CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-256

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

8/29/08

Clinical Pharmacology Review

NDA: 22-256	**Dates of Submission:** December 18, 2007 January 4, 2008 June 26, 2008 July 8, 2008
Generic Name	Milnacipran
Brand Name:	**N/A**
Formulation:	Tablets
Strengths:	12.5, 25, 50, and 100 mg
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Route of Administration:	Oral
Indication:	Treatment of Fibromyalgia
Dosage and Administration:	12.5 to 100 mg BID (Maximum 200 mg per day)
Proposed Titration Process:	In two divided doses per day as follows: • 12.5 mg on the first day and increase to 100 mg/day over a 1-week period • Day 1: 12.5 mg • Days 2-3: 25 mg/day (12.5 mg twice a day) • Days 4-7: 50 mg/day (25 mg twice a day) • After Day 7: 100 mg/day (50 mg twice a day) • Target maintenance dose is 100 mg/day • May be increased to 200 mg/day based on individual patient response • Dose should be adjusted in patients with severe renal impairment
Type of Submission:	NME, Standard
Sponsor:	Forest Laboratories, Jersey City, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable provided that a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant.

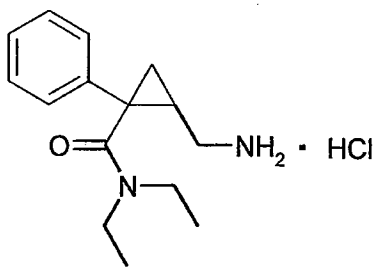
1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

Currently, pregabalin and duloxetine are approved for the treatment of fibromyalgia.

Milnacipran is a novel norepinephrine-serotonin reuptake inhibitor (NSRI) proposed for the treatment of Fibromyalgia Syndrome (FMS). It was first in approved in France in 1997 for major depressive disorder (MDD) and is currently approved in over forty-four countries for the treatment of MDD. Currently, it is not approved anywhere in the world for the treatment of Fibromylagia. Structurally, the drug exists in two racemic forms: *cis*-(*dl*) and racemate (Z form) composed of two (*d*- and *l*-) enantiomers (isomers).



The drug will be marketed as film coated immediate release tablets at 12.5, 25, 50, and 100 mg strengths. The proposed target doses are 50 mg BID and 100 mg BID.

Throughout this review, the racemate (parent drug) is denoted as *d,l*-milnacipran or as F2207, *d*-isomer (enantiomer) as F2695, and *l*-isomer (enantiomer) as F2696.

Approximately, sixty clinical pharmacology related studies were conducted by the sponsor in the course of fibromyalgia and MDD programs. Five clinical efficacy studies were conducted in fibromyalgia patient's population. The two pivotal studies are MLN-MD-02 and FMS03.

The clinical pharmacology and Biopharmaceutics studies investigated protein binding, absolute bioavailability, single dose and multiple dose pharmacokinetics, dose-

proportionality, food effect, bioequivalence of the various formulations used in the clinical development program, mass balance, drug-drug interactions, and special populations (effect of age, gender, hepatic impairment, and renal impairment). The drug-drug interaction studies were conducted during the course of the MDD program in Europe. In addition, several *in vitro* metabolism and *in vivo* drug-drug interaction studies were conducted to characterize the metabolic pathways of the drug and to identify the enzymes responsible for the metabolism of the drug.

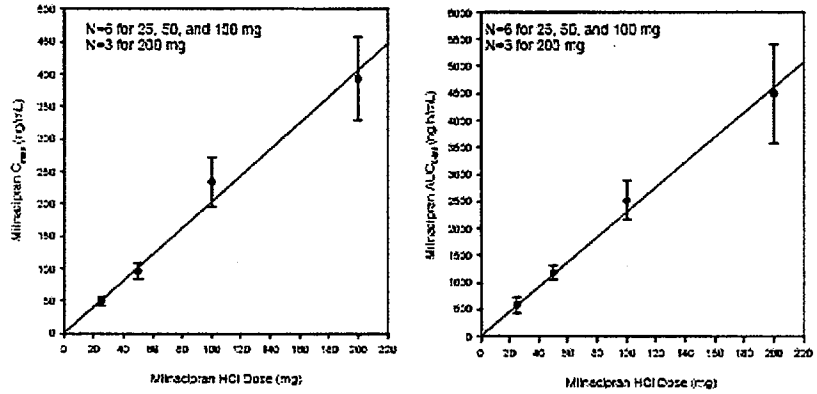
Basic PK Information:

Overall, the PK characteristics of milnacipran appear to be comparable across studies. The Cmax is attained by approximately 2 to 4 hours after oral administration. The absolute bioavailability ranges from 85% to 90% (Studies M038 and M046). No food effect was observed with the capsule and tablet dosage forms (Study # M039/M124 and Study MLN-PK-04).

The elimination half-life of milnacipran averaged 6-8 hours in all studies (Study M037, M038, M130, M141, MLN-PK-01, MLN-PK-04). However, the enantiomer *d*-milnacipran had a longer elimination half-life (8-10 hours) than *l*-milnacipran (4 to 6 hours) as reported in several studies (Studies M115, M146, M126, and MLN-PK-01). The steady state level was achieved within 36 to 48 hours and is approximately 70% higher than that achieved after a single dose (Studies M037 and M146). The plasma protein binding of milnacipran is approximately 13% and is independent of the concentration (Study # M013).

Dose proportionality was observed after single and multiple dose administration (Studies M036, M037, M040, M146, MLNPK-01, and MLN-PK-10). Depending on the study, the dose proportionality was established between 25 to 200 or 300 mg (**Figure 1.3.1**). The dose proportionality studies were limited by the high incidences of nausea and vomiting and increases in heart rate that precluded the administration of the drug beyond 300 mg (see below). The elimination half life of the parent drug and its isomers did not change with dose or duration after multiple dosing.

Figure 1.3.1. Dose-Proportionality for Milnacipran in Healthy Subjects (Study # M040)



Metabolism and Excretion:

Approximately 90% to 97% of radioactivity of ^{14}C-milnacipran dose is excreted in urine (**Table 1.3.1**, Studies #M002 and MLN-PK-05). Of this, approximately 55% of the milnacipran dose was excreted unchanged and the remaining as metabolites (Study # MLN-PK-05, M002/M034, M037, M039/M124, M040, M126, M135, and M244). The metabolites include *1*-milnacipran carbamoyl O-glucuronide (17%), *d*-milnacipran carbamoyl O-glucuronide (2%) and N-desethyl milnacipran (8%). The metabolic Pathway involved in this minor de-ethylation pathways is unknown. However, N-desethyl milnacipran is considered to be inactive based on pre-clinical data. Sponsor proposes that the carbomoyl O-glucuronide metabolites are the result of a nonenzymatic reversible reaction of the primary amine function of milnacipran with carbondioxide to form a carbamic acid and subsequent conjugation with glucuronic acid.

Table 1.3.1 . Excretion of radioactivity (%) of ^{14}C Milnacipran

Study	*Milnacipran HCl Dose*	*Urine*	*Feces*	*Total*
M002/M034	50 mg	90.3	1.6	91.9
MLN-PK-05	100 mg	93.3	3.6	96.9

In all PK studies it was noted that the plasma level of *d*-enantiomer was consistently higher (~20% to 50%) than that of *1*-enantiomer (e.g., Study # M146 and MLN-PK-01). There was no evidence of inter-conversion between the two enantiomers (see Study M115).

Drug-Drug Interactions:

A slow biotransformation was observed for milnacipran in human hepatic microsomes, hepatocytes, and cDNA expressed human CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 isoenzymes (Study # PK07MXH1). The inhibition and induction potential of milnacipran to CYP 450 isozymes was low (Studies # PRD-RPT-BDM-00051, XT08318, and M244).

The co-administration of various drugs did not show a significant effect on the PK of milnacipran. These include, levomepromazine (Study # M126), carbamazepine (Study # M130), warfarin (Study # MLN-PK-07), digoxin (Study # MLN-PK-08), lithium (Study M125), lorazepam (Study # M138), fluoxetine (Study # F2207 GE M212), clomipramine (Study # F2207 GE M213), and alcohol (Study # F2207 95 GE 103). As such, based on *in vitro* and *in vivo* studies, the potential for interactions with drugs that are substrates, inhibitors or inducers of CYP450 enzymes is low or not clinically significant. Based on the limited information with the interaction of the drug with digoxin, a known p-glycoprotein (P-gp) intestinal and renal substrate, the drug does not appear to be transported via P-gp.

Special Populations:

The exposure was markedly increased (Cmax ~60% and AUC ~200%) and clearance was markedly reduced (65%) in patients with severe renal impairment (**Table 1.3.2**, Studies # M045/M117 and MLN-PK-02). Therefore, dose adjustment is necessary in patients with renal impairment, especially in severe cases. No information is available in end-stage renal disease or patients on dialysis.

Table 1.3.2. Mean Percent Change in PK Parameters in Patients with Renal Impairment Compared to Healthy Subjects (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.

Two studies were conducted by the sponsor to investigate the PK profiles in patients with hepatic impairment (Studies # MLN-PK-11 and M046). In one study, the data was inconclusive due to the fact that there was decrease in Cmax rather than increase in patients with severe hepatic impairment compared to mild or moderate relative to healthy subjects (Study # MLN-PK-11). Overall, from both studies the AUC increased by approximately 30% to 60% in severe liver impairment compared to control following IV and oral administration. Based on the high variability in the data and the limited number

of subjects in each group (n=3 to 7) in both studies, milnacipran should be administered with caution in patients with severe hepatic impairment.

As expected from the excretion pathway of the drug and the expected renal status in elderly, the exposure in this population was generally higher by approximately 35% to 65% than young subjects (Study # M042 and M116). Overall, elderly patients in the clinical trials did not show differences in safety. Based on these data, although no specific dosage adjustment is needed in the elderly, milnacipran should be used with caution in elderly patients as their renal function decreases with age.

There were no clinically meaningful differences in the PK of milnacipran in male and female subjects. The C_{max}, but not the AUC was approximately 22% higher in females than males (Study # M116). This difference in exposure may not be of clinical significance.

In terms of pediatric indications, the sponsor is requesting deferral to assess the safety and effectiveness of the product in pediatric **population. Based on the sponsor's request,** the Agency granted pediatric deferral on September 11, 2007.

No information is available on the PK of drug in different ethnic groups. In addition, the drug is not known if it is excreted in human milk or transfer via placenta in humans. Therefore, there is limited information in nursing mothers and pregnant women. However, the drug is categorized as pregnancy Category C.

Dose Selection:

The first formal evaluation in FMS was performed in the Phase II study FMS-021 in which the drug was given at 200 mg QD or 100 mg BID for 8 weeks. Milnacipran was up-titrated starting from 12.5 mg BID or 25 mg QD. These doses were selected based on the favorable safety profile at the labeled dose of 100 mg BID in MDD program and literature information suggesting that patients with fibromyalgia might respond better to higher doses of anti-depressants than those typical used for depression. From the safety and efficacy perspective, 100 mg BID was found to be optimal compared to 200 mg QD based on the effect on overall pain relief and tolerability. In the subsequent fibromyalgia clinical studies, doses of 50 mg BID and 100 mg BID were tested.

Dose-Response for Efficacy:

From the clinical pharmacology perspective, it does not appear that there is dose-response for efficacy in the two pivotal studies (Studies # MLN-MD-02 and # FMS031) where 50 mg BID and 100 mg BID were tested. There was no appreciable separation for either the syndrome end-point or pain end-point between 100 mg and 200 mg daily doses (**Figures 1.3.2 A-C**). For example, in study MLN-MD-02 the composite responder rates for the pain end-point for placebo patients was 16.5%, compared to 22.8 % for 100 mg/day and 24.8% for 200 mg/day doses. Similarly, for study FMS031 the response rate

in the placebo patients was 19.3%, compared to 27.2% for 100 mg/day and 26.8% for 200 mg/day doses (**Table 1.3.3**).

