 ± 8,80	69,94 ± 6,22 81,25 ± 7,04 81,31 ± 6,89 82,69 ± 7,72

Table 2.2.15.5. Mean Variations in Heart Rate (bpm) Holter From 0 to 24 h (Study # M146/C241)

MEAN VARIATIONS OF HEART RATE (bpm) Holter 24 hours

	D1 – D0 mean ± SD	D3 – D0 mean ± SD
Placebo	– 1,44 ± 4,34	1,69 ± 4,69
50 mg	4,25 ± 3,71	12,44 ± 5,93
100 mg	5,56 ± 4,80	13,19 ± 5,27
200 mg	8,88 ± 4,84	17,88 ± 7,01

Table 2.2.15.6. Maximum Supine Systolic Blood Pressure (Study # M146/C241)
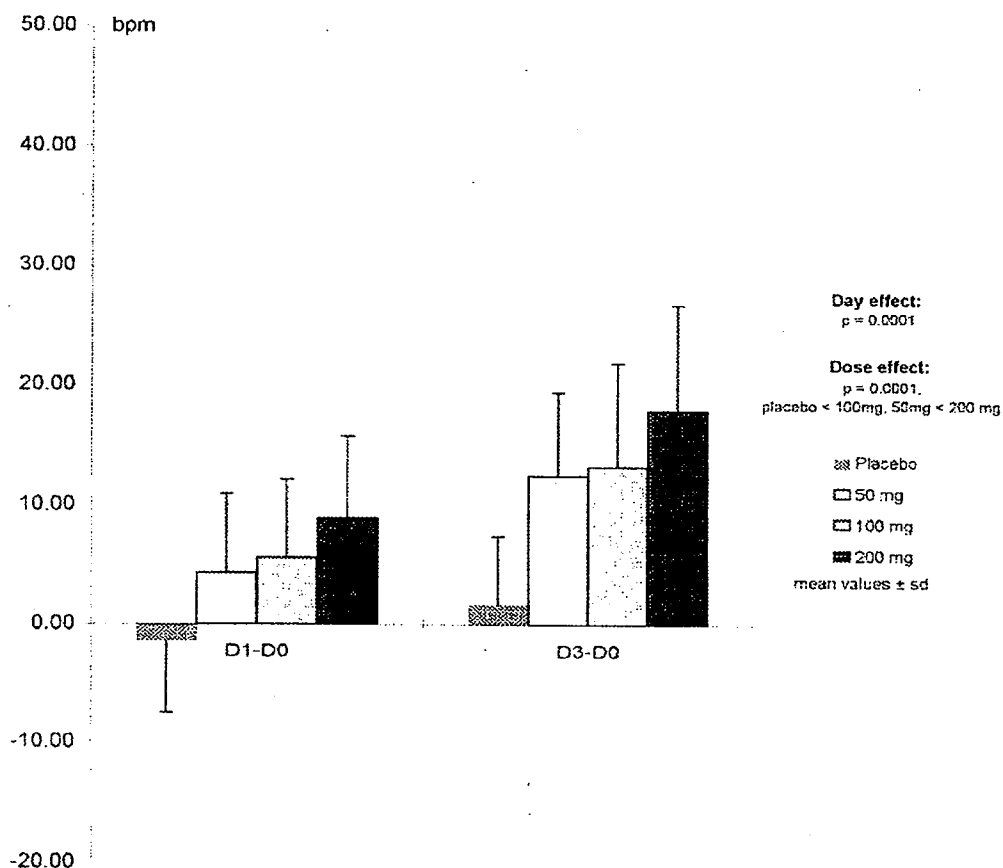
MAXIMAL SUPINE SYSTOLIC BLOOD PRESSURE (mmHg)

	D1 mean ± SD	D2 mean ± SD	D3 mean ± SD
Placebo	131,00 ± 7,55	130,06 ± 8,43	129,50 ± 7,16
50 mg	137,94 ± 8,98	136,13 ± 9,98	134,63 ± 7,48
100 mg	135,38 ± 6,65	133,63 ± 6,88	133,38 ± 8,29
200 mg	139,88 ± 10,77	138,31 ± 6,48	135,44 ± 6,28

Table 2.2.15.7 Maximum Supine Diastolic Blood Pressure (Study # M146/C241)
MAXIMAL SUPINE DIASTOLIC BLOOD PRESSURE (mmHg)

	D1 mean ± SD	D2 mean ± SD	D3 mean ± SD
Placebo	74,13 ± 5,26	72,81 ± 4,92	71,81 ± 5,49
50 mg	77,38 ± 6,47	79,25 ± 6,84	79,19 ± 7,76
100 mg	76,81 ± 5,71	79,00 ± 7,18	79,81 ± 6,75
200 mg	78,88 ± 8,07	78,81 ± 5,21	80,06 ± 6,80

Figure 2.2.15.4. Effect on Dose and Duration on Heart Rate on Day 1 (D 1) and Day 3 (D 3) as Normalized for Baseline Day 0 (D0) Following Single (Day 1) and Multiple Doses (BID X 3 Days) of Milnacipran (Study # M146/C241).

Variations of Mean Heart Rate
24H Holter (bpm)

Reviewer's Comments:

The study show dose linearity in exposure (Cmax and AUC) after single and multiple doses (BID X 3 days). The exposure for d-isomer appears to be consistently higher than l-isomer. The effect on heart rate and other physiological parameters appears to be duration dependent (See also Dr. Gail Moreschi review).

Conclusions:

The main conclusion from this study is that milnacipran Cmax and AUC increase linearly with dose. In addition, the cardiovascular effect appears to be dependent on duration of treatment compared to placebo.

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4.2.16 Study # MLN-PK-10 (QT Study)

Objective:

The primary objective of this study was to evaluate the effect of milnacipran on QT prolongation.

Study Design:

This study was reviewed by CDER QT-IRT group and the final assessment of the study is deferred to them (review dated June 18, 2008). This was a double-blind, placebo, and active controlled at doses ranging from 12.5 mg to 300 mg giving BID in up to 38 days. The active control was 400 mg moxifloxacin and was administered on Day 1. Blood samples were collected at appropriate intervals on Day 1 and the last day (Day 37/38). In addition, ECGs were collected at screening and End of Study, as well as on Days 22, 26, 30, and 34.

Briefly, the study design was as follows:

- **Part A:** Was conducted in 15 subjects at escalating doses from 12.5 mg to 300 mg BID X 36 days (active and placebo).
- **Part B:**
    o **Part B 1:** Was conducted in 100 subjects also at escalating doses from 12.5 mg to 300 mg BID X 38 days (active and placebo).
    o **Part B2:** Placebo sub-arm for 400 mg moxifloxacin encapsulated and placebo for 100 mg milnacipran capsule. A single dose of 400 mg of moxifloxacin was administered on Day 1 of the placebo arm.

Results:

- It appears that there was increase in heart rate in Part A and Part B by approximately 20 to 26 bpm (**Tables 4.2.16.1 and 4.2.16.2 and Figure 4.2.16.1**). According to the sponsor's analysis using Fridericia's formula (QTcF) there was no change in QTc in either part A or Part B. However, using the Bazzett's formula, there was approximately 17 to 20 ms increase in QTc in milnacipran arm compared to placebo.

Table 4.2.16.1. Mean EEG Values (± SD) at Screening and End of the Study in Part A (Study # MLN-PK-10).

	Placebo (N=3)			Milnacipran (N=12)		
	Screening	End-of-Study	Change From Screening	Screening	End-of-Study	Change From Screening
PR Interval, ms	146.0 ± 16.4	154.7 ± 21.4	8.7 ± 31.3	148.2 ± 14.6	149.4 ± 15.9	1.3 ± 17.4
QRS Interval, ms	90.0 ± 10.6	97.3 ± 3.2	7.3 ± 8.4	92.3 ± 6.5	94.3 ± 7.3	1.9 ± 7.1
QT Interval, ms	402.0 ± 26.2	377.0 ± 17.3	−25.0 ± 11.4	393.7 ± 22.9	346.8 ± 17.1	−46.9 ± 19.4
QTcF Interval, ms	401.57 ± 11.83	403.28 ± 17.14	1.71 ± 24.82	397.43 ± 19.50	394.23 ± 21.31	−3.2 ± 25.7
QTcB Interval, ms	401.53 ± 8.95	417.36 ± 24.77	15.82 ± 33.71	399.56 ± 22.71	420.44 ± 25.22	20.88 ± 34.81
Ventricular Heart Rate, bpm	60.3 ± 7.8	74.0 ± 10.6	13.7 ± 9.0	62.3 ± 7.6	88.3 ± 6.5	26.1 ± 11.2

QTcF = QT interval corrected for heart rate using the Fridericia formula (QTc = QT/[60/HR]$^{\frac{1}{3}}$);
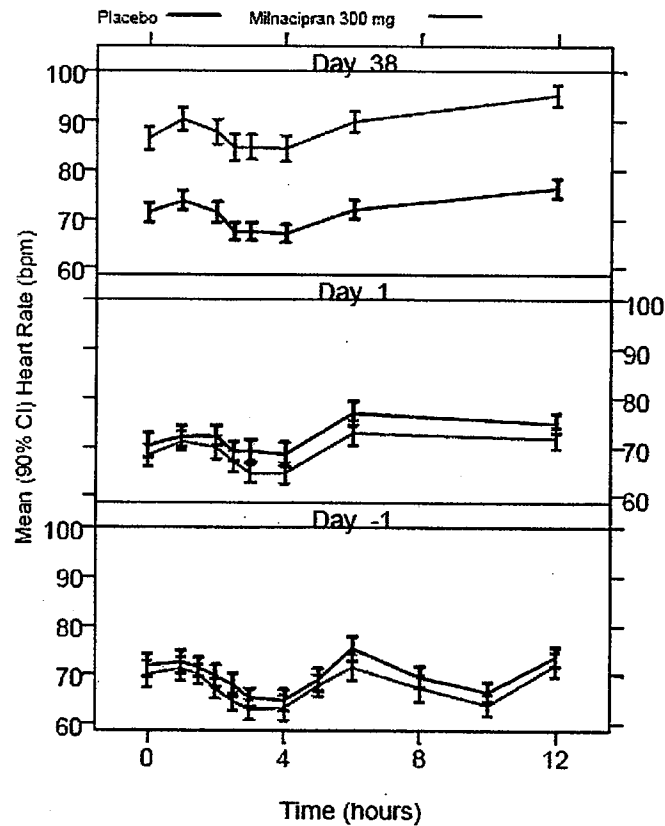 QTcB = Bazett's correction (QTc = QT/[60/HR]$^{\frac{1}{2}}$).