Figure 1.3.2. A Percentage of Patients Responding to Treatments
Study # MLN-MD-02 **Study # FMS031**

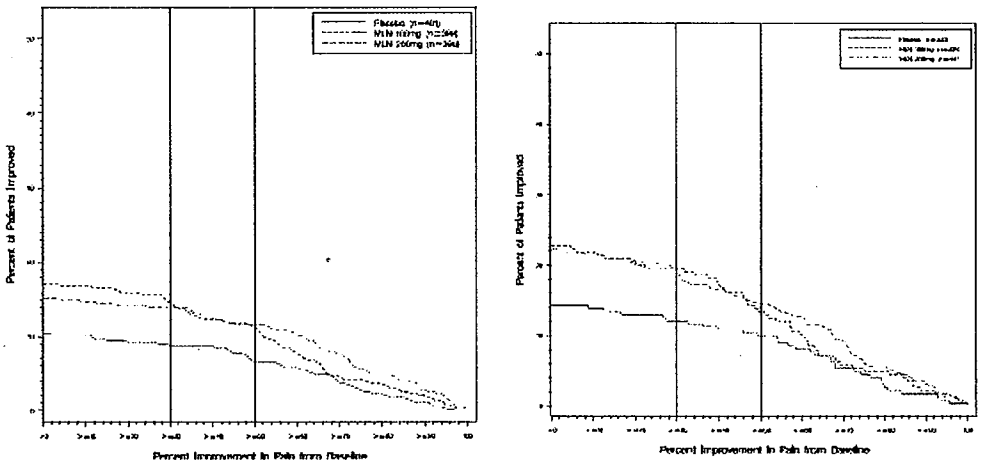


Figure 1.3.2 B. Time Weighted Average of Weekly Average 24-Hour Recall Pain (AUC) for the 3-Month Stable-Dose Period (Last Observation Carried Over-LOCF)
Study # MLN-MD-02 **Study # FMS031**

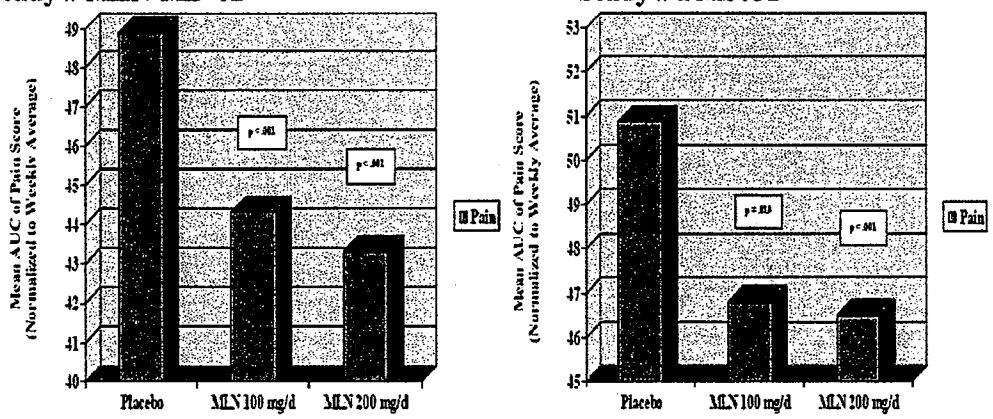


Figure 1.3.2 C. Weekly Average 24-Hour Recall Pain for the 3-Month Treatment Period (Last Observation Carried Over-LOCF)

Study # MLN-MD-02 **Study # FMS031**

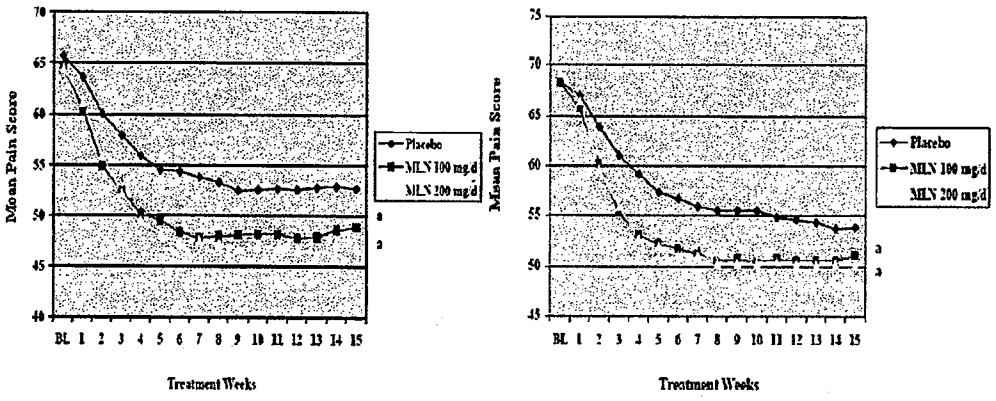


Table 1.3.3. Summary of Pivotal Efficacy Studies: Composite Responders Rate (%) for Milnacipran Versus Placebo for Syndrome and Pain at the 3-Month Landmark (BOCF, ITT Population)

Indication	*Syndrome*			*Pain*		
Treatment Group	*Placebo*	*Milnacipran*		*Placebo*	*Milnacipran*	
		100 mg/d	200 mg/d		100 mg/d	200 mg/d
MLN-MD-02 N	401	399	396	401	399	396
% responders	8.7	14.5	13.9	16.5	22.8	24.8
OR (95% CI)		1.79 (1.15, 2.81)	1.74 (1.11, 2.74)		1.50 (1.05, 2.14)	1.67 (1.18, 2.37)
p-Value		.011	.016		.024	.004
FMS031 (UPA) N	223	224	441	223	224	441
% responders	12.1	19.6	19.3	19.3	27.2	26.8
OR (95% CI)		1.84 (1.07, 3.17)	1.80 (1.11, 2.94)		1.55 (0.99, 2.42)	1.54 (1.04, 2.28)
p-Value		.028	.017		.056	.032

BOCF = baseline observation carried forward; all patients who did not have adequate observation for the evaluation of composite responder status at the 3-month landmark were defined as nonresponders.

UPA = Uniform Program Analysis. UPA definition of response with respect to pain, patient global (ie, PGIC = 1 or 2) and physical function (using SF-36 as agreed upon with the FDA) for syndroma. For the BOCF (UPA) analysis, the alternative model without baseline–value-score-by-treatment-group interaction (the model for the MLN-MD-02 primary efficacy analysis) had nominal p-values (FMS031) of .035 and .020 for composite syndrome and .048 and .032 for composite pain, respectively, for the comparison of 100 mg/d with placebo and 200 mg/d with placebo (see ISE After-Text Table 3.1B and 6.1B).

CI = confidence interval; ITT = Intent-to-Treat; N = population size; OR = odds ratio.

From these data it can be seen that there seems to be a drug effect compared to placebo in both studies but that the response following 100 mg and 200 mg daily doses is overlapping. Sponsor proposes that there is incremental benefit with the 200 mg daily dose in patients with higher Beck Depression Inventory scores and in elderly. See Clinical review by Dr. Jane Filie and Biostatistical review by Dr. Joan Buenconsejo for final assessment of the Clinical Efficacy and Safety.

Dose-Response for Safety:

The most prominent adverse events for milnacipran were related to gastrointestinal tolerability such as nausea and vomiting and cardiovascular effects such as increases in blood pressure and heart rate.

Heart Rate and Blood Pressure-
As expected, based on its pharmacological activity, milnacipran increases the blood pressure and heart rate (Studies M146, C241, MLN-PK-10, MLN-PK-01, MLN-PK-02, MLN-PK-11, MLN-PK-04, MLN-PK-05). In healthy volunteers, this increase in heart rate seems to occur in time and somewhat dose dependent manner. In study M146/C241, the heart rate increases significantly on Day 3 compared to baseline on Day 0 and this increase seems higher at 200 mg dose compared to 100 mg dose (**Table 1.3.4**). At 200 mg dose, the heart rate increases by a mean of about 18 bpm on Day 3.

For the blood pressure, the maximal supine systolic and diastolic blood pressure are higher in milnacipran treatments compared to placebo treatment but this increase does not seem to show a clear dose-dependency (**Tables 1.3.5 and 1.3.6**).

Table 1.3.4. 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 1.3.5 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 1.3.6. 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

The data from study MLN-PK-10 clearly show a consistent increase in both systolic and diastolic blood pressure and heart rate with milnacipran compared to placebo . This study was discussed in more detail by the QT Interdisciplinary Review Team (IRT) in their review dated 6/18/2008. At the end of the study, where milnacipran was administered at a dose of 300 mg BID (supra therapeutic dose), the heart rate increased by a mean of 22 bpm compared to baseline (**Table 1.3.7**).

Figure 1.3.7. Mean (± SD) Vital Signs in Part B (n=100) (Study # MLN-PK-10)

Vital Signs	*Moxifloxacin/Placebo (N=51)*			*Milnacipran (N=49)*			*All Subjects (N=100)*		
	Screening	*End of Study*	*Change From Screening*	*Screening*	*End of Study*	*Change From Screening*	*Screening*	*End of Study*	*Change From Screening*
Systolic BP, mm Hg	113.8 ± 10.3	112.4 ± 11.3	−1.5± 10.7	117.5 ± 10.5	119.4 ± 14.1	2.0± 13.7	115.6 ± 10.5	115.8 ± 13.2	0.2 ± 12.4
Diastolic BP, mm Hg	71.5 ± 6.6	67.1 ± 8.6	−4.5± 7.8	75.4 ± 6.9	76.4 ± 6.2	0.9± 6.1	73.5 ± 7.0	71.6 ± 8.9	−1.8± 7.5
Pulse, bpm	70.3 ± 7.9	75.4 ± 8.9	5.1 ± 9.2	69.4 ± 8.8	92.0 ± 13.4	22.5± 14.2	69.9 ± 8.3	83.5 ± 14.0	13.6 ± 14.8
Temperature, °C	36.7 ± 0.4	36.3 ± 0.4	−0.4 ± 0.5	36.6 ± 0.4	36.2 ± 0.3	−0.4 ± 0.4	36.6 ± 0.4	36.3 ± 0.4	−0.4± 0.5
Respiratory Rate, min^{-1}	14.6 ± 2.4	14.6 ± 2.6	0.0 ± 3.8	14.5 ± 2.5	14.8 ± 3.4	0.3 ± 4.2	14.6 ± 2.5	14.7 ± 3.0	0.2± 4.0
Weight, kg	69.8 ± 10.5	69.3 ± 10.6	−0.5 ± 1.5	76.9 ± 11.1	75.5 ± 11.3	−1.4 ± 1.9	73.3 ± 11.4	72.3 ± 11.3	−0.9± 1.7

BP = blood pressure.

Based on the sponsor's analysis of Phase III data, it shows that overall the mean change from baseline in systolic blood pressure (SBP) is -0.1, 3.1, and 3.0 mm Hg and for diastolic blood pressure (DBP) was 0.4, 3.1, and 2.6 mm Hg in placebo, 100 mg/day, and 200 mg/day groups, respectively.

Similarly, the overall increase in heart rate in patients on milnacipran was 7 to 8 bpm greater than patients on placebo. At the end of the study, the average heart rate was 80 bpm in milnacipran group and 72 bpm in placebo group.

It should be noted that overall the trend of increase in heart rate by >10 bpm was higher in milnacipran-treated patients compared to placebo. The magnitude was 34% of patients receiving 100 mg/day and 40% at 200 mg/day doses compared to 7% in placebo group. The magnitude was reduced for those patients with heart rate >20 bpm to 8% in both 100 mg/day and 200 mg/day compared to 0.3% in placebo group. Only 1% of the patients had heart rate >30 bpm in both doses compared to zero in placebo group.

Based on this data, it can be concluded that all patients on milnacipran had higher blood pressure and heart rate than placebo at all doses and the effect at 200 mg dose appears to be either similar or only marginally higher compared to 100 mg daily dose.

Nausea and Vomiting:
Significant incidences of nausea and vomiting were observed in several clinical pharmacology studies leading to some subjects dropping out from the study. In healthy volunteers, the incidence appeared to be dose dependent (**Tables 1.3.8 and 1.3.9**). For example, in the dose proportionality study M036, all subjects receiving 400 mg doses vomited which precluded the use of the data from these subjects. Food was found to reduce the rates of nausea and vomiting and also delay the onset of these adverse events (Study # 039/M124). In addition, the incidence of nausea and vomiting was found to decrease with a slow up-titration regimen (Studies # C241/M146, MLN-PK-07. MLN-PK-08, and MLN-PK-10).

Table 1.3.8. Across Studies Comparisons for the Incidence (% of Subjects) of Nausea and Vomiting in Healthy Subjects Following Single Oral Administration of Milnacipran

Study	*Treatment*[a]	*Nausea (%)*	*Vomiting (%)*
MLN-PK-04	100 mg, fasted	71	58.1
	100 mg, fed	51.6	51.6
C220	50 mg, fed	46	13
C223	50 mg, fasted	50	10

a [redacted] apsule formulations.

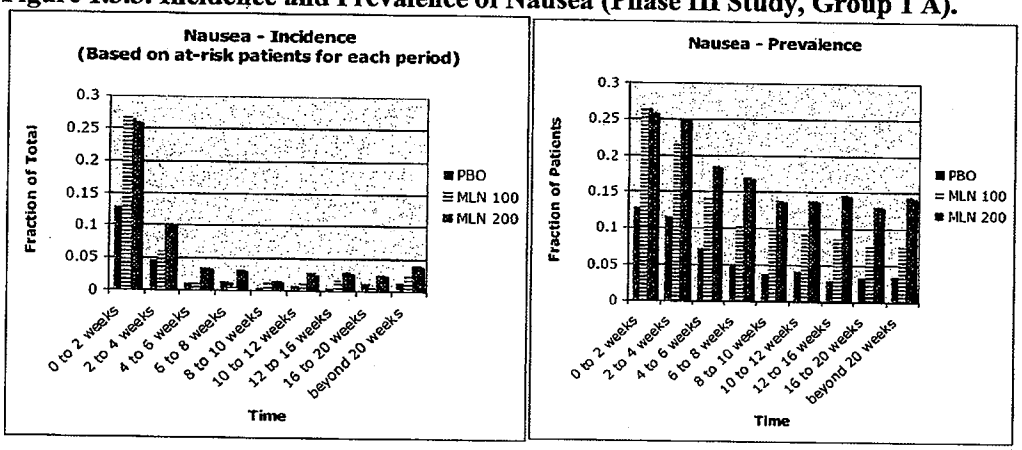
b(4)

Table 1.3.9. Across Studies Comparisons for the Incidence (% of Subjects) of Nausea and Vomiting Following Multiple Oral Administration of Milnacipran

Study	*Treatment*	*Nausea (%)*	*Vomiting (%)*
C241/M146	25 mg BID for 3 days	11.1	5.6
	50 mg BID for 3 days	29.4	11.8
	100 mg BID for 3 days	64.7	23.5
MLN-PK-07	10-day milnacipran HCl treatment starting at 25 mg BID and uptitrated to 100 mg BID	22.2	7.4
MLN-PK-08	9-day milnacipran HCl treatment starting at 12.5 mg and uptitrated to 100 mg BID	13.8	0
MLN-PK-10	37-day milnacipran HCl treatment starting at 12.5 mg and uptitrated to 300 mg BID	30.6	20.4

In the controlled clinical trials, milnacipran was slowly up-titrated to build tolerability of the patients. The incidence of nausea appears to be higher during the first two weeks of drug administration (~27%) and then reduce with time to approximately 5% (**Figure 1.3.3**). Similarly, the prevalence gradually subsided over the first 8 weeks and stabilized at approximately 7% to 14%. The incidence and prevalence appears to be marginally higher at 200 mg/day than 100 mg/day after the first two weeks of administration. According to the sponsor, the drop out rate due to nausea is approximately 3.5 to 7% in patients receiving milnacipran at 100 mg or 200 mg daily doses.