Table 4.2.16.2. Mean EEG Values (± SD) at Screening and End of the Study in Part B (Study # MLN-PK-10)

	Moxifloxacin/Placebo (N=51)			Milnacipran (N=49)		
	Screening	End of Study	Change From Screening	Screening	End of Study	Change From Screening
PR Interval, ms	148.6 ± 18.2	156.8 ± 16.5	8.2 ± 14.8	150.7 ± 19.6	148.4 ± 17.8	−2.3 ± 12.6
QRS Interval, ms	91.5 ± 9.0	94.7 ± 8.6	3.2 ± 5.2	94.9 ± 9.7	94.4 ± 10.6	−0.5 ± 6.3
QT Interval, ms	391.2 ± 22.2	382.2 ± 24.9	−9.0 ± 20.0	402.6 ± 20.9	363.3 ± 21.0	−39.3 ± 26.4
QTcF Interval, ms	398.23 ± 17.81	396.25 ± 19.22	−1.98 ± 13.09	405.00 ± 14.23	402.44 ± 14.00	−2.56 ± 14.07
QTcB Interval, ms	401.99 ± 19.78	403.75 ± 21.40	1.76 ± 15.31	406.49 ± 17.85	423.96 ± 19.63	17.47 ± 18.93
Ventricular Heart Rate, bpm	63.8 ± 7.7	67.6 ± 8.8	3.8 ± 8.6	61.8 ± 8.8	82.7 ± 12.4	21.0 ± 13.7

QTcF = QT interval corrected for heart rate using Fridericia formula (QTc = QT/[60/HR]$^{\frac{1}{3}}$);
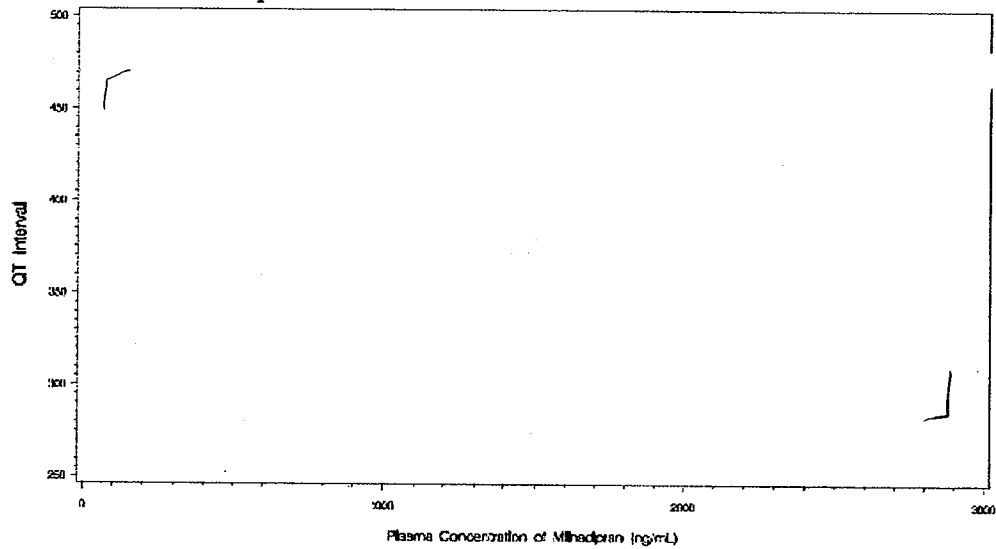 QTcB = Bazett's correction (QTc = QT/[60/HR]$^{\frac{1}{2}}$).

Figure 4.2.16.1. Time Course of Mean Heart Rate (90% CI) by Treatment Group and Day (Source: Figure 7, Page 19 of IRT Review dated June 18, 2008).

- According to the IRT-QT review, the drug caused increase in heart rate with a mean of 22 bpm (**Figure 4.2.16.1**). Based on IRT-QT analysis, the drug appears to have a mean change in QTcF of 8 ms. The effect appears to have no relationship relationship with milnacipran plasma concentration based on the sponsor's analysis (**Figure 4.2.16.2**) and a shallow relationship based on IRT-QT analysis (**Figure 4.2.16.3**).
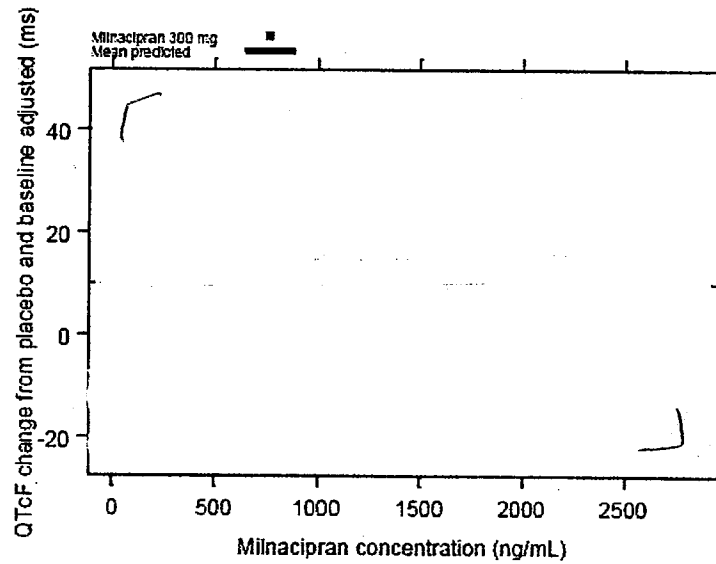
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Figure 4.2.16.2. Sponsor's Analysis for the Relationship Between Uncorrected QT Intervals and Milnacipran Concentration

Figure 4.2.16.3. IRT Analysis for the Relationship Between QT Intervals and Milnacipran Concentration

IRT-QT Team Conclusions

Recommendation:
The following is an excerpt of the recommendation from QT-IRT team based on their assessment of the data obtained from this study;

1.1 QT-IRT'S RECOMMENDATION

There are several limitations to the study which decrease our confidence in the study results. The main limitations are:

(1) At a dose of 300 mg bid, milnacipran increased the heart rate by a mean of 22 bpm. The sponsor derived an individual-specific heart rate correction factor (QTcNi) using interval data collected at rest on day -1. This is not suitable to apply to a drug that increases heart rates outside the resting range because it assumes that the QT/RR relationship remains linear outside the resting range. According to the sponsor's analysis, the mean increase in $\Delta\Delta$QTcNi is -5 (-9.4, -0.08) ms. If, however, the same analysis is performed using QTcF, the mean increase in $\Delta\Delta$QTcF is 7.7 (3.5, 12.0) ms. We used QTcF in our analysis of the data.

(2) The study is not optimally designed to assess assay sensitivity. Moxifloxacin was administered to subjects on day 1 followed by dosing with placebo or milnacipran for 37 days. The moxifloxacin should be

conducted concurrently with the other treatment arms in order to demonstrate that the study was designed and conducted to detect an effect on the QT/QTc interval of around 5 ms.

We recommend that the sponsor performs a repeat TQT study incorporating the following elements:

- Use exercise or 24-h ambulatory ECG monitoring at baseline as a method to increase the range of heart rates to compute an individual-correction factor.

- Collect additional ECGs during the titration of milnacipran to determine the dose/concentration-response relationship for QT prolongation.

- Moxifloxacin control should be conducted concurrently with the other arms.

- In this study, over-encapsulation of the moxifloxacin tablet may have caused a decrease in moxifloxacin exposure. We recommend that blinding is performed using a double-dummy approach.

In the absence of a repeat TQT study, the QT-IRT team recommended the following labeling language;

Cardiovascular Electrophysiology. The effect of BRAND on the QTcF interval was measured in a double-blind placebo- and positive-controlled parallel study in 88 healthy subjects using 600 mg/day BRAND (3 to 6 times the recommended therapeutic dose for FMS). After baseline and placebo adjustment, the maximum mean QTcF change was 8 ms (1-sided 95% Upper CI: 12 ms).

4.3 Consult Review (Pharmacometric Review)

Not Applicable.