Figure 1.3.3. Incidence and Prevalence of Nausea (Phase III Study, Group 1 A).



Effect on QTc:

The effect on QTc was investigated in a active drug and placebo controlled thorough QT (TQT) study where milnacipran dose was escalated from 12.5 mg to a final dose of 300 mg bid (three times the intended therapeutic dose) for 37 days or placebo (Study # MLN-PK-10). Encapsulated moxifloxocin at a single dose of 400 mg was administered as active control on Day 1 of the placebo arm. This study was reviewed by CDER QT-IRT group (review dated June 18, 2008). The QT-IRT review concluded that after baseline and placebo adjustment, the maximum mean change in QTcF was 8 ms. Due to study

design limitations, the IRT group recommended that the sponsor should repeat the TQT study as follows (see IRT review for details);.

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.

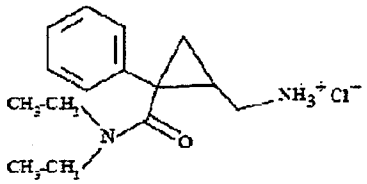
Overall, in this NDA, sponsor has provided adequate data investigating the clinical pharmacology and biopharmaceutics aspects of milnacipran.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Milnacipran is a novel norepinephrine-serotonin reuptake inhibitor (NSRI) developed for the treatment of fibromyalgia syndrome (FMS). As NSRI it inhibits the reuptake of norepinephrine (NE) and 5-HT. Structurally it exists as *cis*-(*d*,*l*) in racemate form with *d* and *l* enantiomers (isomers). The structural formula for milnacipran is shown below:



It should be noted that throughout this review, the racemate parent drug, is denoted as *d*,*l*-milnacipran or as F2207, *d*-isomer coded as F2695, and *l*-isomer is coded as F2696. These codes are mainly shows in some tables and figures generated by the sponsor.

The drug will be available as immediate release tablets in the following strengths: 12.5, 25, 50, and 100 mg of oral administration.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.2.1 Mechanism of Action:

The exact mechanism in the treatment of pain associated with fibromyalgia is unknown. However, the sponsor believes that it is associated with norepinephrine (NE) over serotonin activity in the CNS. Milnacipran inhibits NE uptake by approximately 3 fold higher potency than that of serotonin reuptake.

2.1.2.2.2 Indications:

Milnacipran is indicated for the treatment of fibromyalgia.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose of milnacipran is 100 to 200 mg/day. Drug should be titrated according to the following schedule:
Day 1: 12.5 mg
Days 2-3: 25 mg/day (12.5 mg twice a day)
Days 4-7: 50 mg/day (25 mg twice a day)

After Day 7: 100 mg/day (50 mg twice a day)

Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice a day). Doses above 200 mg/day have not been studied.

2.1.4 What are the Core Studies Submitted in this NDA?

From the clinical pharmacology perspective, the sponsor conducted approximately 60 studies to characterize the PK, PD, and metabolism of the drug *in vitro* and *in vivo*. These include 49 Phase I studies after a single dose (25-400 mg) and multiple-dose (25-300 mg BID), mainly in healthy subjects (47 studies), depression subjects (one study) and pediatric patients (one study). Two of the Phase I studies consisted of both PK and PD components (Study # M126 and M146) and with a separate report for the PD data (# C221 and C241).

In addition, 5 *in vitro* studies were conducted to evaluate the protein binding, blood distribution, and *in vitro* metabolism of milnacipran, as well as the inhibition potential of milnacipran on cytochrome P450 system (CYP450) isozymes.

Furthermore, from the biopharmaceutics perspective, seven comparative bioavailability and bioequivalence studies were conducted to establish the link between the different formulations used in the different phases of product development. In most of the PK studies, the *d*-and *l*-isomers were determined in addition to the parent drug, milnacipran. It should be noted that in most of the figures and table the three components are denoted as follows:

- F2207 = Milnacipran parent drug (or *d,l*-milnacipran for racemate)
- F2695 = *d*-enantiomer (or isomer)
- F2696 = *l*-enantiomer (or isomer)

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

Efficacy:

In a Phase II study milnacipran was administered at 200 mg QD or 100 mg BID for 8 weeks (Study # FMS-021). In this study, the dug was initially up-titrated starting from 12.5 mg BID or 25 mg QD doses. Overall, from a safety and efficacy perspective, 100 mg BID was found to be optimal compared to 200 mg QD (**Table 2.2.1.1**). The GI Tract AEs (especially nausea) were lower after 100 mg BID than after 200 mg QD regimen.

Table 2.2.1.1. Summary of Phase II Data for 100 mg BID and 100 mg QD (Study # FMS-021)

Change From Baseline to End of Study (Tx7-8) in Patient Electronic Diary Pain Scores— Intent-to-Treat Population (LOCF)					
	Milnacipran BID (N=51)	*Milnacipran QD (N=46)*	*Placebo (N=28)*	*p-Value vs Placebo*	
	Mean (SD)			*BID*	*QD*
Random-prompt pain	-2.5 (3.2)	-2.0 (3.5)	-1.6 (3.7)	0.244	0.603
Daily pain	-3.0 (3.5)	-2.2 (3.2)	-1.9 (3.7)	0.191	0.635
Weekly-recall pain	-3.1 (3.5)	-2.5 (3.9)	-1.1 (3.8)	0.025	0.139

Tx7-8 = Treatment Weeks 7 and 8; LOCF = last observation carried forward; BID = twice a day; QD = once daily.

Based on Phase II data, the sponsor conducted two pivotal studies (Studies # MLN-MD-02 and FMS031) and two extension studies (MLN-MD-04 and FMS034). The primary efficacy parameters used in Phase III studies are 1) Pain (know as morning 24-hour recall), 2) Patient global status as measured by Global Impression of Change (PGIC), and 3) Physical function as measured by Short-36 Health Survey Physical Component Summary (SF-36 PCS). For detailed discussion and analysis of these parameters see Clinical and Biostatistics reviews.

From the clinical pharmacology perspective, it does not appear there was a good separation in responses between 100 mg and 200 mg daily doses in Phase III pivotal studies MLN-MD-02 and FMS031(**Figures 2.2.1-2.2.3 and Table 2.2.1.2**). In study MLN-MD-02 the composite responder rates for the pain endpoint for placebo patients was 16.5%, compared to 22.8 % for 100 mg/day and 24.8% for 200 mg/day doses. Similarly, for study FMS031 the responder rate in the placebo patients was 19.3%, compared to 27.2% for 100 mg/day and 26.8% for 200 mg/day doses (**Table 2.2.1.2**)

Figure 2.2.1.1. Percentage of Patients Responding to Treatments

Study # MLN-MD-02 **Study # FMS031**

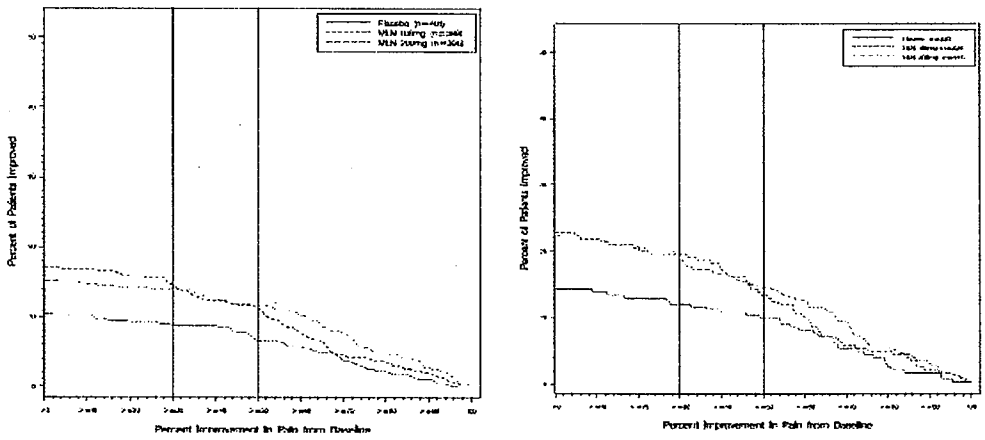


Figure 2.2.1.2. Time Weighted Average of Weekly Average 24 Hour 24-Hour Recall Pain (AUC) for the 3-Month Stable-Dose Period (Las Observed Carried Over-LOCF)

Study # MLN-MD-02 **Study # FMS031**

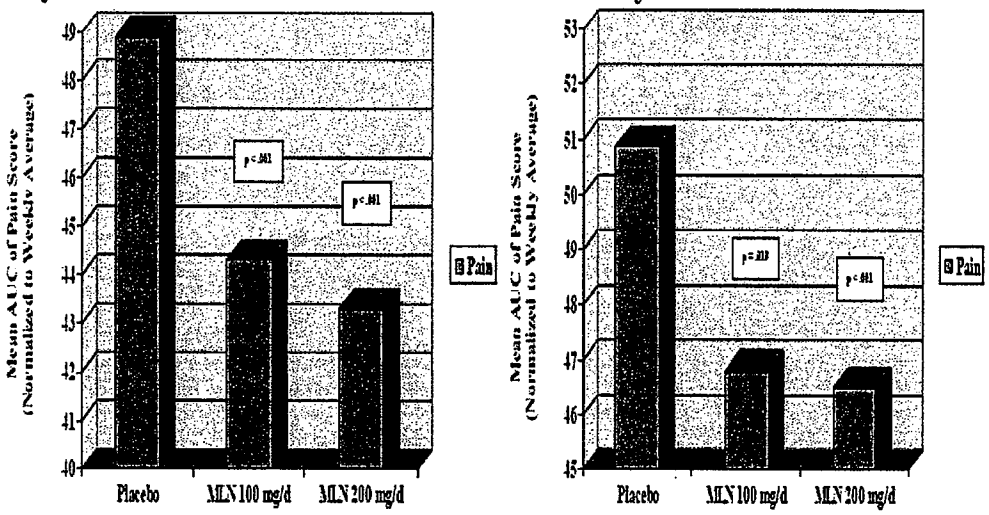


Figure 2.2.1.3. Weekly Average 24-Hour Recall Pain for the 3-Month Treatment Period (Las Observed Carried Over-LOCF)

Study # MLN-MD-02 **Study # FMS031**

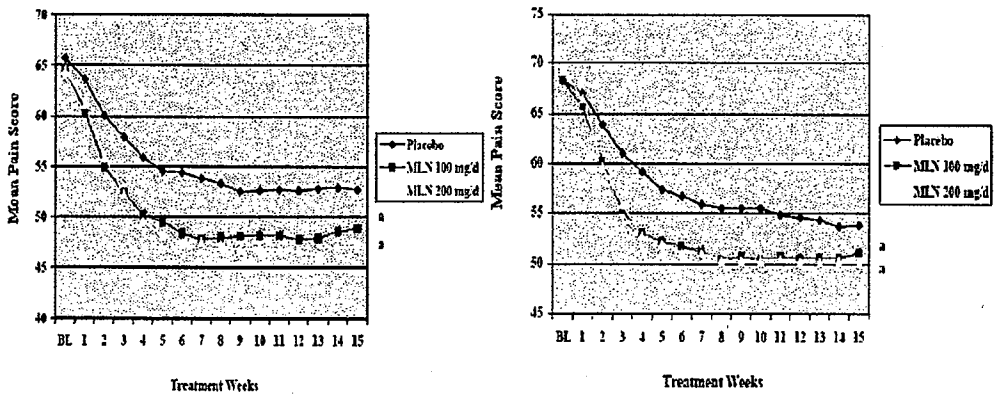


Table 2.2.1.2. Summary of Efficacy Data as Responder Rates (%) After 3 months of Treatments (Study MLN-MD-02 and FMS031).