4.4 Filing Memo:

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-256	Brand Name	
OCP Division (I, II, III, IV, V)	II	Generic Name	Milnacipran
Medical Division	Anesthesia, Analgesia, and Rheumatology Products	Drug Class	NSRI (Norepine/Serotonin reuptake inhibitor)
OCP Reviewer	Sayed (Sam) Al-Habet, RP.h., Ph.D.	Indication(s)	Treatment of Fibromyalgia Syndrome (FMS)
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Tablet
		Dosing Regimen	12.5-100 mg BID
Date of Submission	December 18, 2007	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Forest and Cypress
PDUFA Due Date		Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	2		
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -	▮	▮		
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	x			
multiple dose:				
Dose proportionality -	▮			
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -	▮	▮		
In-vivo effects on primary drug:	x			

	X			
In-vivo effects of primary drug:	x			
In-vitro:	x			
Subpopulation studies -		■		
ethnicity:	x			
gender:	x			
pediatrics:	x			
geriatrics:	x			
renal impairment:	x			
hepatic impairment:	x			
PD:				
Phase 2:				
Phase 3:				
PK/PD:		■		
Phase 1 and/or 2, proof of concept:	x			
Phase 3 clinical trial:	x			
Population Analyses -				
Data rich:	x			
Data sparse:				
II. Biopharmaceutics		■		
Absolute bioavailability:	X	1		
Relative bioavailability -	■	■		
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -		■		
traditional design; single / multi dose:	x			
replicate design; single / multi dose:	x			
Food-drug interaction studies:	X			
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS	x			
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		~60	~60	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	The sponsor did not conduct enzyme induction studies with milnacipran. Therefore, the sponsor should be advised in the 74 days letter to provide information on enzyme induction potential with milnacipran.
QBR questions (key issues to be considered)		Has the sponsor adequately characterized the PK of the drug product? The sponsor conducted extensive PK studies to fully characterize the PK and the clinical pharmacology of the drug. Approximately 60 in vivo and in vitro studies were conducted as listed above. For details, see the attached filing slides.
Other comments or information not included above		

Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

Filing Slides

Clinical Pharmacology Review
Filing Meeting
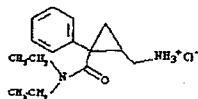## (NDA 22-256 Milnacipran)
(January 25, 2008)

Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Suresh Doddapaneni, Ph.D.

1

Submission Summary

NDA #:	22, 256
Date of Submission:	December 18, 2007
Generic Name:	Milnacipran
Trade Name:	N/A
Formulation:	Tablet (12.5, 25, 50, and 100 mg)
Route of Administration:	Oral
Indications:	Fibromyalgia Syndrome (FMS)
Proposed Dose:	12.5 mg to 100 mg BID (max)
Type of Submission:	NME
Sponsor:	Forest Laboratories and Cypress Bioscience
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Suresh Doddapaneni, Ph.D.

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Overview

- NME
- Discovered in 1997 in France
- Selective Norepinephrine and serotonin reuptake inhibitor (NSRI)
- Current indication: Approved outside the US for major depression
- Indication: Fibromyalgia Syndrome (FMS)
- Strengths: 12.5, 25, 50, and 100 mg IR tablets
- Proposed Dose: 12.5 mg to 100 mg/day or 100 BID (200 mg/day Max)
- Co-developed by Cypress Biosciences, Inc. and Forest Lab.
- Structural configuration: Racemate (*d* and *l* enantiomers)

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What Has been Submitted?

- Five clinical studies:
  - Two Pivotal:
    - MLN-MD 02
    - FMS 031 (or MLN-MD-01)

- 49 Phase I PK studies (including 7 BA/BE studies):

  - 47 in healthy subjects
  - 1 in Depressed patients
  - 1 in pediatric patients

- Five *in vitro* studies:

  - Metabolism
  - CYP 450
  - Plasma Protein binding studies

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Bio-Waiver Request

- Bio-waiver request for the tablet (to be marketed) and the capsule used in Phase I and III was granted on December 13, 2006 (IND 63,736).

- Bio-waiver was based on in vitro data aas well as BCS classification:

  - □ Class I:
    - Highly soluble
    - Highly permeable

Note: At this point all the 7 BE/BA studies will be reviewed to establish the link among several formulations and lots.

Summary of PK Studies

General/Basic PK Info:

- Plasma protein binding: 12.9% (independent of concentration)
- Tmax: 2–4 h
- Absolute F = 85% to 90% (M038 and M046)
- T ½ = 8-10 h (d enantiomer) and 4-6 h (l enantiomer)) and
- Css = 36 to 48 h (M037)
- Isomers: d and l enantiomer (d is higher than l) (M112, M113, M115, MLN-PK-01, M146, and M120))
- Dose proportional: 25 to 300 mg (M040 and M036)
- Food: no effect (MLN-PK-04, M039, and M124)
- Mass Balance: ^{14}C 100 mg PO: 93% of ^{14}C and 55% unchanged in urine (MLN-PK-05, M002, M034)

Summary of PK Studies

(Special Population)

Hepatic Impairment

- Two Studies: # MLN-PK-11 PO only and # M046 PO and IV)
  - Dose: 50 mg single oral and IV dose
  - Severe: No change in Cmax (13 to 17% lower than healthy)
  - Severe: ~55% increase in AUC (46 % to 60%)

Table 2.6.3.1-1. Pharmacokinetic Parameters (Mean ± SD) of Milnacipran Following a Single 50-mg Dose of Milnacipran HCl in Healthy Subjects and Subjects With Various Degrees of Hepatic Impairment

Pharmacokinetic Parameter	Healthy Subjects (N = 7)	Hepatic Impairment Group		
		Subjects With Mild Hepatic Impairment (N = 7)	Subjects With Moderate Hepatic Impairment (N = 6)	Subjects With Severe Hepatic Impairment (N = 4)
C_{max} (ng/mL)	157.26 ± 30.1	136.17 ± 51.33	130.48 ± 43.43	132.78 ± 37.57
T_{max} (h)	2.6 ± 1.4	4.0 ± 1.2	2.5 ± 0.8	3.8 ± 1.0
AUC_{0-t} (ng·h/mL)	1458 ± 467	1528 ± 729	1280 ± 621	1955 ± 573
$AUC_{0-\infty}$ (ng·h/mL)	1591 ± 455	1635 ± 762	1403 ± 655	2062 ± 588
$T_{1/2}$ (h)	8.0 ± 1.4	8.7 ± 1.7	8.4 ± 2.1	12.4 ± 1.1
A_e (mg)	19.02 ± 5.55	24.65 ± 6.59	19.1 ± 8.3	26.05 ± 5.33*
CL, (L/h)	33.6 ± 5.7	17.9 ± 7.6	13.4 ± 5.3	14.7 ± 0.5*
fe (% dose)	43.7 ± 12.7	56.7 ± 15.1	44.0 ± 19.1	59.9 ± 12.7*

Summary of PK Studies

Renal Impairment

(Studies: # ML-N-PK-02 Mild to Severe and M045/M117 chronic failure)

- Dose = 50 mg single dose
- Exposure is ~60 to 200% higher in severe than healthy
- L enantiomer is more affected than d
- Renal clearance (Clr) decreased linearly with decrease in renal function

Table 1.1.3.2-1. Changes in Mean Milnacipran Pharmacokinetic Parameters Following a Single, 50-mg, Oral Dose of Milnacipran HCl in Subjects With Renal Impairment Compared With Healthy Subjects[a]

Renal Impairment Group	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$T_{1/2}$ (h)	CL/F (L/h)
Mild	12%	16%	38%	−14%
Moderate	26%	52%	41%	−28%
Severe	59%	199%	122%	−65%

a Subjects without vomiting

C_{max} = maximum plasma drug concentration; $AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{1/2}$ = terminal elimination half-life; CL/F = apparent total clearance of drug from plasma after oral administration.

Summary of PK Studies
(Metabolism and Drug-Interaction)

Genetic Polymorphism (Study # M244):

- Single and multiple dose evaluating various probes for CYP450 (M24):

    Examples:

    Sparteine (2D6), Mephenytoin (2C19), and caffeine (1A2), 6β-cortisol (3A4)

- EM vs PM metabolizers using Sparteine (2D6) and Mephenytoin (2C19) (Study # M24)

- Glucuronidation appears to be the major pathway (~20% carbamoyl o-glucuronide and 8 N-desethyl milnacipran)

- Low *in vitro* metabolism using hepatic microsomes

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Summary of PK Studies
(Drug Interaction)

Drug Interaction Studies

- Digoxin (#MLN-PK-08 and M135)
- Warafrin (#MLN-PK-07)
- Levomepromazine (# M126 and C221)
- Carbamazepine (M130)
- Lithium (M125)
- Lorazepam (# M138)
- Fluoxetine (# M212)
- Clomipramine (# M213)
- Alcohol (#GE 103)
- TCA (e.g. amitriptyline) (Study # C012)

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Summary of PK Studies

QT and Cardiovascular Study (# MLN-PK-10 and # C 241)

- Multiple dose in healthy subjects

- Moxifloxacin used as positive control (400 mg on Day 1, then placebo days 2 to 28)

- Doses: Up titrated from 12.5 mg to 300 mg BID (Days 2 to 38)

- At glance no major signal on QTc

Deliverable at Mid Cycle Meeting

Specific Studies:

- Evaluation of dose response.
- Assessment of any additional drug-drug interaction studies
- Mass Balance and metabolic pathways

General Evaluation (From Clinical Pharmacology Perspective)

- Any PK/PD relationship?
- Is the selected dose (s) adequate to establish PK/PD relationship?
- Optimal dose an dose range assessment
- Assessment of dose in special population (adequacy of dose, duration, and designs)
- Identification of any critical issues that may preclude approval

Recommendation

From the clinical pharmacology perspective,
the application is fileable.

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Back Up Slides

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Labeling Highlights (1 of 2)

Dosage and Administration:

b(4)

15

Labeling Highlights (2 of 2)

Basic PK:

b(4)

16

Formulation Development

- 7 + 2 BA/BE studies, including addendums (M038, MLN-PK-04, M039/M124, M048, M112/M113, M140, M141)

- Absolute BA (M038)

- Effect of Food on 50 mg capsule (M039/M124) and 100 mg capsule (MLN-PK-04)

- Relative BA: Four studies for tablets and capsules (M048, M112/M113, M149, and M141)

- Both enantiomers (*d* and *l*) were measured in most of the studies

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Clinical Formulations (Phase I and III)
(Capsules vs Tablets)

b(4)

18

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PK Summary

Pediatrics (7 to 12 years): Study # M041

- Small study (n=12)
- Dose= 25 mg single dose
- Cmax and AUC where 67% and 10% higher in children compared to adults from study # M040)

Note: Not recommended in pediatric patients (Proposed label)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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/s/
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Sayed Al-Habet
8/29/2008 09:51:18 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/29/2008 10:35:19 AM
BIOPHARMACEUTICS

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: October 7, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Resolution of Abuse and Dependence Assessment
NDA 22-256 (Milnacipran)
Indication: Treatment of Fibromyalgia (100, 200 mg/day)
Sponsor: Forest Laboratories, Inc.

Summary

On October 7, 2008, CSS met with representatives of the Division of Anesthesia, Analgesia and Rheumatology Products and the Office of Drug Evaluation II to discuss the abuse potential and physical dependence of milnacipran[1]. The discussion focused on an analysis of available data from animal and human studies conducted with milnacipran. In two previous consults, CSS had considered the need for additional information from the Sponsor before a decision could be made regarding appropriate labeling of milnacipran on abuse-related issues.

1) From the review of the data submitted in the NDA regarding the abuse potential of milnacipran, CSS draws the following conclusions:

* There are no data from animal studies conducted with milnacipran that are suggestive of abuse potential. Specifically:

-- The receptor binding profile and biochemical pharmacology of milnacipran shows that it is a serotonin-norepinephrine reuptake inhibitor (SNRI). This mechanism of action is not recognized as one associated with abuse potential and no marketed drugs with this pharmacology are scheduled under the Controlled Substances Act (CSA).

-- The overt behavioral profile following administration of milnacipran to mice and

---

[1] Attendees included Curt Rosebraugh, MD; Bob Rappaport, MD; Mwango Kashoki, MD; Diana Walker, PhD; Michael Klein, PhD; Katherine Bonson, PhD.

monkeys did not include a constellation of behaviors indicative of abuse potential.

* The data from clinical studies conducted with milnacipran do not suggest that milnacipran has abuse potential. Specifically:

-- There was a low incidence of abuse-related adverse events (AEs) in Phase 1 clinical studies conducted with milnacipran, compared to placebo. The euphoria-related AEs of "euphoria" and "feeling drunk" were each reported in 1 of 203 subjects who received milnacipran (0.5%) and in 0 of 60 subjects who received placebo (0%). The AEs of "somnolence" and "sedation" were reported in (respectively) 4 and 2 of 203 subjects (2.0% and 1.0%) who received milnacipran, compared to 0 of 60 subjects who received placebo (0%). The AE of "cognitive disorder" was reported in 1 of 203 subjects who received milnacipran (0.5%) and in 0 of 60 subjects who received placebo (0%).

-- There was a low incidence of abuse-related adverse events (AEs) in Phase 2/3 clinical studies conducted with milnacipran, compared to placebo (see Table 1 below). The incidence of AEs that may indicate abuse potential (anxiety, somnolence, disturbance in attention, mood altered, affect lability) following milnacipran administration was lower than or equal to that observed in placebo-treated patients. Three AEs resulting from milnacipran administration showed an incidence that was higher for milnacipran than that in the placebo group: confused state (0.7% vs. 0.2%), hallucination (0.3% vs. 0%) and disorientation (0.1% vs. 0%). The incidence of the AE insomnia was higher in the milnacipran group than in the placebo group, but both treatment groups reported high rates that were similar to each other (12% vs. 10%, respectively). Notably, there were no reports of euphoria in the milnacipran-treated group.

Table 1: Possible Abuse-Related AEs During Phase 2/3 Studies with Milnacipran

Abuse-Related AE	Milnacipran (n = 1557)	Placebo (n = 652)
Insomnia	189 (12%)	65 (10%)
Anxiety	62 (4.0%)	26 (4.0%)
Somnolence	19 (1.2%)	13 (2.0%)
Confused State	12 (0.7%)	1 (0.2%)
Disturbance in Attention	12 (0.7%)	7 (1.1%)
Hallucination	3 (0.3%)	0 (0%)
Mood Altered	2 (0.2%)	5 (0.8%)
Affect Lability	1 (0.1%)	3 (0.5%)
Disorientation	1 (0.1%)	0 (0%)

* Thus, the data submitted in the NDA do not indicate that milnacipran has abuse potential.

* Therefore, the drug label for milnacipran should accurately reflect the data on abuse-related signs from the animal and human studies.

* Further studies to address the abuse potential of the drug are not needed at this time. If new data showing an abuse potential signal are reported post-marketing, we will revise our recommendation and require the studies proposed in previous consults.

2) The following conclusions were drawn from the data submitted in the NDA regarding physical dependence of milnacipran:

* Prospective studies on the ability of milnacipran to produce physical dependence in humans were not submitted in the NDA.

* However, the Sponsor acknowledged in their proposed label wording that milnacipran produced a withdrawal syndrome in non-fibromyalgia patients. Since the presence of a withdrawal syndrome is the basis of determining the presence of physical dependence, this label statement indicates that milnacipran produces physical dependence.

* DAARP noted that there were reports of withdrawal-like adverse events following discontinuation of milnacipran in clinical trials with fibromyalgia patients.

* As described above, milnacipran is an SNRI. The ability of other SNRIs and serotonin-selective reuptake inhibitors (SSRIs) to produce physical dependence is well-known and is reflected in their drug labels. Thus, the ability of milnacipran to produce physical dependence is consistent with what is known about drugs in this pharmacological class.

* Therefore, the drug label for milnacipran should accurately reflect the known withdrawal syndrome associated with SNRIs and SSRIs and should state that milnacipran has the ability to produce physical dependence.

Recommended Label Wording:

b(4)

3

___2___ Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

9/23/08

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: September 23, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Deficiencies in Abuse and Dependence Data in NDA
NDA 22-256 (Milnacipran)
Indication: Treatment of Fibromyalgia (100, 200 mg/day)
Sponsor: Forest Laboratories, Inc.

Deficiencies in Abuse and Dependence Data in the NDA

The information submitted in the NDA regarding the abuse potential and dependence of milnacipran in humans is incomplete. Specifically:

* Section 5.13 Discontinuation of Treatment of the proposed drug label states that milnacipran produced a withdrawal syndrome in clinical trials with non-fibromyalgia patients, indicating that milnacipran produces physical dependence. However, the signs and symptoms of the milnacipran-associated withdrawal syndrome were not delineated in the NDA or in the label.

* The methodology used in the two epidemiological assessments of milnacipran for abuse and dependence (by the National Commission on Narcotics and Psychotropics and by Pierre Fabre) is not described in detail and outcome data are limited. No information is provided regarding how many total patients received milnacipran in this database, which makes it impossible to create a ratio of abuse-related case reports per number of prescriptions. Thus, it is not possible to independently assess the adequacy of the conclusions of both assessments that milnacipran has no abuse potential and does not produce dependence.

Thus, additional data are required in order to fully assess the abuse potential of milnacipran and prepare appropriate wording for the Drug Abuse and Dependence section of the label. The Office of Safety and Epidemiology will be consulted regarding evaluation of the epidemiological data submitted.

Data Needed for the Assessment of Abuse Potential and Dependence of Milnacipran in Humans

A. Clinical data obtained during the development of milnacipran for depression

1) Data related to the abuse potential of milnacipran as observed during administration of the drug:

* Submit data from all clinical studies regarding psychiatric and neurological adverse events related to abuse potential (based on MedDRA terminology below) reported with frequency of greater than 0.5%. These data should be submitted in tables, sorted by dose and duration of drug administration, along with a summation of all doses tested in both acute and chronic administration studies, compared to placebo.

* The following MedDRA terms associated with abuse potential should be used in assessing adverse events in clinical studies (including all lower level terms under each term listed): a) Euphoria and euphoria-related terms, b) Subjective response terms indicative of impaired attention, cognition, mood, and psychomotor events that are often associated with drugs of abuse, c) Dissociative/psychotic terms. Verbatim comments coded under these terms should also be submitted.

* The MedDRA terms that are most important for assessing abuse potential are the ones related to euphoria. If the AE profile of a drug does not show a high incidence of euphoria-related events, then it may be unlikely that a high incidence of somnolence or insomnia, for example, would be considered an abuse potential issue. However, if euphoria-type AEs are present, then it is necessary to characterize the other psychiatric and neurological AEs that co-occur.

2) Data related to the ability of milnacipran to produce a withdrawal syndrome following discontinuation of the drug:

* Submit data from all clinical studies in which adverse events occurring during milnacipran discontinuation were assessed, either prospectively in a discontinuation phase of a clinical study or retrospectively via reports from subjects followed after study completion. A description of the methodology for collecting the data should be provided. All adverse events reported with frequency of greater than 0.5% during discontinuation from milnacipran should be submitted in tables, sorted by dose, duration of drug administration, and duration of drug discontinuation, along with a summation of all doses tested in both acute and chronic administration studies, compared to placebo.

* Note that in order to identify the scope of the withdrawal syndrome associated with milnacipran, all adverse events, not just those related to neurological or psychiatric symptoms, should be reported.

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B. Epidemiological data obtained from the marketing experience with milnacipran:

1) Data related to the ability of milnacipran to produce abuse and dependence, including a withdrawal syndrome, following discontinuation of the drug:

* Submit full methodology used in evaluating adverse events indicative of abuse or dependence identified in epidemiological databases, including:

      -- Information about how data were collected and analyzed
      -- Limitations of the databases
      -- Patient characteristics (sex, age, diagnosis, medical history, concomitant drugs)
      -- Duration of drug use (and duration of drug discontinuation, if applicable) and
           dose of milnacipran prior to or at time of adverse event
      -- Description of adverse event and outcome
      -- Time to onset and duration of adverse event
      -- Intensity of event and seriousness criteria
      -- Corrective treatment, including hospitalization, if necessary

* In searching the databases, WHOART or MedDRA terminology related to drug abuse and dependence should be used.