Indication	*Syndrome*			*Pain*		
Treatment Group	*Placebo*	*Milnacipran*		*Placebo*	*Milnacipran*	
		100 mg/d	200 mg/d		100 mg/d	200 mg/d
MLN-MD-02						
N	401	399	396	401	399	396
% Responders	8.7%	14.5%	13.9%	16.5%	22.8%	24.8%
OR (95% CI)		1.79 (1.15, 2.81)	1.74 (1.11, 2.74)		1.50 (1.05, 2.14)	1.67 (1.18, 2.37)
p value		0.011	0.016		0.024	0.004
FMS031 (UPA)						
N	223	224	441	223	224	441
% Responders	12.1%	19.6%	19.3%	19.3%	27.2%	26.8%
OR (95% CI)		1.84 (1.07, 3.17)	1.80 (1.11, 2.94)		1.55 (0.99, 2.42)	1.54 (1.04, 2.28)
P value		0.028	0.017		0.056	0.032

BOCF = baseline observation carried forward; all patients who did not have adequate observation for the evaluation of composite responder status at the 3-month landmark visit were defined as nonresponders; CI = confidence interval; ITT = intent to treat population; N = population size; OR = odds ratio; UPA= Uniform Program Analysis. UPA definition of response with respect to pain, patient global (ie, PGIC = 1 or 2), and physical function (SF-36 PCS) for syndrome. For the BOCF (UPA) analysis of Study FMS031, the alternative model without baseline value score-by-treatment group interaction (the model for MLN-MD-02 primary efficacy analysis) had nominal P values 0.035, 0.020 for composite syndrome and 0.048 and 0.032 for composite pain, respectively, for the comparison of 100 mg/d to placebo and 200 mg/d to placebo.

Cross-references: ISE Tables 3.1C, 6.1C; FMS031 UPA Tables 4.1A, 4.8A.

Safety-Blood Pressure and Heart Rate:

In terms of safety, the drug clearly increases the blood pressure and heart rate compared to placebo (Studies M146, C241, MLN-PK-10, and MLN-PK-01). In healthy volunteers, this increase in heart rate seems to occur in time and somewhat dose dependent manner. In study M146/C241, the heart rate increases significantly on Day 3 compared to baseline on Day 0 and this increase seems higher at 200 mg dose compared to 100 mg dose (**Tables 2.2.1.3-2.2.1.5**). For the blood pressure, the maximal supine systolic and diastolic blood pressure are higher in milnacipran treatments compared to placebo treatment but this increase does not seem to show a clear dose-dependency.

Table 2.2.1.3 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 2.2.1.4 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 2.2.1.5 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

The data from study MLN-PK-10 clearly show a consistent increase in both systolic and diastolic blood pressure and heart rate with milnacipran compared to placebo. This study was discussed in more detail by the QT Interdisciplinary Review Team (IRT) in their

review dated 6/18/2008. At the end of the study, where milnacipran was administered at a dose of 300 mg BID, the heart rate increased by a mean of 22 bpm compared to baseline.

Table 2.2.1.6. Mean (± SD) Vital Signs in Part B (n=100) (Study # MLN-PK-10)

Vital Signs	*Moxifloxacin/Placebo (N=51)*			*Milnacipran (N=49)*			*All Subjects (N=100)*		
	Screening	*End of Study*	*Change From Screening*	*Screening*	*End of Study*	*Change From Screening*	*Screening*	*End of Study*	*Change From Screening*
Systolic BP, mm Hg	113.8 ± 10.3	112.4 ± 11.3	−1.5± 10.7	117.5 ± 10.5	119.4 ± 14.1	2.0± 13.7	115.6 ± 10.5	115.8 ± 13.2	0.2 ± 12.4
Diastolic BP, mm Hg	71.5 ± 6.6	67.1 ± 8.6	−4.5± 7.8	75.4 ± 6.9	76.4 ± 6.2	0.9± 6.1	73.5 ± 7.0	71.6 ± 8.9	−1.8± 7.5
Pulse, bpm	70.5 ± 7.9	75.4 ± 8.9	5.1 ± 9.2	69.4 ± 8.8	92.0 ± 13.4	22.5± 14.2	69.9 ± 8.3	83.5 ± 14.0	13.6 ± 14.8
Temperature, °C	36.7 ± 0.4	36.3 ± 0.4	−0.4 ± 0.5	36.6 ± 0.4	36.2 ± 0.3	−0.4 ± 0.4	36.6 ± 0.4	36.3 ± 0.4	−0.4± 0.5
Respiratory Rate, min^{-1}	14.6 ± 2.4	14.6 ± 2.6	0.0 ± 3.8	14.5 ± 2.5	14.8 ± 3.4	0.3 ± 4.2	14.6 ± 2.5	14.7 ± 3.0	0.2± 4.0
Weight, kg	69.3 ± 10.5	69.3 ± 10.6	−0.5 ± 1.5	76.9 ± 11.1	75.5 ± 11.3	−1.4 ± 1.9	73.3 ± 11.4	72.3 ± 11.3	−0.9± 1.7

BP = blood pressure.

It should also be noted that in the dose escalating PK study MLN-PK-01, the MTD was not defined due to the high drop out as a result of cardiovascular effects associated with high blood pressure and sinus tachycardia.

In Clinical efficacy and safety Phase II/III studies, the sponsor's analysis shows that overall the mean change from baseline in systolic blood pressure (SBP) is -0.1, 3.1, and 3.0 mm Hg in placebo, 100 mg/day, and 200 mg/day groups, respectively. Similarly, for the diastolic blood pressure (DBP) the mean change from baseline was 0.4, 3.1, and 2.6 mm Hg in placebo, 100 mg/day, and 200 mg/day groups, respectively (**Table 2.2.1.7**). Based on this data, there is a clear trend of increase in SBP and DBP compared to baseline and placebo. However, there does not appear to be a clear separation between 100 mg and 200 mg/day doses.

Table 2.2.1.7. Mean Change from Baseline in Supine Blood Pressure at End-of-Study Visit. Placebo-Controlled Fibromyalgia Studies-Group 1 A (Phase II/III data).

Parameter	*Placebo N = 652*		*Milnacipran*			
			100 mg/d N = 623		*200 mg/d N = 934*	
	N	Mean ± SD	N	Mean ± SD	n	Mean ± SD
Systolic BP, mm Hg						
Baseline	641	122.1 ± 14.5	614	122.8 ± 14.5	912	121.7 ± 14.1
End of Study	641	122.0 ± 14.5	614	126.0 ± 14.5	912	124.7 ± 14.3
Change	641	−0.1 ± 13.7	614	3.1 ± 14.0	912	3.0 ± 12.9
Diastolic BP, mm Hg						
Baseline	641	75.9 ± 9.1	614	77.2 ± 8.9	912	76.3 ± 8.5
End of Study	641	76.3 ± 9.2	614	80.3 ± 9.2	912	78.9 ± 9.2
Change	641	0.4 ± 9.5	614	3.1 ± 9.4	912	2.6 ± 9.0

End-of-Study values are last observation carried forward.
BP = blood pressure

Overall, the increases in SBP and DBP at a magnitude of >10 or >20 mm Hg were more common in milnacipran treated patients than placebo treated patients (**Table 2.2.1.8**).

Table 2.2.1.8. Mean Increase in Supine Blood Pressure by Magnitude of Change at End of Study in Group 1 AA (Phase III data only).

Group	*Placebo (N = 624)*			*Milnacipran 100 mg (N = 623)*			*Milnacipran 200 mg (N = 837)*		
Total	*M*	*n*	*%*	*M*	*n*	*%*	*M*	*n*	*%*
SBP, mm Hg	615			614			820		
Δ ≥ 10		74	12.0		141	23.0		167	20.4
Δ ≥ 20		9	1.5		27	4.4		27	3.3
Δ ≥ 30		1	0.2		3	0.5		5	0.6
Δ ≥ 40		0	0		0	0		0	0
DBP, mm Hg	615			614			820		
Δ ≥ 5		109	17.7		223	36.3		281	34.3
Δ ≥ 10		31	5.0		91	14.8		107	13.0
Δ ≥ 15		6	1.0		31	5.0		33	4.0
Δ ≥ 20		2	0.3		4	0.7		4	0.5
Δ ≥ 25		0	0		2	0.3		0	0
Δ ≥ 30		0	0		0	0		0	0

M = number of patients with available baseline and End-of-Study values.
SBP = systolic blood pressure; Δ = change from baseline; DBP = diastolic blood pressure.

Similarly, in Phase III studies, the overall increase in heart rate in patients on milnacipran was 7 to 8 bpm greater than patients on placebo (**Table 2.2.1.9**). At the end of the study the average heart rate was 80 bpm in milnacipran group and 72 bpm in placebo group. However, there was no difference in 100 mg/day and 200 mg/day doses.

Table 2.2.1.9. Mean Change in Heart Rate in Group 1AA.

Group	*Placebo (N = 624)*			*Milnacipran 100 mg/d (N = 623)*			*Milnacipran 200 mg/d (N = 837)*		
	B (bpm)	*ES (bpm)*	*Δ (bpm)*	*B (bpm)*	*ES (bpm)*	*Δ (bpm)*	*B (bpm)*	*ES (bpm)*	*Δ (bpm)*
GROUP 1AA		**M = 615**			**M = 614**			**M = 820**	
Mean	72	72	0	73	80	7	73	80	8
SD	8	8	7	8	10	9	8	10	9
Median	71	72	0	72	79	6	72	80	7
Range	46-101	49-100	–28 - +24	51-100	50-116	–25 - +35	45-98	55-120	–23 - +39

B = baseline; ES = End of Study; Δ = change from baseline; bpm = beats per minute. M = number of patients with available baseline and End-of-Study values.

It should be noted that overall the trend of increase in heart rate by >10 bpm was higher in milnacipran-treated patients compared to placebo (**Table 2.2.1.10**). The magnitude was 34% of patients receiving 100 mg/day and 40% at 200 mg/day doses compared to 7% in placebo group. The magnitude was reduced for those patients with heart rate >20 bpm to 8% in both 100 mg/day and 200 mg/day compared to 0.3% in placebo group. Only 1% of the patients had heart rate >30 bpm in both doses compared to zero in placebo group.

Based on this data, it can be concluded that all patients on milnacipran had higher heart rate than placebo at all doses.

Table 2.2.1.10. Mean Change in Heart Rate by Magnitude at End of Study in Group 1AA.

Group	*Placebo*			*Milnacipran 100 mg/d*			*Milnacipran 200 mg/d*		
	M	*n*	*% (n/M)*	*M*	*n*	*% (n/M)*	*M*	*n*	*% (n/M)*
Group 1AA									
Δ = ≥ 0 bpm		317	52		498	81		676	82
Δ = ≥ 10 bpm	615	42	7	614	208	34	820	330	40
Δ = ≥ 20 bpm		2	0.3		47	8		68	8
Δ = ≥ 30 bpm		0	0		7	1		9	1

Note: End-of-Study values are based on at least 1 postbaseline assessment or the average of up to 3 postbaseline assessments if available.
M = number of patients with available baseline and End-of-Study values; Δ = change from baseline; bpm = beats per minute.

N*ausea and Vomiting*:

In addition to elevation in blood pressure and heart rate, other reasons for drop out that was observed in clinical pharmacology and clinical studies were the high incidences of nausea and vomiting. The incidence appears to be dose dependent in healthy volunteers **(Tables 2.2.1.11 and 2.2.1.12).**

For example, in the dose proportionality study M036, all subjects received 400 mg doses vomited which precluded the use of the data from these subjects. Food was found to reduce the rates of nausea and vomiting and delay the onset of these adverse events (Study # 039/M124). In addition, the incidence of nausea and vomiting decreases with slow up-titration regimen (Studies # C241/M146, MLN-PK-07. MLN-PK-08, and MLN-PK-10). In the same token, the incidence of GI tract AEs was higher at 200 mg QD than at 100 BID in Phase II (Study # FMS-021).

Table 2.2.1.11. Across Studies Comparisons for the Incidence (% of Subjects) of Nausea and Vomiting in Healthy Subjects Following Single Oral Administration of Milnacipran

Study	*Treatment*[a]	*Nausea (%)*	*Vomiting (%)*
MLN-PK-04	100 mg, fasted	71	58.1
	100 mg, fed	51.6	51.6
C220	50 mg, fed	46	13
C223	50 mg, fasted	50	10

a [redacted] capsule formulations.

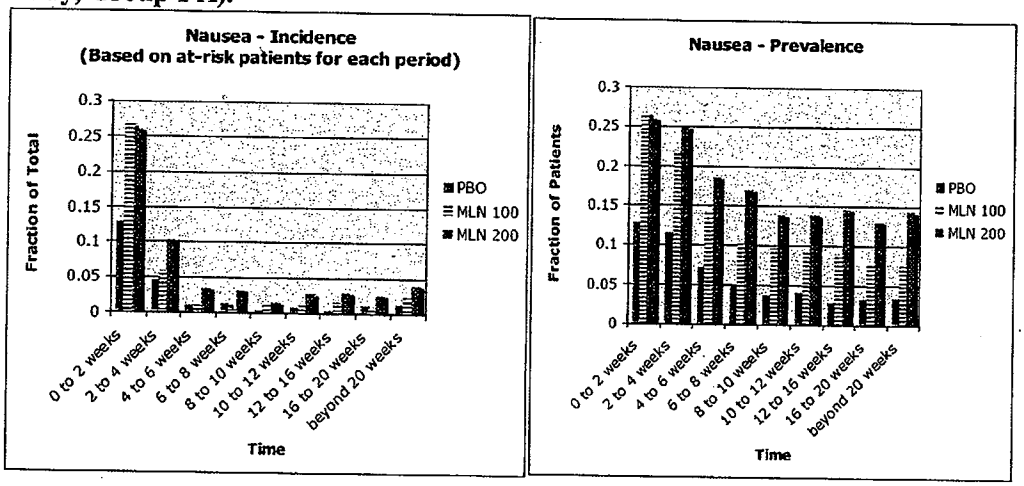
b(4)

Table 2.2.1.12. Across Studies Comparisons for the Incidence (% of Subjects) of Nausea and Vomiting Following Multiple Oral Administration of Milnacipran

Study	*Treatment*	*Nausea (%)*	*Vomiting (%)*
C241/M146	25 mg BID for 3 days	11.1	5.6
	50 mg BID for 3 days	29.4	11.8
	100 mg BID for 3 days	64.7	23.5
MLN-PK-07	10-day milnacipran HCl treatment starting at 25 mg BID and uptitrated to 100 mg BID	22.2	7.4
MLN-PK-08	9-day milnacipran HCl treatment starting at 12.5 mg and uptitrated to 100 mg BID	13.8	0
MLN-PK-10	37-day milnacipran HCl treatment starting at 12.5 mg and uptitrated to 300 mg BID	30.6	20.4

In the Clinical trials, the incidence of nausea appears to be higher during the first two weeks of drug administration (~27%) and then reduce with time to approximately 5% (**Figure 2.2.1.4**). The incidence and prevalence appears to be somewhat higher at 200 mg/day than 100 mg/day after the first two weeks of administration. Similarly, the prevalence gradually subsided over the first 8 weeks and stabilized to approximately 7% to 14%. According to the sponsor, the drop out rate due to nausea is approximately 3.5 to 7% in patients receiving milnacipran 100 mg or 200 mg daily doses.

Figure 2.2.1.4. Incidence and Prevalence Rates of Nausea With Time (Phase III Study, Group 1 A).



2.2.2 What are the Characteristics of Drug Metabolism?

2.2.2.1 *In vitro* Metabolism:

Based on *in vitro* data using cDNA-expressed human CYPs none of the tested isozymes CYP1A2, 2A^, WB6, 2C9, 2C19, 2D6, 2E1, and 3A4 were found to be responsible for the metabolism of the parent drug, *d*, or /isomers (Study # PK07MXH1). The incubation of milnacipran in human hepatic microsomes resulted in only 14.8% transformation (Study PK07MXH1). The only metabolite formed after milnacipran is N-desethyl milnacipran through N-dealkylation. This is a minor metabolite (excreted as 8% of the dose in urine) and in pre-clinical studies was found to be inactive.

2.2.2.2 *In vitro* Inhibition of CYP Isozymes

The inhibitory potential of milnacipran on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 isozymes was evaluated in hepatic microsomes. The data show that the IC_{50} of milnacipran for most of the substrates is >500 μM and the lowest was approximately 85 μM **(Table 2.2.2.1, Study #MLN-BDM-001).**

Table 2.2.2.2.1. IC50 of Milnacipran on Activity of Enzymes of Pooled Human Hepatic Microsomes (Study MLN-BDM-001).

Isozyme (CYP)	IC_{50} (μM) of Milnacipran (μM)	Model Substrate, Concentration (μM)	Metabolite of the Model Substrate
1A2	> 500	Ethoxyresorufin, 1.0	Resorufin
2A6	> 500	Coumarin, 5	7-Hydroxycoumarin
2C9	> 500	Tolbutamide, 200	4-Hydroxytolbutamide
2C19	> 500	S-Mephenytoin, 80	4'-Hydroxymephenytoin
2D6	409.0	Dextromethorphan, 20	Dextrorphan
2E1	> 500	Chlorzoxazone, 75	6-Hydroxychlorzoxazone
3A4	84.4 442.0	Midazolam, 2.5 Testosterone, 80	1'-Hydroxymidazolam 6ß-Hydroxytestosterone

Another study showed similar data in which the IC_{50} of milnacipran was >50 μM (Study # PRD-RPT-BDM-00051). From these studies it can be concluded that milnacipran is unlikely to inhibit CYP P450 isozymes.

2.2.2.3 *In vitro* Induction of CYP Isozymes

The sponsor conducted *in vitro* study to investigate the enzyme induction potential of milnacipran in human hepatocytes (Study # XT08318). This study was submitted on June 26, 2008. Milnacipran was incubated with human hepatocytes at 3, 10, or 30 μM and tested against three positive controls: omeprazole (100 μM), phenobarbital (750 μM) and rifampin (10 μM).

Based on the data generated from this study it does not appear that milnacipran has induction potential at the recommended therapeutic dose on any of the CYP 450

isozymes. In addition, based on this study and the average milnacipran Cmax following 100 mg dose which is approximately 500 ng/ml (<3 μM), it does not appear that milnacipran has a potential to induce any of the CYP 450 enzymes, even at 10 μM concentration (**Table 2.2.2.3.1**). However, at 30 μM concentration there is some trend of increase in enzyme activities but at much lower magnitude compared to respective isozyme positive controls.

Table 2.2.2.3.1. Fold increase (Treated/vehicle control) for the Effects of Treating Cultured Human Hepatocytes with Milnacipran or Prototypical Inducers on CYP450.

Treatment	Concentration	Fold Increase [a]					
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Amodiaquine *N*-dealkylation (CYP2C8)	Diclofenac 4'-hydroxylation (CYP2C9)	S-Mephenytoin 4'-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.80	1.00 ± 0.52	1.00 ± 0.31	1.00 ± 0.34	1.00 ± 0.69	1.00 ± 0.35
Milnacipran hydrochloride	3 μM	1.04 ± 0.15	1.11 ± 0.13	1.06 ± 0.21	1.05 ± 0.03	1.02 ± 0.13	1.24 ± 0.34
Milnacipran hydrochloride	10 μM	1.15 ± 0.08	1.69 ± 0.30	1.18 ± 0.11	1.09 ± 0.09	1.08 ± 0.26	1.75 ± 0.78
Milnacipran hydrochloride	30 μM	1.15 ± 0.08	2.59 ± 0.62 †	1.22 ± 0.06	1.11 ± 0.11	0.980 ± 0.172	2.15 ± 0.83
Omeprazole	100 μM	36.8 ± 32.5 ‡	6.70 ± 3.66 ‡	3.75 ± 1.76	1.40 ± 0.31	1.39 ± 1.05	1.75 ± 1.64
Phenobarbital	750 μM	2.22 ± 0.62	10.1 ± 5.3 ‡	4.19 ± 1.21 ‡	1.80 ± 0.14 ‡	2.92 ± 0.89	4.35 ± 2.34 *
Rifampin	10 μM	1.86 ± 0.37	5.59 ± 2.33 ‡	4.91 ± 1.05 ‡	2.13 ± 0.33 ‡	6.31 ± 1.99 *	4.21 ± 1.53 *

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H838, H840 and H841).

‡ Statistical significance found among the treatment groups according to Kruskal-Wallis One Way Analysis of Variance on ranks ($p < 0.05$) and Dunnett's Method when the positive control groups (omeprazole, phenobarbital and rifampin) were included in the statistical analysis.

† Significantly different from the vehicle control (dimethyl sulfoxide) according to Dunnett's Method ($p < 0.05$) when the positive control groups (omeprazole, phenobarbital and rifampin) were excluded from the statistical analysis.

* Significantly different from the vehicle control (dimethyl sulfoxide) according to Dunnett's Method ($p < 0.05$) when the positive control groups (omeprazole, phenobarbital and rifampin) were included in the statistical analysis.

In Vivo Metabolism:

Based on the mass balance study using ^{14}C milnacipran, there was almost complete recovery of the radioactivity (~97%) in urine and <5% in feces (**Tables 2.2.2.2.1-2**). The plasma profiles of radioactivity and milnacipran and the PK parameters are shown in **Figure 2.2.2.2.1 and Table 2.2.2.2.3.**

Table 2.2.2.2.1. Mass Balance Data. Mean Excretion of Radioactivity in Urine and Feces in Healthy Subjects (Study # MLN-PK-05).

	Excretion (%Dose)		
Subject #	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 2.2.2.2.2. % 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**

Figure 2.2.2.2.1. Mean Plasma Profiles of Radioactivity and Milnacipran (Study # MLN-PK-05).

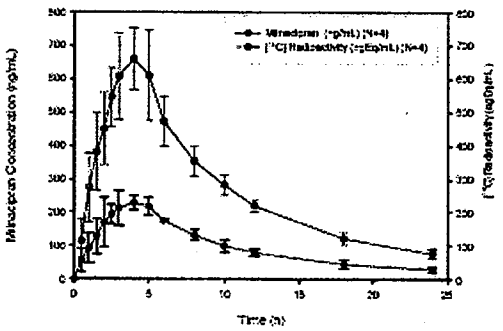


Table 2.2.2.2.3. Summary of PK Parameters of the Mass Balance Study (Study # MLN-PK-05).

Pharmacokinetic Parameters[a]	*[^{14}C] Radioactivity*[b] *(N = 4)*	*Milnacipran (N = 4)*	*Ratio % Milnacipran: [^{14}C] Radioactivity*
C_{max} (ng/mL)	679.0 ± 112.6	239.6 ± 33.2	35.3
T_{max} (h)	4.3 ± 0.5	3.5 ± 1.0	–
AUC_{24} (ng·h/mL)	6446 ± 666	2343 ± 252	36.3
AUC_{∞} (ng·h/mL)	7225 ± 622	2757 ± 413	37.8
$T_{1/2}$ (h)	7.7 ± 1.0	8.9 ± 3.2	–

a C_{max} and AUC parameters reflect fasting values
b Units for C_{max} = ng Eq/mL; AUC_{24} and AUC_{∞} = ng Eq·h/mL.

C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; AUC_{24} = area under the plasma concentration vs time curve from time 0 to t; AUC_{∞} = area under the plasma concentration vs time curve from time 0 to infinity; $T_{1/2}$ = terminal elimination half-life.
Cross-reference: Study MLN-PK-05, Tables 14-3 and 14-4.

From this data it can be concluded that kidneys are the primary route of elimination of milnacipran. Approximately 55% of the dose was excreted as unchanged milnacipran in urine (24% as *l*- and 31% as *d*-isomer) (**Table 2.2.2.2.2**). According to the sponsor, both isomers undergo conjugation process to their respective carbamoyl O-glucuronides which account for approximately 20% of the dose (~17% for *l* and ~2% for *d*). In addition, 8% of the dose undergoes oxidative pathway to form N-desethyl-milnacipran metabolite and excreted in urine.

Genetic Polymorphism:

The sponsor conducted a formal study to address the potential of genetic polymorphism and the metabolism of milnacipran in poor (PM) and extensive metabolizers-EM (Study # M244).

The study was conducted to evaluate the influence of single and repeated administration of milnacipran on various probes of the activity of CYP450 isozymes, namely sparteine (CYP2D6), mephenytoin (CYP2C19), caffeine (CYP1A2), and endogenous 6β-hydroxycortisol excretion (CYP3A4). In addition, the study objective was to compare the PK of milnacipran in extensive metabolizers (EM) to poor metabolizers (PM) of sparteine and mephenytoin.

The study was conducted as a single dose and multiple-dose in parallel group of 25 healthy subjects as follows:

Day-2 (baseline):
Day 1: 50 mg milnacipran
Days 2 to 7: 50 mg BID milnacipran
Day 8: 50 mg milnacipran

Study Schedule (Study # M244):

Period	pre-study (1 day)	Study period (9 days)	Post-study (1 day)
Hospitalisation	▬▬	▬▬▬▬▬▬▬▬▬▬	▬▬
	12 h	D1 D9	12 h
Metabolic probe tests	D-2	D1 D8	D20
Milnacipran 50mg b.i.d		D1 D2 ▬▬ D8	
PK days		D1 D8	

Blood samples for PK analysis of milnacipran and N-dealkylated metabolite (F2800) were collected on Days 1 and 8. Metabolic probe tests were performed on Days –2, 1, 8, and 20 after administration of 100 mg sparteine, 100 mg mephenytoin, and 200 mg caffeine. Cortisol excretion in urine was also evaluated.

There was not much difference in exposure (C_{max} and AUC) of milnacipran and its N-dealkylated metabolite (F2800) in sparteine between PMs and EM subjects (**Table 2.2.2.2.4 and 2.3.3.2.5**). The Cmax and AUC for milnacipran were reduced about 20%, while the N-dealkylated metabolite (F2800) was increased by approximately 10%. Thus CYP2D6 is not involved in the metabolism of milnacipran. Similarly, there were no changes in the PK of milnacipran in PM subjects of mephenytoin. In addition, minor increase (20%) in urinary excretion of sparteine or its metabolites was noted in EM subjects. This also suggests low CYP2D6 involvement.

The metabolism of mephenytoin via CYP2C19, measured by the S/R-mephenytoin urine ratio, was unaffected by administration of milnacipran indicating that milnacipran does not affect the activity of CYP2C19. Caffeine clearance before and after single and multiple dose administration of milnacipran remained unchanged indicating no effect of milnacipran on the CYP1A2 isoenzyme. Cortisol excretion was also unaffected by milnacipran treatment indicating that milnacipran does not affect the activity of CYP3A4.