* For drug abuse assessment, WHOART terms should align with the following MedDRA terms associated with abuse potential (including all lower level terms under each listed term): a) Euphoria and euphoria-related terms, b) Subjective response terms indicative of impaired attention, cognition, mood, and psychomotor events that are often associated with drugs of abuse, c) Dissociative/psychotic terms.

* For physical dependence and withdrawal assessment, all adverse event reports occurring during drug discontinuation should be evaluated. Summation of these reports should be categorized according to MedDRA terminology.

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Katherine Bonson
9/23/2008 09:43:16 AM
PHARMACOLOGIST

Michael Klein
9/23/2008 09:48:54 AM
PHARMACOLOGIST

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: **August 1, 2008**

To: **Bob Rappaport, M.D., Director**
Division of Anesthesia, Analgesia and Rheumatology Products

Through: **Michael Klein, Ph.D., Director**
Controlled Substance Staff

From: **Katherine Bonson, Ph.D., Pharmacologist**
Controlled Substance Staff

Subject: **Evaluation of Abuse Potential of Milnacipran**
Labeling Recommendations
NDA 22-256
Indication: Treatment of Fibromyalgia (200 mg/day)
Sponsor: Forest Laboratories, Inc.

Summary:

This CSS consult evaluates the abuse potential of milnacipran (NDA 22-256), as requested by the Division of Anesthesia, Analgesia and Rheumatology Products, to help determine appropriate labeling of the drug and to assess whether the drug should be recommended for scheduling. Milnacipran is proposed for the treatment of fibromyalgia at an oral daily dose of 200 mg (100 mg BID). A tradename has not been selected for milnacipran for US marketing. Since 1997, milnacipran has been marketed in more than 52 countries under the tradename Ixel as a noncontrolled antidepressant. The Sponsor does not propose milnacipran for scheduling under the Controlled Substances Act.

After evaluating the abuse-related data submitted in the NDA, CSS concludes that insufficient information was provided to adequately assess the abuse potential of milnacipran. However, based on the presence of a withdrawal syndrome in non-fibromyalgia patients following milnacipran discontinuation (as cited in the proposed drug label), CSS concludes that milnacipran can induce physical dependence.

Background:

Milnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI) that has negligible binding for the dopamine transporter. Milnacipran also produces <65% inhibition of binding at the phencyclidine (PCP) site of the N-methyl-D-aspartate (NMDA) receptor-channel complex and the serotonin (5-hydroxy-tryptamine; 5HT)

5HT2A receptor. Although milnacipran is structurally similar to the monoamine oxidase (MAO) inhibitor tranylcypromine, it has no apparent MAO inhibitory activity. Milnacipran is a racemate that has one minor metabolite (<10%) in humans (F-2800, the N-desethyl metabolite).

Conclusions:

Upon review of data submitted in the NDA, CSS concludes that insufficient information was provided to adequately assess the abuse potential of milnacipran. However, based on the presence of a withdrawal syndrome in non-fibromyalgia patients following milnacipran discontinuation (as cited in the proposed drug label), CSS concludes that milnacipran can induce physical dependence. These conclusions are based on the following:

1) The binding profile of milnacipran (Study #9700105, f220719459, f220719460, f220719461, 173, 138) shows that the primary mechanism of action of milnacipran is through inhibition of the serotonin transporter (SERT) and the norepinephrine transporter (NET). Milnacipran has no affinity for the dopamine transporter (DAT), the site of action of stimulants like cocaine and amphetamine. It also produces low (~50-60%) inhibition of binding at the 5HT2A receptor (site of action of hallucinogens) and the PCP site of the NMDA receptor-channel complex. No information is provided regarding the binding profile of the human metabolite.

2) In animal behavioral studies, sedative-like behaviors were observed following administration of milnacipran to mice and monkeys (including sedation, somnolence, decreased muscle tone, motor incoordination) (Study #144, 154, 166, 180). However, these sedative-like behaviors in monkeys were concurrent with vomiting and other signs of drug intolerance, so it is likely that they reflect general signs of malaise resulting from gastrointestinal disturbance. Notably, no behaviors were observed that are indicative of activation of 5HT2A receptors or the PCP site of the NMDA receptor-channel complex.

3) The self-administration study in monkeys (Study #142) was improperly designed to evaluate the rewarding properties of milnacipran. Specifically, animals were not trained to lever-press prior to drug trials and were thus unfamiliar with general test procedures. The study also did not test a positive control, so it is not possible to validate the study. Other design flaws include a lack of justification about the doses selected, especially with regard to the equivalency between plasma levels produced by any dose of milnacipran and those produced in humans by the proposed therapeutic dose.

4) In eight Phase 1 pharmacokinetic studies in healthy individuals (Study #MLN-PK-01, MLN-PK-02, MLN-PK-04, MLN-PK-05, MLN-PK-07, MLN-PK-08, MLN-PK-10, MLN-PK-11), milnacipran (~50 to ~200 mg/day) produced a low incidence (<0.5%) of the AEs euphoria and feeling drunk compared to placebo (0%). Milnacipran produced AE reports of somnolence (2%) and sedation (1%) at an incidence higher than placebo (0%). Although these CNS depressant effects can indicate a sedative-hypnotic profile,

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they are also a common AE profile for drugs, such as SNRIs, that produce a strong serotonergic response.

5) In three Phase 2/3 placebo-controlled clinical studies in patients with fibromyalgia (Study # FMS021, MS031, MLN-MD-02), milnacipran (25 to 200 mg/day for 12-27 weeks) produced a low incidence (<0.7%) of the abuse-related AEs of confused state, hallucination and disorientation compared to placebo (<0.2%). The incidence of the AE insomnia was high in the milnacipran group (12%) but similar to that in the placebo group (10%). Although insomnia can indicate a stimulant-like profile, it is possible that insomnia in these studies is reflective of chronic noradrenergic stimulation resulting from the SNRI mechanism of action. Notably, there were no reports of euphoria in the milnacipran-treated group and the incidence of hallucinations was low (0.3% vs. 0% from placebo).

6) The epidemiological information provided regarding abuse potential signs resulting from milnacipran administration are inadequate. The methodology used is described very briefly, without details concerning extent of data collection and limits on the design of the study. The data were submitted only in summarized form, so it is not possible to evaluate the variations in responses among various populations. Finally, milnacipran was often used in conjunction with other drugs, which does not allow a comprehensive evaluation of the abuse signals resulting from milnacipran use alone.

7) Section 5.13 Discontinuation of Treatment of the label states that milnacipran produces a withdrawal syndrome in clinical trials with non-fibromyalgia patients. Since the presence of a withdrawal syndrome is the definitive test for the presence of physical dependence, this label statement indicates that milnacipran produces physical dependence. The specific signs and symptoms of the milnacipran-associated withdrawal syndrome were not delineated, however, and a prospective physical dependence study was not conducted with fibromyalgia patients. Given that drugs with an SNRI mechanism of action, such as venlafaxine, are known to produce serious withdrawal syndromes after chronic administration, the withdrawal syndrome that occurs following discontinuation of milnacipran treatment should be evaluated prospectively in fibromyalgia patients.

Recommendations:

1) The label text proposed by the Sponsor does not include Section 9.0 (Drug Abuse and Dependence). CSS proposes that Section 9.0 be added to the label, with proposed text as follows below:

b(4)

9.2 Abuse

b(4)

9.3 Dependence

b(4)

2) Milnacipran is an SRNI that has a mechanism of action identical to currently marketed antidepressants such as venlafaxine and desvenlafaxine. In 2004, FDA began to require a black box warning in the label for antidepressants concerning the risk of suicidal thinking and behavior (suicidality) in children and adolescents. Additional label changes were also required in the Warnings and Precautions sections of the label on the same risk. The standard FDA letter to Sponsors regarding these label changes can be found at:

<http://www.fda.gov/CDER/drug/antidepressants/SSRIlabelChange.htm>

Thus, CSS recommends that the Division consider whether milnacipran should have similar label statements as other marketed SNRIs regarding the risk of suicidality.

Post-Marketing Commitments

As noted above, insufficient information was submitted for the adequate assessment of the abuse potential of milnacipran. In order for milnacipran to be assessed for abuse potential, CSS recommends that the studies listed below be conducted in the post-marketing period, dependent on concurrence by the Office of Surveillance and Epidemiology. CSS is available to review protocols prior to study initiation, if desired.

1) A receptor binding study should be conducted with F-2800, the N-desethyl metabolite of milnacipran. If the receptor binding study should show significant binding at sites associated with abuse potential, animal abuse studies may need to be conducted with the metabolite.

2) An appropriately-designed self-administration study with milnacipran should be conducted in rats or monkeys. Animals should be trained to lever-press in response to

food reward prior to introduction of drugs. A positive control drug with known abuse potential should be used in order to validate the study.

3) Depending on the results of the self-administration study and the metabolite study, a human abuse potential study may be necessary.

4) A prospective human physical dependence study should be conducted in fibromyalgia patients to characterize the withdrawal syndrome that occurs following milnacipran discontinuation. The results from this study will provide information to health care professionals and patients on the incidence and duration of adverse events that occur upon withdrawal.

Discussion of Preclinical and Clinical Data Related to Abuse Potential Assessment of Milnacipran

This section provides summaries of the abuse potential-related data on milnacipran (also known as F-2207 during development) submitted in NDA 22-256, followed by Discussion of the submitted material.

I. Summary of Data Related to Abuse Potential from Preclinical Studies

A. Receptor Binding Studies
   (Study #9700105, f220719459, f220719460, f220719461, 173, 138, 158)

Study Design and Results

A comprehensive binding profile of more than 85 sites was conducted with milnacipran at concentrations of 10 micromolar. In one study (Study #9700105), milnacipran was shown to produce inhibition of binding greater than 90% at the SERT site (100%) and the NET site (92%) but less than 10% for the DAT. In another study (Study #158), milnacipran was shown to have high affinity for SERT (IC50 = 205 nM) and NET (IC50 = 69 nM) but no affinity at DAT (IC50 >10,000). Milnacipran also produces ~61% inhibition of binding at the PCP site and ~53% inhibition of binding at the 5HT2A site. Inhibition constant (Ki) values for milnacipran were not provided for any site.

Discussion

The PCP site is a part of the NMDA receptor-channel complex and is the site of action of the dissociative anesthetic drugs PCP and ketamine, which are listed (respectively) in Schedule II and Schedule III under the CSA. The 5HT2A receptor is the site of action of hallucinogenic drugs such as LSD, psilocybin and mescaline, all of which are Schedule I drugs under the CSA. Given that Ki values were not provided for the PCP or 5HT2A sites, it is difficult to predict the clinical relevance of the observed degree of inhibition of

milnacipran at these sites separate from analyses of behavioral effects in animals and in humans (see below).

B. Preclinical Abuse-Related Behavioral Studies

Preclinical behavioral studies conducted with milnacipran related to abuse potential include general behavioral observations, self-administration and physical dependence.

i. General Behavioral Responses to Milnacipran in Mice (Study #154, 166, 180)

Study Designs

Mice (n = 3/dose) received intraperitoneal doses of milnacipran ranging from 16 to 512 mg/kg and were observed for general behavioral responses based on a standardized list of behaviors (Irwin test). The only active metabolite in humans, F-2800, was also tested at doses ranging from 16 to 2048 mg/kg (i.p.). Mice were observed at the following timepoints: 15, 30, 60, 120, 180 minutes and again at 24 hours post-dose.

Additionally, mice (n = 3/dose) were tested in the rotorod test of muscle control and coordination following administration of milnacipran at doses of 16, 32, and 64 mg/kg (p.o.). All drugs were administered with a 30 minute pretreatment time.

Results

Milnacipran produced no observable effects in mice at 16 mg/kg (i.p.). At doses of 32 and 64 mg/kg (i.p.), milnacipran produced sedation and mydriasis, with the higher dose also producing tremor, decreased muscle tone, decreased traction, decreased reactivity to touch and hypothermia. At doses of 128 mg/kg (i.p.) and greater, milnacipran produced convulsions and lethality. As with the parent, F-2800 produced signs of sedation, with threshold changes occurring at 128 mg/kg (i.p.).

In the rotorod test in mice, the 64 mg/kg dose of milnacipran produced a statistically significant 91% reduction in performance by mice, but a non-significant dose-dependent reduction in performance of less than 20% at the two lower doses. F-2800 was also tested at doses of 128, 256, and 512 mg/kg (p.o.), but produced no changes in the rotorod test. In contrast, the positive control, diazepam (4 mg/kg, p.o.), produced a statistically significant 94% reduction in performance.

Discussion

The sedation, decreased muscle tone, decreased rotorod performance produced by milnacipran are similar to the effects of benzodiazepines. However, these sedative-like could also be the result of the serotonin reuptake inhibitory properties of milnacipran.

ii. General Behavioral Responses to Milnacipran in Monkeys (Study #144)

Study Design

Two naive cynomolgus monkeys (one male, one female) were given oral doses of milnacipran ranging from 25 to 100 mg/kg in a dose-rising fashion (except that the 100 mg/kg dose came before the 75 mg/kg dose). Following drug administration, monkeys were observed for changes in overt behavior for 48 hours and were also measured for changes in rectal temperature at baseline and at 3.5 hours after dosing. Throughout the study, monkey weights and food intake were measured.

Results

At the 25 mg/kg dose, piloerection was observed in both animals at 60 minutes (female) and 75 minutes (male). The female was also observed to engage in increased grooming. Both of these behaviors has subsided within 105 minutes post-dose. At the 50 mg/kg dose, no overt behaviors were observed in either animal.

At 100 mg/kg, the male animal vomited four times within the first 30 minutes after dosing, in addition to piloerection and stereotyped chewing motions. This was followed at 45 minutes by a reduction in locomotor activity and restlessness. In the female monkey, however, piloerection was the only behavior observed during the first hour after dosing. After three hours, the female monkey was observed to have a reduction in locomotor activity, restlessness, fearfulness and aggression that lasted until 4.5 hours post-dose.

When the 75 mg/kg dose was administered, vomiting was observed in the female monkey, in addition to retching and salivation at 2 hours post-dose. At the 2 hour timepoint, the male monkey was observed to have ptosis, a slight reduction in locomotor activity and restlessness that lasted until 3.5 hours post-dose.

For rectal temperature results, the female monkey was more sensitive than the male monkey to changes in body temperature. At the two highest doses (75 and 100 mg/kg), the female monkey showed a 2.5 and 2.6 degree Centigrade reduction in temperature (respectively) while the male monkey showed a decrease of 0.6 degree Centigrade.

Throughout the study, there were no abnormal changes in the bodyweights of the two monkeys, nor in their daily food intake.

Discussion

The sedative-like behaviors in monkeys were concurrent with vomiting and other signs of drug intolerance, so it is possible that they reflect general signs of malaise resulting from gastrointestinal (GI) disturbance. These indications of GI distress were not observed in the behavioral study with mice (above) because they do not have an emetic response. However, a high incidence of nausea (39%) was observed in Phase 2/3 clinical studies

with milnacipran (see below). Notably, no behaviors were observed that are indicative of activation of 5HT2A receptors or the PCP site of the NMDA receptor-channel complex.

iii. Self-Administration in Monkeys (Study #142)

Study Design

Cynomolgus monkeys (n = 4) were placed in a test cage with two levers: one that delivered an intravenous injection of milnacipran and one that delivered an intravenous injection of saline, based on an FR1 schedule of reinforcement. When an animal was first exposed to the test cage, the animal received a single priming dose of both milnacipran and saline prior to placement into the cage.

The first dose of milnacipran available to monkeys in response to pressing the drug-lever was 0.125 mg/kg/injection (i.v.). Monkeys were allowed access to the 0.125 mg/kg/injection dose for 14 days. The dose was then doubled (0.25 mg/kg/injection, i.v.) for another 14 day period, and then doubled again (0.50 mg/kg/injection, i.v.) after that for an additional 56-day exposure period.

Following this initial exposure to the three drug doses, animals entered into a second testing regimen in which they received a single priming dose of both milnacipran (0.50 mg/kg/injection, i.v.) and saline every three hours during the daily 24-hour test sessions. This second phase of testing lasted for an additional 14 days.

During all test sessions, the infusion rate (0.9-1.1 ml/min) and the dose volume (1.0 ml/kg) were constant. However, the schedule of reinforcement was allowed to change if "a monkey showed a marked tendency to press for drug more than for vehicle". No numerical definition of "marked tendency" is given. However, if this higher degree of lever-pressing occurred, the initial FR1 schedule of reinforcement would be increased to FR3, and then to FR10. The narrative denotes "etc" after the FR10 description, implying that the schedule of reinforcement would continue to increase, "until such time as the monkey ceased to press for drug." The narrative also states that "the ratio of lever presses to injections was altered simultaneously on both the drug and saline injection systems."

Results

None of the monkeys had a daily lever pressing for milnacipran that exceeded 30/day. During one daily 24-hour session, one of the four monkeys lever-pressed 26 times for the 0.50 mg/kg/injection dose of milnacipran. For all other sessions at any dose, the lever pressing for milnacipran was eight times or less for each of the monkeys.

Notably, the daily lever pressing for saline was considerably greater and more varied across the monkeys. Although monkeys did not receive an active drug, three of the four monkeys pressed the saline lever between 20-87 times in at least one of the 24 hour

sessions. The fourth monkey did not lever-press for saline greater than 4 times in any session.

Discussion

The design of this study is inappropriate for evaluating whether milnacipran induces self-administration. There are two major deficits in study design, as well as numerous minor deficits.

The first major deficit in the study design is that monkeys were not trained to lever-press prior to testing nor were they trained to self-administer a known drug of abuse prior to exposure to milnacipran. Typically in a self-administration study, animals are first trained to press a lever for a food reward in the test cage. After responding for food reward is stable (usually using a fixed ratio (FR) 10 schedule of reinforcement), the food reward is replaced by an intravenous delivery of a known drug of abuse in response to lever-pressing. Animals are then monitored for their interest in self-administering the known drug of abuse and those animals that do not self-administer the drug are not allowed to continue in the study. Following stable self-administration of the known drug of abuse, animals are then challenged with intravenous saline or vehicle, to assure that lever-pressing extinguishes when animals do not receive a reward. Only after this extensive training are animals then allowed access to the test compound to see if they will lever-press for an intravenous injection. Thus, in the present study design, the animals' natural curiosity about the environment appears to be the only reason an animal would attempt to press either the saline-associated or drug-associated lever during the 24-hour daily test sessions. This is inadequate.

The second major deficit is a lack of use of a positive control. Without a positive control, the study cannot be validated. It is also difficult to interpret the milnacipran data without a comparison to a positive control.

Minor deficits include the following:

* It is unclear from the protocol narrative why administration of both compounds at the same time prior to the test session would act as a priming factor for either specific lever.

* No justification was provided regarding the doses selected. No pharmacokinetic information was submitted regarding the equivalency between plasma levels produced by any dose of milnacipran and those produced in humans by the proposed therapeutic dose.

* No information is provided regarding the criteria for alterations in schedule of reinforcement over the course of the study.

Finally, the occasionally high rate of saline lever-pressing is difficult to understand, especially in comparison with the consistently low rate of milnacipran lever-pressing. Theoretically, monkeys should not show a preference between the two levers if neither of them led to rewarding effects. Although there appears to be a "signal" from the saline

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data, it may also be that lever pressing up to 87 times in a 24-hour access period is typical for a placebo response and is much less than that of a positive control that is known to produce rewarding properties.