Table 2.2.2.2.4. Mean PK Parameters of Milnacipran and its N-Dealkylated Metabolite (F2800) After Single Oral Administration in PM and EM Sparteine and Mephenytoin Subjects (Study # M244).

	Milnacipran			*F2800*		
	50 mg Milnacipran HCl (Single Dose)					
Pharmacokinetic Parameter[a]	**EM_{spart}/ EM_{meph} (N = 11)**	**PM_{spart}/ EM_{meph} (N = 8)**	**EM_{spart}/ PM_{meph} (N = 4)**	**EM_{spart}/ EM_{meph} (N = 11)**	**PM_{spart}/ EM_{meph} (N = 8)**	**EM_{spart}/ PM_{meph} (N = 4)**
C_{max} (ng/mL)	121.0 ± 21.6	95.4 ± 16.0	132.7 ± 16.7	9.5 ± 3.3	9.3 ± 2.7	12.9 ± 2.2
T_{max} (h)	3.8 ± 1.4	3.5 ± 0.9	3.5 ± 1.0	6.9 ± 2.2	7.9 ± 1.6	6.3 ± 2.1
$AUC_{0-\infty}$ (ng•h/mL)	1225 ± 279	1062 ± 158	1224 ± 168	177 ± 68	220 ± 54	238 ± 22
$T_{½}$ (h)	6.3 ± 0.5	6.9 ± 0.9	6.2 ± 0.5	8.6 ± 0.8	11.3 ± 2.5	9.2 ± 1.8
CL/F	37.4 ± 9.3	41.8 ± 6.9	36.1 ± 5.0	–	–	–
V_d/F (L)	340 ± 98	415 ± 85	321 ± 46	–	–	–
CL_r (L/h)	15.8 ± 4.4	15.2 ± 2.0	15.1 ± 3.7	–	–	–
MR (%)[b]	–	–	–	14.1 ± 3.2	18.7 ± 7.2	19.3 ± 3.2

Table 2.2.2.2.5. Mean PK Parameters of Milnacipran and its N-Dealkylated Metabolite (F2800) After Multiple Oral Administration in PM and EM Sparteine and Mephenytoin Subjects (Study # M244).

	Milnacipran			*F2800*		
	50 mg BID Milnacipran HCl (Multiple Dose)					
Pharmacokinetic Parameter[a]	**EM_{spart}/ EM_{meph} (N = 12)**	**PM_{spart}/ EM_{meph} (N = 9)**	**EM_{spart}/ PM_{meph} (N = 4)**	**EM_{spart}/ EM_{meph} (N = 12)**	**PM_{spart}/ EM_{meph} (N = 9)**	**EM_{spart}/ PM_{meph} (N = 4)**
C_{max} (ng/mL)	186.6 ± 37.7	144.3 ± 29.8	186.6 ± 2.4	18.7 ± 6.1	20.9 ± 3.7	24.6 ± 1.3
T_{max} (h)	3.3 ± 1.0	3.1 ± 1.1	2.5 ± 1.0	6.3 ± 2.6	5.6 ± 2.1	5.0 ± 1.2
AUC_{0-12} (ng•h/mL)	1367 ± 308	1088 ± 188	1286 ± 70	189 ± 64	208 ± 35	248 ± 11
$T_{½}$ (h)	6.9 ± 0.6	7.1 ± 0.9	6.7 ± 0.6	8.7 ± 1.0	9.1 ± 1.0	8.3 ± 0.7
CL/F	33.5 ± 8.5	41.1 ± 7.3	33.9 ± 1.8	–	–	–
V_d/F (L)	334 ± 102	426 ± 109	330 ± 34	–	–	–
CL_r (L/h)	14.5 ± 4.4	15.9 ± 1.5	13.7 ± 2.4	–	–	–
fe (%)	55.5 ± 9.0	50.9 ± 8.6	50.6 ± 6.4	–	–	–
MR (%)[b]	–	–	–	15.7 ± 4.0	22.2 ± 6.6	21.8 ± 1.0

a C_{max} and AUC parameters of milnacipran reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

b Metabolic ratio, calculated as AUC metabolite/AUC milnacipran.

C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; $AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{½}$ = 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; CL_r = renal clearance; MR = metabolic ratio; AUC_{0-12} = area under the plasma concentration vs time curve from time 0 to 12 hours (steady-state dosing interval); fe = fraction of dose excreted as unchanged drug in urine.

Based on these data, it can be concluded that milnacipran does not appear to be metabolized via CYP2C19, CYP2D6, CYP2C19, CYP1A2, and CYP3A4.

2.2.3 Dose-Proportionality

2.2.3.1 What are the characteristics of the dose-systemic exposure relationships?

Several studies were conducted to establish the dose-systemic exposure to milnacipran after a single and multiple doses (M040, M036, M120, and M146). Overall, the exposure of milnacipran appears to increase proportionally with dose up to 200 mg and 300 mg, depending on the study (**Figures 2.2.3.1.1 to 3 and Table 2.2.3.1.1**). The same trend is shown for its isomers, *d* and *l*.

Figure 2.2.3.1.1. Dose-Proportionality response for Milnacipran and its Enantiomers Following Single Doses-Day 1 (Study # M146).

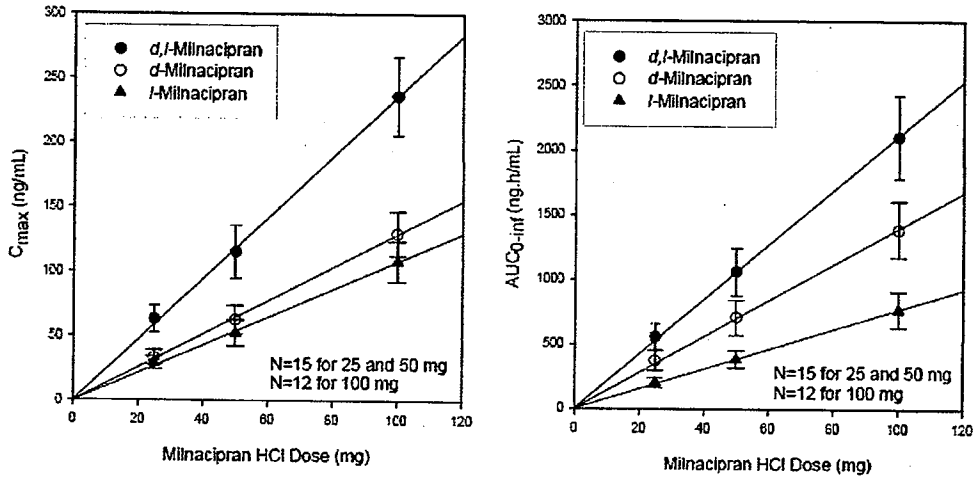


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Figure 2.2.3.1.2. Dose-Proportionality for Milnacipran and its Enantiomers Following Multiple Doses (BID X 3 Days) (Study # M146).

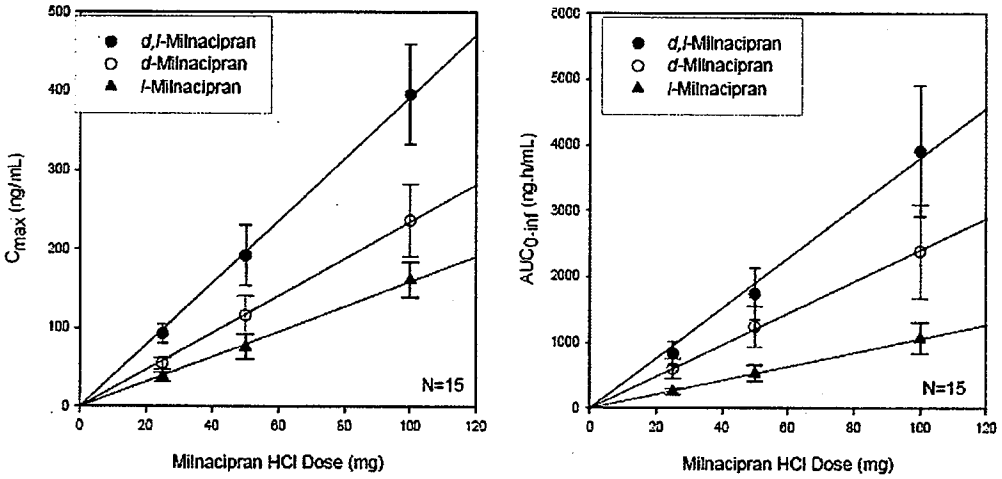

Figure 2.2.3.1.3. Mean Plasma Concentration-Time Profiles of Milnacipran and its Enantiomers Following Single (Day 1) Multiple Doses (BID X 3 Days) (Study # M146).

A: Milnacipran

Day 1 **Day 3**

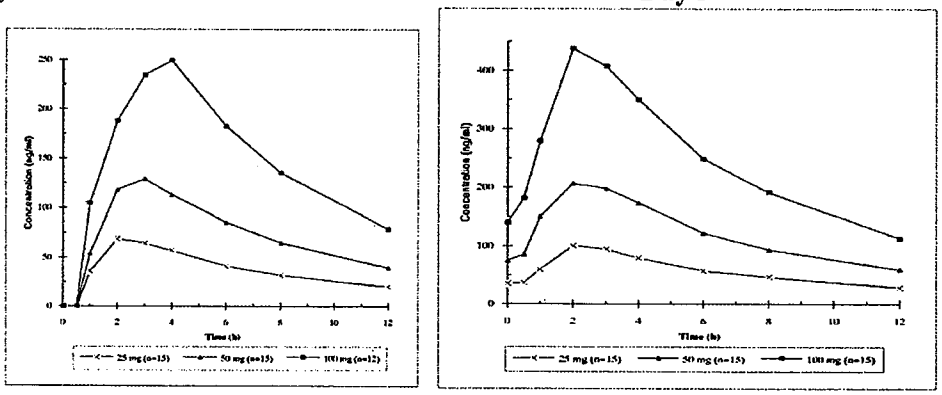

Figure 2.2.3.1.3 (Continued)
B: *d*-Isomer

Day 1 **Day 3**

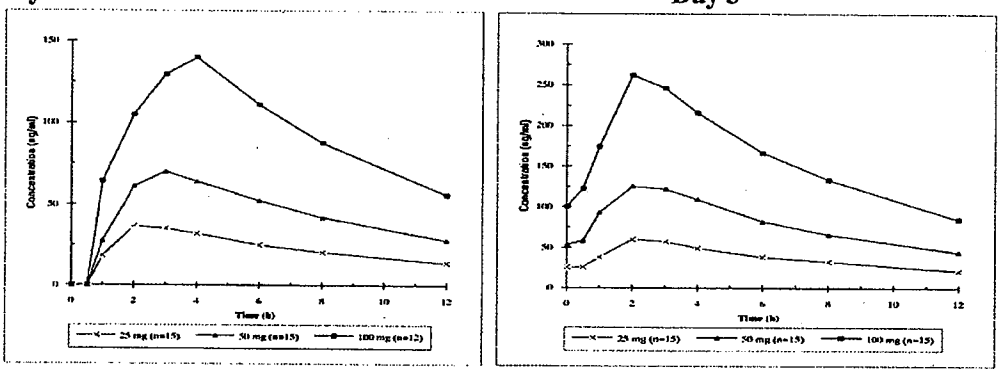

Figure 2.2.3.1.3 (Continued)
C: *l*-Isomer

Day 1 **Day 3**

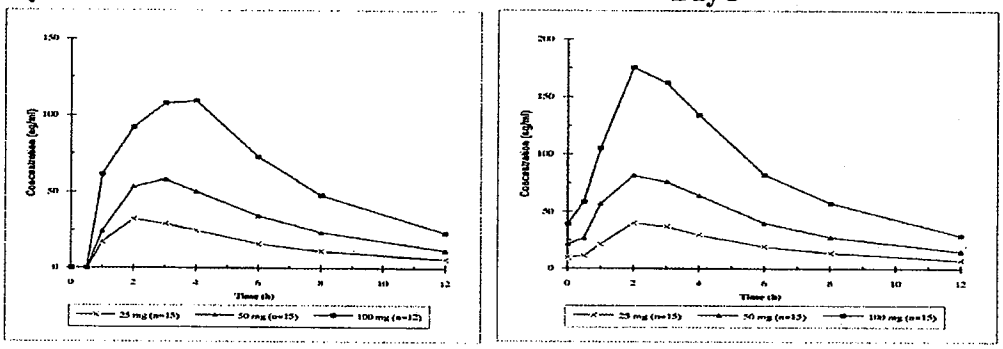

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Table 2.2.3.1.1. Mean PK Parameters Following Single and Multiple Doses (Study # M146).

	Single Dose—Day 1			*Multiple Dose—Day 3*		
Pharmacokinetic Parameter[b]	*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]
$T_{½}$ (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]
$T_{½}$ (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

	Single Dose—Day 1			*Multiple Dose—Day 3*		
Pharmacokinetic Parameter[b]	*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]
$T_{½}$ (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).

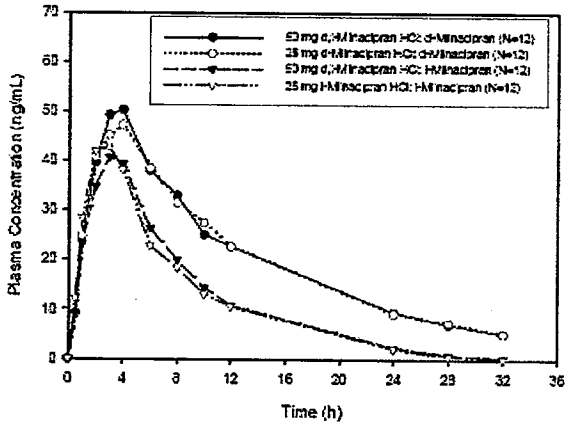
c $AUC_{0-\tau}$

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; $T_{½}$= 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.

In Study # M115 the drug was administered alone or in combination with its two isomers (*d* and *l*) to investigate the interaction when administered together. From this study and all other studies in this NDA, the exposure for both isomers was dose dependent but the expsoure has been consistently higher for *d*-isomer than *l*-isomer **(Figure 2.2.3.1.4).**

Figure 2.2.3.1.4. Mean Plasma Concentration-Time Profiles of Milnacipran and its *d* and *l*- isomers in Healthy Subjects (Study # M115).



The same trend was seen in Study # MLN-PK-01 in which milnacipran was administered at escalated doses ranging from 2.5 mg to 100 mg BID in healthy subjects **(Figure 2.2.3.1.5 and Table 2.2.3.1.2)**

Figure 2.2.3.1.5. Mean Steady State Plasma Concentration (Prior dosing) of the Parent Milnacipran, *d*-isomer, and *l*-isomer on Days 7, 8, and 9 (Study # MLN-PK-01).

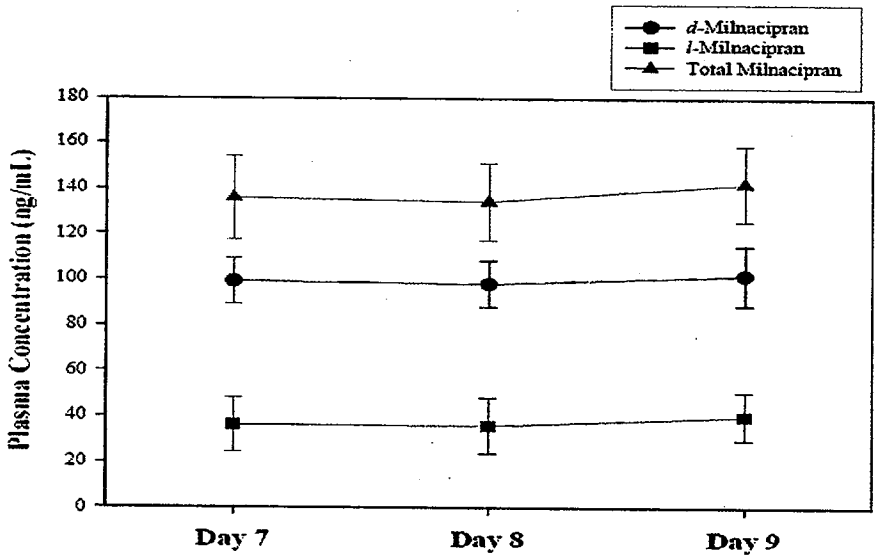


Table 2.2.3.1.2. Mean Steady State PK Parameters of the Parent Milnacipran, *d*-isomer, and *l*-isomer on Following 100 mg BID Dose (Study # MLN-PK-01).

Pharmacokinetic Parameter[a]	*d-Milnacipran (N = 6)*	*l-Milnacipran (N = 6)*	*d, l-Milnacipran (N = 6)*
C_{max} (ng/mL)	325.0 ± 52.8	213.7 ± 60.8	538.6 ± 108.1
T_{max} (h)	2.75 ± 0.42	2.67 ± 0.41	2.67 ± 0.41
$AUC_{0-\tau}$ (ng•h/mL)	2175 ± 236	1150 ± 280	3325 ± 437
C_{tr} (ng/mL)	181.2 ± 19.7	95.8 ± 23.4	277.1 ± 36.4
C_{min} (ng/mL)	85.8 ± 4.3	29.7 ± 9.5	115.1 ± 8.2
Fluctuation (%)	130.8 ± 20.1	191.1 ± 30.8	151.0 ± 23.1
Swing (%)	2.81 ± 0.74	6.56 ± 2.24	3.68 ± 0.98
$T_{½}$ (h)	8.38 ± 0.91	5.08 ± 0.75	7.35 ± 0.80

a C_{max}, C_{min} and $AUC_{0-\tau}$ parameters reflect freebase values

It should be noted that in this study the additional arms of 200 mg BID dosing were discontinued due to the elevation in blood pressure, heart rate or development of tachycardia is some subject. Due to the high rate of drop out as a result of increase in blood pressure the maximum tolerated dose (MTD) could not be defined for milnacipran.

2.2.3.2 Does this Drug Prolong the QT or QTc Interval?

The sponsor conducted a thorough QT (TQT) study to investigate the effect of milnacipran on the QTc (Study MLN-PK-10). The study was double-blind, placebo, and active controlled at escalating doses ranging from 12.5 mg to 300 mg given BID for up to 38 days. The active control was 400 mg moxifloxacin and it 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.

The study design and analysis are discussed in detail in QT-IRT review (see review dated 6/18/08). Briefly, the study design consisted of two main parts:

- **Part A**: Was conducted in 15 subjects at escalating doses from 12.5 mg to 300 mg BID X 36 days (active and placebo) to assess the safety and tolerability of minacipran at doses up to 300 mg BID.
- **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) to determine if highest dose determined to be safe and tolerable from Part A had any effect on cardiac repolarization.
- **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.

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 ΔΔQTcNi is -5 (-9.4, -0.08) ms. If, however, the same analysis is performed using QTcF, the mean increase in ΔΔQTcF 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).

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of milnacipran and its metabolites? How do the PK parameters change with time following chronic dosing?

Study # M037 shows the PK after a single 50 mg dose and repeat dose administration of 50 mg BID for 15 days in parallel group of healthy subjects (**Table 2.2.4.1.1**). The steady-state was achieved by Day 3. On Day 15, the AUC and Cmax was 1.2 and 1.7 fold higher than on Day 1. The half life did not change from Day 1 to Day 15.

Table 2.2.4.1.1. Summary of PK Data (Study # M037)

Pharmacokinetic Parameter[a]	*Single Dose of 50 mg Milnacipran HCl (N = 9)*	*50 mg BID Milnacipran HCl (N = 9)*
C_{max} (ng/mL)	140.9 ± 31.3	245.3 ± 60.0
T_{max} (h)	2.8 ± 0.3	1.6 ± 0.3
AUC_{0-t} (ng•h/mL)	1207 ± 243	–
$AUC_{0-\infty}$ (ng•h/mL)[b]	1277 ± 264	1565 ± 376
$T_{½}$ (h)	6.3 ± 1.2	7.5 ± 1.2
CL/F (L/h)	35.4 ± 7.8	–
CL_r (L/h)	20.8 ± 1.6	–
V_d/F (L)	318 ± 66	–

a C_{max} and AUC parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

b AUC_{0-t} for 50 mg BID milnacipran HCl

Dose proportionality was established after a single dose in various studies (See next section). In study #M040 the exposure (Cmax and AUC) were dose proportional up to 200 mg (**Figure 2.2.4.1.1 and Table 2.2.4.1.2**).

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Figure 2.2.4.1.1 Dose-Proportionality for Milnacipran in Healthy Subjects (Study # M040)

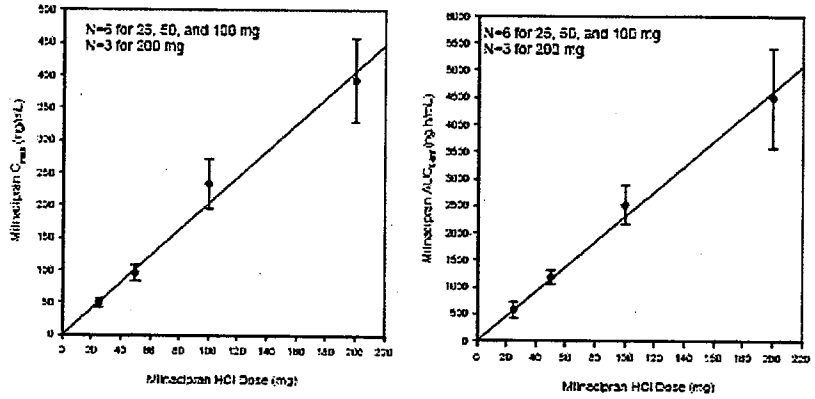

Figure 2.2.4.1.1 Mean PK Parameters After Single Dose of Milnacipran in Healthy Subjects (Study # M040)

Pharmacokinetic Parameter[a]	*25 mg (N = 6)*	*50 mg (N = 6)*	*100 mg (N = 6)*	*200 mg (N = 6)*	*200 mg No Vomiting (N = 3)*
C_{max} (ng/mL)	49.8 ± 7.5	95.3 ± 12.8	234 ± 38.8	328.1 ± 84.8	393.1 ± 65.1
T_{max} (h)	2.6 ± 1.0	3.8 ± 1.5	4.2 ± 0.5	3.1 ± 2.0	5.0 ± 0.0
AUC_{0-t} (ng•h/mL)	489 ± 102	1063 ± 149	2389 ± 387	3214 ± 1461	4392 ± 848
$AUC_{0-\infty}$ (ng•h/mL)	579 ± 145	1181 ± 127	2516 ± 362	3293 ± 1512	4502 ± 917
$T_{½}$ (h)	10.5 ± 3.9	8.9 ± 2.7	10.2 ± 3.9	7.2 ± 2.7	8.2 ± 2.9
CL/F (L/h)	39.9 ± 11.0	37.2 ± 4.4	34.9 ± 5.4	66.0 ± 38.0	39.9 ± 9.2
CL_r (L/h)	19.7 ± 16.9	15.2 ± 5.9	18.5 ± 7.1	20.5 ± 10.3	18.7 ± 8.0
V_d/F (L)	567 ± 142	464 ± 103	509 ± 174	615 ± 225	455 ± 120
fe (%)	46 ± 29	41 ± 15	54 ± 20	40 ± 27	51 ± 28

a C_{max} and AUC parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

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2.2.4.2 Is the PK of milnacipran dose-proportional?

The sponsor conducted several studies to determine the dose proportionality of milnacipran following a single and multiple doses (Studies #M036, M040, M120, M146). Based on across studies analysis, the Cmax and AUC increase with increase in dose (**Table 2.2.4.1.1**).

Table 2.2.4.1.1. Cross Studies Dose Proportionality Analysis

Study No.	*Duration (days)*	*Dose (mg), BID*	C_{max} *(ng/mL)*[a]	$AUC_{0-\tau}$ *(ng•h/mL)*[a]
M146	3	25 mg	93 ± 12	609 ± 85
		50 mg	192 ± 38	1292 ± 225
		100 mg	396 ± 64	2613 ± 515
M037	15	50 mg	245 ± 60	1565 ± 376
MLN-PK-01	9	100 mg	539 ± 108	3325 ± 437
MLN-PK-10	37	300 mg	1815 ± 488	11544 ± 3105

a Based on milnacipran freebase values

Specifically study # M146 shows dose proportional increase in exposure for milnacipran and its enantiomers (*d* and *l*) after a single and multiple doses up a total dose of 200 mg/day in 16 healthy subjects (**Figures 2.2.4.1.1 and 2.2.4.1.2**).

Figure 2.2.4.1.1. Dose-Proportionality for Milnacipran and its Enantiomers Following Single Doses-Day 1 (Study # M146).

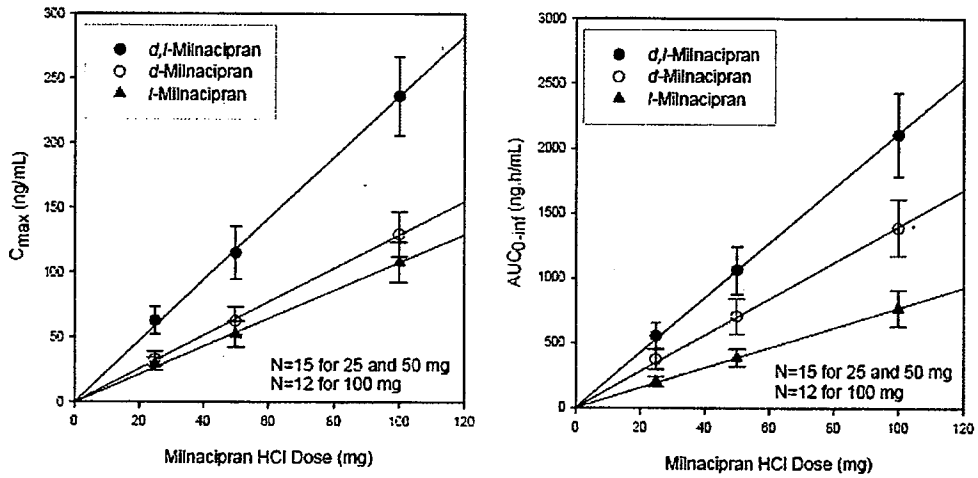
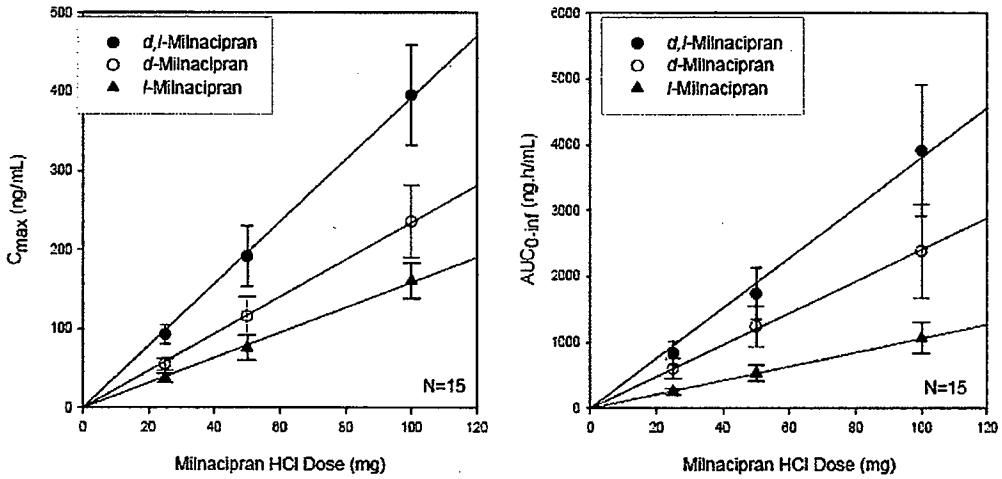


Figure 2.2.4.1.2. Dose-Proportionality for Milnacipran and its Enantiomers Following Multiple Doses (BID X 3 Days) (Study # M146).