Therefore, this self-administration study is not valid for assessing the rewarding properties of milnacipran.

C. Physical Dependence Study in Monkeys (Study #143)

Study Design

Cynomolgus monkeys were used to assess the ability of milnacipran and diazepam to induce physical dependence. For the milnacipran-treated group, monkeys (n = 4) were given 100 mg/kg/day (p.o., 50 mg/kg BID) for Weeks 1-2, at which time the dose was increased to 150 mg/kg/day (p.o., 75 mg/kg BID) for Weeks 3-4. The 100 mg/kg/day dose of milnacipran was justified on the basis of "preliminary acute behavioral study and background data" provided by the Sponsor.

For the diazepam-treated group, monkeys (n = 2) were given 10 mg/kg/day (p.o., 5 mg/kg BID) for Weeks 1-2, at which time the dose was increased to 20 mg/kg/day (p.o., 10 mg/kg BID) for Weeks 3-4. The 5 mg/kg/day dose of diazepam was justified on the basis of its known ability "to induce moderate behavioral depressant effects".

During the drug administration period, animals were observed twice daily after dosing, but the duration of the observation period was not given. On one day of the week (Days 1, 10, 19 and 24), "detailed observations" were performed at baseline, and 1, 2 and 4 hours post-dose, but the duration of the observation period was not given.

After a total of four weeks of treatment, drug administration was discontinued at the beginning of Week 5. Animals were observed for 30 minutes twice a day for seven days for signs of withdrawal, including: apprehension, hyperirritability, tremor, piloerection, muscle rigidity, motor function, retching, convulsions, nystagmus, delirium, hallucinations, and dissociation. Additional measures during the study included rectal temperature, body weight and food consumption.

Drug treatments were recommenced on Week 6. Milnacipran-treated monkeys received 150 mg/kg/day (p.o., 75 mg/kg BID) for Weeks 6-9. No justification was given for this dose of milnacipran. Diazepam-treated monkeys received 20 mg/kg/day (p.o., 10 mg/kg BID) during Weeks 6-7, and received 30 mg/kg/day (p.o., 15 mg/kg BID) during Weeks 8-9.

During the drug administration period, animals were observed twice daily after dosing, but the duration of the observation period was not given. On one day of the week (Days 39, 45, 53, 60), "detailed observations" were performed at baseline, and 1, 2 and 4 hours post-dose, but the duration of the observation period was not given.

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After the second four weeks of treatment, drugs were discontinued again and animals were observed daily for signs of withdrawal during Week 10 as described above for Week 5.

An additional assessment of physical dependence was conducted by giving monkeys in both the milnacipran- and diazepam-treated groups a 5 mg/kg (i.m.) challenge dose of the benzodiazepine antagonist Ro-1788 on two separate occasions. The antagonist was administered four hours after the morning treatment dose on Day 24 during the first dosing period (during Week 4) and on Day 59 during the second dosing period (During Week 9). Animals were observed for signs of withdrawal for one hour after antagonist administration.

Results

Milnacipran Testing

During the first four-week dosing period with milnacipran, the following behaviors were observed in the four monkeys in the first week of drug administration at 100 mg/kg/day: mydriasis (n = 4), vomiting (n = 2) and piloerection (n = 1). During the second week at this dose, these behaviors were no longer observed, perhaps indicating the development of tolerance to these effects. On Day 10, there was a "slight increase" in grooming and vocalization (n =2), but no further behaviors were observed at this dose level. When the dose of milnacipran was increased to 150 mg/kg/day during Weeks 3-4, ptosis was observed throughout the next two weeks (n = 4). Occasional observations of mydriasis (n =1), vomiting (n = 2), increase in grooming (n = 1), slight reduction in locomotion (n = 1) and restlessness (n =1) also occurred. During the first 28-day exposure to milnacipran, there were minimal changes in bodyweight, a decrease in food intake and minimal changes in rectal temperature.

Following milnacipran discontinuation at Week 5, the only behaviors seen during the one-week observation period were piloerection (n =1) and increased grooming (n = 1), both of which were also observed during drug dosing. No other overt behaviors were observed indicative of a withdrawal syndrome. However, decreases in bodyweight and food intake were recorded during the first withdrawal phase, with erratic changes in rectal temperature that trended towards a decrease.

On Week 6, a second four-week dosing period with milnacipran began in the four monkeys, using a dose of 150 mg/kg/day. During administration of the higher dose of milnacipran, animals were observed occasionally vomiting (n = 3) and showing signs of ptosis (n = 4). One animal also showed mydriasis and increased grooming. During this second 28-day exposure to milnacipran, there were slight increases in bodyweight, decreases in food intake and minimal changes in rectal temperature.

Milnacipran was again discontinued at Week 10. During the one-week observation period, one monkey showed signs of withdrawal, including apprehension, piloerection,

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agitation, cage biting and vocalization. Sporadic signs in other animals included piloerection, increased grooming, scratching and occasional vocalization. As with the first withdrawal period, decreases in bodyweight and food intake were recorded during the second withdrawal phase, with erratic changes in rectal temperature that trended towards a decrease.

Diazepam Testing

During the first four-week dosing period with diazepam (10 mg/kg/day), the two monkeys were both observed to have reductions in locomotion, restlessness, alertness, motor incoordination and aggression. In one monkey, there were also signs of tremor, piloerection and reduced fearfulness. Increases in bodyweight and food intake were recorded for both animals during the first 28-day exposure to diazepam, with erratic changes in rectal temperature that trended towards a decrease.

Following diazepam discontinuation at Week 5, both animals exhibited apprehension, mild tremor and hyperirritability, which are mild signs of benzodiazepine-associated withdrawal. One of the monkeys also exhibited muscle rigidity and impaired motor function, which are known signs of intermediate benzodiazepine-associated withdrawal. Additional occasional behaviors observed in the monkeys during the discontinuation period included scratching, head shaking, restlessness, cage biting, and increased grooming. During the first withdrawal phase, bodyweight decreased in both animals despite increases in food intake over baseline, with erratic changes in rectal temperature that trended towards a decrease.

On Week 6, both monkeys started a second four-week dosing period with diazepam. During Weeks 6-7, monkeys received 20 mg/kg/day (p.o., 10 mg/kg BID) and were observed to have muscle incoordination, decreased locomotion and restlessness. There were also incidents of tremor and cage biting. During Weeks 8-9, the dose of diazepam was increased to 30 mg/kg/day (p.o., 15 mg/kg BID). In addition to the behaviors seen at lower doses, there were observations of increased apathy and reductions in fearfulness and aggression as well as an increase in scratching. Increases in bodyweight and food intake were recorded for both animals during the second 28-day exposure to diazepam, with erratic changes in rectal temperature that trended towards an increase.

On Week 10, diazepam was discontinued again. Both animals exhibited withdrawal signs, including apprehension, hyperirritability, mild tremor, impair motor function and piloerection. Additional behaviors included cage biting, licking, subdued behavior, grooming, scratching, head-shaking and aggression. During the second withdrawal phase, bodyweight decreased in both animals despite increases in food intake over baseline, with erratic changes in rectal temperature that trended towards a decrease.

Ro 15-1788 Induced Withdrawal

During Week 4 and Week 9 of milnacipran and diazepam administration, a single
challenge dose of the benzodiazepine antagonist Ro 15-1788 was administered to animals
to determine whether it would precipitate an acute withdrawal syndrome.

In milnacipran-treated animals, one of four monkeys showed piloerection following Ro
15-1788 administration during Week 4. Other than this behavior, none of the monkeys
showed any behaviors associated with withdrawal. In the second Ro 15-1788
administration during Week 9, after the dose of milnacipran was increased, three of four
monkeys displayed piloerection and ptosis. Cage biting was also observed in one animal.
These behaviors were also observed during milnacipran administration.

In diazepam-treated animals, classic signs of benzodiazepine withdrawal were observed
in both monkeys after administration of Ro 15-1788 during Week 4. These behaviors
were of intermediate severity and included tremor, impaired motor function, vomiting,
piloerection and hyperirritability. Additional behaviors included teeth grinding,
grooming and aggression. In the second Ro 15-1788 administration in Week 9, after the
dose of diazepam was increased, both monkeys were observed to have similar
intermediate withdrawal behaviors as those observed during the Week 4 challenge.

Discussion

Data were also not provided regarding the plasma levels produced by the drug doses
selected in terms of their relation to human plasma levels after therapeutic doses.
However, general information about behavioral responses to milnacipran during drug
discontinuation can be obtained from this study.

During discontinuation of milnacipran after the first four-week dosing period (100-150
mg/kg/day, p.o.) minimal behavioral changes were observed. During discontinuation of
milnacipran after the second four-week dosing period (150 mg/kg/day, p.o.), 1 of 4
monkeys showed signs of withdrawal. In contrast, the positive control, diazepam (10-30
mg/kg/day, p.o.) produced significant signs of withdrawal during the discontinuation
periods following the two 4-week dosing periods.

These data do not suggest that milnacipran produces a strong withdrawal syndrome in
monkeys after chronic high doses. However, these conclusions are tentative because no
information was provided regarding the behaviors or the relationship between plasma
levels produced by the animal dose and those produced after the proposed human
therapeutic dose.

Finally, the benzodiazepine antagonist Ro 15-1788 was unable to produce a withdrawal
syndrome in milnacipran-treated animals, although it did produce a withdrawal syndrome
in diazepam-treated animals. These data suggest that milnacipran does not produce
physical dependence through the benzodiazepine site of the GABA receptor.

II. Summary of Data Related to Abuse Potential from Clinical Studies

A. Abuse-Related AEs in Phase 1 Pharmacokinetic Studies
(Study #MLN-PK-01, MLN-PK-02, MLN-PK-04, MLN-PK-05, MLN-PK-07, MLN-PK-08, MLN-PK-10, MLN-PK-11)

Study Design

Eight Phase 1 pharmacokinetic studies were conducted with milnacipran using single-dose (n = 4 studies) or multiple-dose (n = 4 studies) drug administration. A total of 203 subjects received milnacipran (n = 66 for single-dose studies, n = 137 for multiple-dose studies) at doses ranging from less than 50 mg/day to greater than 200 mg/day. Only the multiple-dose studies had subjects who received placebo (n = 60).

Results

In the Phase 1 studies, there was a low incidence of abuse-related AEs compared to placebo. The euphoria-related AEs of "euphoria" and "feeling drunk" were each reported in 1 of 203 subjects who received milnacipran (0.5%) and in 0 of 60 subjects who received placebo (0%). The AEs of "somnolence" and "sedation" were reported in (respectively) 4 and 2 of 203 subjects (2.0% and 1.0%) who received milnacipran, compared to 0 of 60 subjects who received placebo (0%). The AE of "cognitive disorder" was reported in 1 of 203 subjects who received milnacipran (0.5%) and in 0 of 60 subjects who received placebo (0%).

Discussion

Oral administration of milnacipran produced a low incidence (<0.5%) of abuse-related AEs compared to placebo (0%) in eight Phase 1 pharmacokinetic studies in healthy control subjects. In addition, milnacipran produced an incidence of 1-2% for sedative-type AEs compared to placebo (0%). Although the CNS depressant effects can indicate a sedative-hypnotic profile, they are also a common AE profile for SNRIs like milnacipran that produce a strong serotonergic response.

B. Abuse-Related AEs in Phase 2/3 Clinical Efficacy Studies
(Study # FMS021, FMS031, MLN-MD-02)

Study Design

In two Phase 3 studies (Study # FMS031 and Study #MLN-MD-02), milnacipran was tested at two doses: 100 mg/day (n = 623; 50 mg BID) and 200 mg/day (n = 837; 100 mg BID) for 15-27 weeks. In a Phase 2 study (Study #FMS021), milnacipran was tested at "flexible doses" ranging from 25-200 mg/day (n = 97; single doses or 12.5-100 mg BID) for 12 weeks. Placebo was also tested in a total of 652 patients during these studies.

Results

The incidence of abuse-related AEs observed in Phase 2/3 clinical efficacy trials with fibromyalgia patients treated with milnacipran was evaluated in comparison to patients treated with placebo (see Table 1 below).

Table 1: Possible Abuse-Related AEs During Phase 2/3 Studies with Milnacipran

Abuse-Related AE	Milnacipran (n = 1557)	Placebo (n = 652)
Insomnia	189 (12%)	65 (10%)
Anxiety	62 (4.0%)	26 (4.0%)
Somnolence	19 (1.2%)	13 (2.0%)
Confused State	12 (0.7%)	1 (0.2%)
Disturbance in Attention	12 (0.7%)	7 (1.1%)
Hallucination	3 (0.3%)	0 (0%)
Mood Altered	2 (0.2%)	5 (0.8%)
Affect Lability	1 (0.1%)	3 (0.5%)
Disorientation	1 (0.1%)	0 (0%)

The majority of the AEs with milnacipran were mild or moderate in severity. One of 19 incidents of somnolence (5%) was severe in intensity and 2 of 12 incidents of disturbance in attention (17%) were severe in intensity.

The incidence of AEs that may indicate abuse potential (anxiety, somnolence, disturbance in attention, mood altered, affect lability) following milnacipran administration was lower than or equal to that observed in placebo-treated patients. Three AEs resulting from milnacipran administration showed an incidence that was higher for milnacipran than that in the placebo group: confused state (0.7% vs. 0.2%), hallucination (0.3% vs. 0%) and disorientation (0.1% vs. 0%). The incidence of the AE insomnia was higher in the milnacipran group than in the placebo group, but both treatment groups reported high rates that were similar to each other (12% vs. 10%, respectively). Notably, there were no reports of euphoria in the milnacipran-treated group.

Discussion

Milnacipran produced a low incidence (<0.7%) of abuse-related AEs compared to placebo (0%) in three Phase 2/3 double-blind clinical efficacy studies in fibromyalgia patients. The incidence of insomnia was high (12%) but similar to that of placebo (10%), and may be reflective of noradrenergic stimulation resulting from an SNRI like milnacipran. The incidence of somnolence (1.2%) was similar to that observed in Phase 1 pharmacokinetic studies, but was lower than that observed in placebo-treated patients (2.0%).

In monkeys, the sedation observed during behavioral studies with milnacipran was postulated to be the result of overall malaise resulting from GI distress (see above). In

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humans, there was a 39% incidence of nausea in Phase 2/3 studies with milnacipran (compared to 20% from placebo), but a relatively low incidence of somnolence. This apparent discrepancy between species may be explained by the ability of humans to verbalize distinctions in drug response (i.e., actual sleepiness vs. feeling too ill to want to move around), whereas observable behavior is the only method of discerning drug response in animals.

C. Human Physical Dependence

Submitted Information on Milnacipran Physical Dependence

No primary data were submitted for review regarding human physical dependence produced by milnacipran.

Discussion

CSS sought to assess the ability of milnacipran to produce physical dependence and/or withdrawal through information in the NDA and in the scientific literature as follows:

* *Human Physical Dependence Study*

A prospective study of physical dependence in fibromyalgia patients treated with milnacipran was not conducted. Specifically, none of the Phase 2/3 clinical efficacy studies conducted with milnacipran included a taper phase or a discontinuation phase through which physical dependence and withdrawal could be assessed in humans. Thus, no conclusions can be drawn concerning the ability of milnacipran to produce physical dependence on the basis of clinical studies.

* *Label Statements Regarding Physical Dependence*

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The ability to determine physical dependence is reliant on the presence of a withdrawal syndrome following drug discontinuation. Thus, the label statements regarding a withdrawal syndrome associated with milnacipran demonstrate that milnacipran produces physical dependence.

* *Published Reports of Physical Dependence with Milnacipran*

There are no papers in the scientific and medical literature (as accessed through PubMed) that report on placebo-controlled, prospective studies evaluating physical dependence, withdrawal syndromes or discontinuation syndromes following milnacipran administration to humans or animals. However, a brief (2 page) study report was published by Vandel et al. (Hum. Psychopharm. Clin. Exp. 19:585-586, 2004) that compared spontaneously-reported AEs one week following discontinuation of milnacipran (100 mg/day; n = 46) and paroxetine (20 mg/day, n = 44) after 6 and 24 weeks of treatment in patients with major depressive disorder. In that report, paroxetine produced more overall AEs than milnacipran after both treatment durations. Withdrawal symptoms following paroxetine treatment included anxiety, dizziness, nervousness, nausea, insomnia, nightmares, sweating and diarrhea (n = 1-5 for each symptom). Withdrawal symptoms following milnacipran treatment included anxiety, nervousness, nausea and insomnia (n = 1-4 for each symptom). Notably, a standardized list of withdrawal behaviors associated with SNRI drugs was not utilized, patients were not interviewed until one week after drug discontinuation and the study was not placebo-controlled.

Thus, based on the available information, CSS concludes that milnacipran can produce physical dependence and a withdrawal syndrome upon discontinuation.

D. Epidemiological Data on Abuse-Related AEs

The Sponsor submitted information from two sources that they assert provide epidemiological data on abuse-related AEs associated with milnacipran. These sources are: the National Commission on Narcotics and Psychotropics Report and the Pierre Fabre Database:

National Commission on Narcotics and Psychotropics Report

The Sponsor submitted a 6-page portion of an April 2007 report from the (European) National Commission on Narcotics and Psychotropics that assessed whether the available epidemiological data (as compiled by the Centre for Evaluation and Information on Pharmaco-dependency (sic)) showed that milnacipran had abuse potential. According to the report, "any prescription at a dose higher than the maximum dose recommended in the Summary of Product Characteristics for Ixel gave rise to a 'milnacipran alert', which was then subject to a report." The conclusions of the Commission were that: "The current findings of the official inquiry into drug-dependency do not show any argument suggestive of a potential for abuse or for drug-dependency with milnacipran" and that "cases of overdosage may be due to inadequacy of the effect of milnacipran at the doses recommended."

Pierre Fabre Database

A two-page report was submitted by Pierre Fabre, the company that markets milnacipran as Ixel in France, regarding a search conducted of their database for abuse-related case reports. All case reports responsive to the WHOART Preferred Term of "Drug Abuse" from the dates of January 1976 to April 2004 were collected in the search. Thirty case reports were identified that involved overdose events with milnacipran in combination with at least one other drug, primarily for the purpose of a suicide attempt. No other abuse-related events were reported in the database. According to the conclusion provided by Pierre Fabre, milnacipran does not appear to be sought or used for abuse purposes involving rewarding effects.

Discussion

The methodology used by the National Commission on Narcotics and Psychotropics in determining abuse potential or physical dependence is not described in detail and outcome data are limited. The majority of the report is comprised of a comparison of the determination of overdose cases for milnacipran and the antidepressant tieneptine. The report also has a section that reiterates the data described in the Pierre Fabre report. Thus, it is not possible to independently assess the adequacy of the conclusions of the Commission.

The methodology used by the company for the Pierre Fabre search is not described, other than it is responsive to a request "concerning the national inquiry on drug dependency relative to our pharmaceutical product Ixel". Although 30 case reports were found in the database search for the years 1976 to 2004 (a total of 28 years), no information is provided regarding how many total patients received milnacipran in this database. The lack of denominator makes it impossible to create a ratio of abuse-related case reports per prescriptions. Thus, it is not possible to independently assess the adequacy of the conclusions of the company.