From these studies in can be concluded that the exposure is proportional with dose up to 200 mg or 300 mg with respect to both the Cmax and AUC.

2.2.4.3 What is the Extent of Systemic Exposure After Milnacipran Administration?

- The absolute bioavailability of milnacipran capsule was determined in 12 healthy subjects after a single 50 mg dose administered as 2 x 25 mg capsule (**Study # M038**). The absolute bioavailability of milnacipran from the capsule was approximately 85% (**Figure 2.2.4.3.1 and Table 2.2.4.3.1**). The Tmax occurred at approximately 2 hours. The elimination half-life was approximately 6 hours following oral and IV administration. There was no difference in cumulative urinary excretion profiles between oral and IV administration (**Figure 2.2.4.3.2**)

Figure 2.2.4.3.1. Mean Plasma Concentration-Time Profile After 50 mg Oral and IV Doses of Milnacipran (Study # M038).

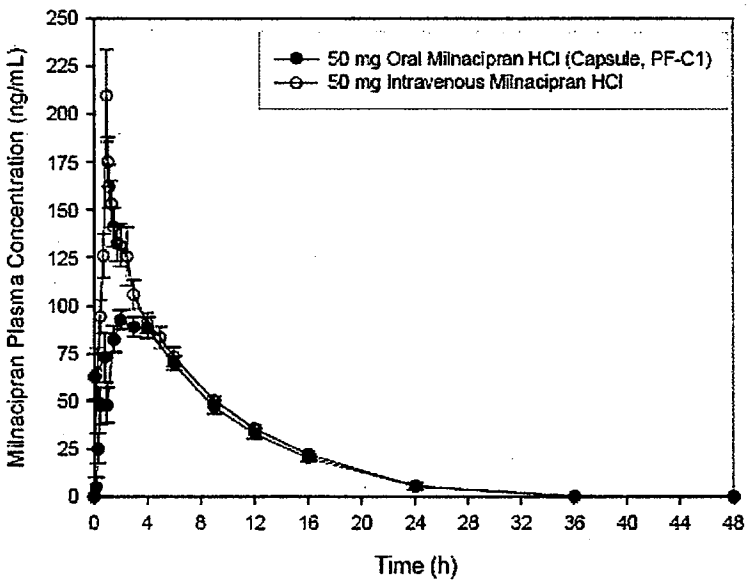


Table 2.3.4.3.1. Mean PK Parameters in Following 50 mg Oral and IV administration of Milnacipran (Study # M038).

Pharmacokinetic Parameter[a]	*50 mg Oral Milnacipran HCl (N=12)*	*50 mg Intravenous Milnacipran HCl (N=12)*
C_{max} (ng/mL)	97.4 ± 18.1	-
T_{max} (h)[b]	2 (0.7 - 6)	-
$AUC_{0-\infty}$ (ng•h/mL)	926 ± 133	1107 ± 172
F	0.85 ± 0.03	-
$T_{½}$ (h)	6.1 ± 1.4	6.4 ± 1.7
Ae_{0-t} (mg)	-	25.3 ± 4.4
CL (L/h)	-	40.2 ± 6.2

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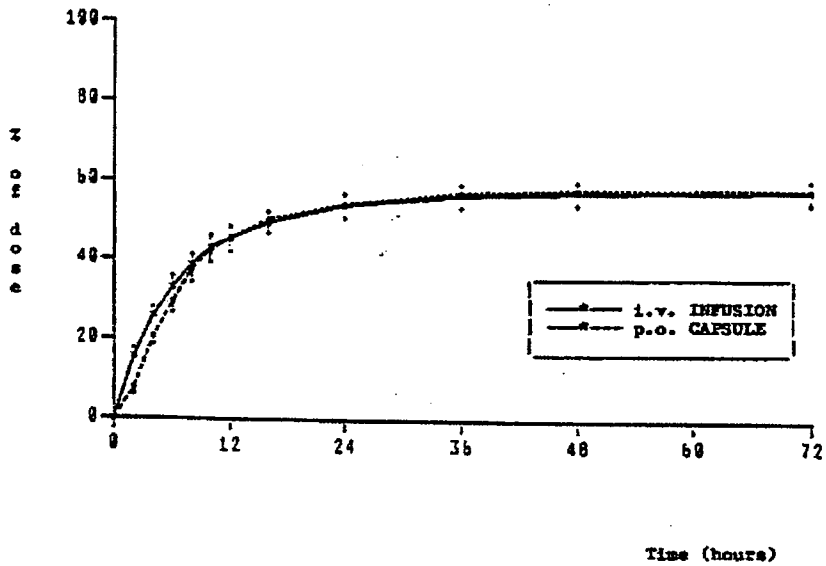
Figure 2.2.4.3.2. Mean (± SEM) Urinary Elimination of Unchanged Milnacipran Following 50 mg Oral and IV administration (Study # M038, Source Study Report Page 65).



2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 Effect of Age:

It appears that the exposure in elderly is somewhat greater than in young adults (Studies M042, M037, M116, and M043).

Across study comparison shows that the C_{max} and AUC were about 35% to 60% greater in elderly subjects (Study # M042) compared with young adults (Study M037). The same trend was observed at steady-state in a more formal study (#M116). In elderly, the exposure (C_{max} and AUC) for the parent drug was greater by 27% to 39% compared to young adults (**Figure 2.3.1.1.1 and Table 2.3.1.1.1**).

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Figure 2.3.1.1.1 Mean Plasma Concentration-time Profiles of *d*- and *l*- Milnacipran Isomers in Young and Elderly Subjects (Study # M116).

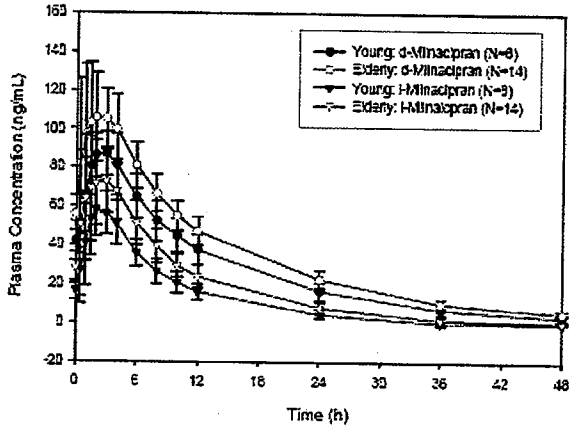

Table 2.3.1.1.1 Mean PK Parameters of *d*- and *l* - Milnacipran Isomers in Young and Elderly Subjects at Steady-State (Study # M116).

	d-Milnacipran		*l-Milnacipran*	
Pharmacokinetic Parameter[a]	*Young Subjects (N = 8)*	*Elderly Subjects (N = 14)*	*Young Subjects (N = 8)*	*Elderly Subjects (N = 14)*
C_{max} (ng/mL)	92.7 ± 12.3	121.5 ± 27.8	62.7 ± 12.3	86.3 ± 24.4
T_{max} (h)	2.4 ± 0.8	2.3 ± 1.3	2.0 ± 0.9	2.2 ± 1.3
AUC_{0-t} (ng•h/mL)	756 ± 101	961 ± 152	433 ± 91	602 ± 140
$T_{½}$ (h)	9.9 ± 1.3	11.1 ± 1.0	6.3 ± 0.8	7.3 ± 1.2
Ae_{0-12}	10.9 ± 0.5	10.3 ± 2.0	9.4 ± 2.6	9.4 ± 2.5
CL/F (L/h)	29.2 ± 3.7	23.2 ± 3.7	52.7 ± 13.4	37.7 ± 7.7

The observed increase in exposure in elderly is associated with age-related decrease in renal function (**Figures 2.3.1.2 A and B**).

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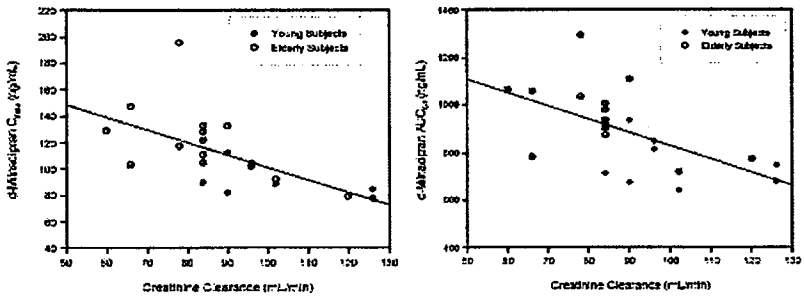
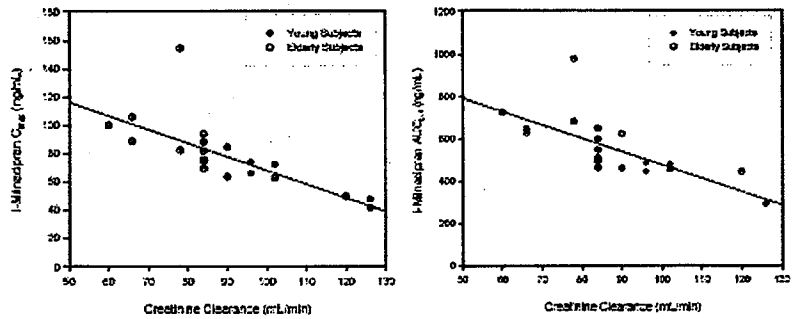
Figure 2.3.1.2. Exposure and Creatinine Clearance for *d*-and *l* -Isomers (Study # M116)

A: *l*-Isomer



B: *d*-Isomer



Based on this data, dose adjustment for milnacipran may be necessary in elderly patients with compromised renal function. However, in the clinical studies the overall safety profile in elderly seems to be similar to otherwise young adults. Since, the renal function decreases with age, milnacipran should be used with caution in the elderly.

2.3.1.2 Effect of Gender:

Across studies and within studies, the exposure (Cmax and AUC) for milnacipran and its *d*-and *l*-isomers in females is slightly higher (12% to 27%) than in males (Studies # M042 and M116, **Figure 2.3.1.2.1 and Table 2.3.1.2.1 and 2.3.1.2.2).**

Figure 2.3.1.2.1. Exposure in Elderly Females and Males (Study # M42)

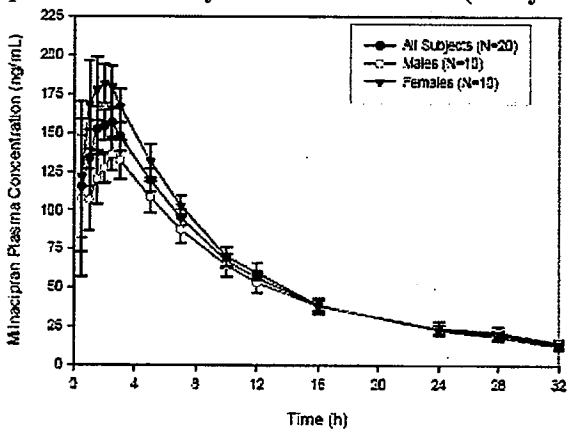


Table 2.3.1.2.1. Mean PK Parameters in Elderly Males and females (Study # M042)

Pharmacokinetic Parameter[a]	*Male Subjects (N = 10)*	*Female Subjects (N = 10)*	*All Subjects (N = 20)*
C_{max} (ng/mL)	171.7 ± 44.6	210.2 ± 45.7	191.0 ± 45.9
T_{max} (h)	2.0 ± 1.6	1.6 ± 0.9	1.8 ± 1.3
AUC_{0-t} (ng•h/mL)	1941 ± 549	1877 ± 420	1782 ± 486
$AUC_{0-\infty}$ (ng•h/mL)	1996 ± 825	2067 ± 496	2032 ± 663
$T_{½}$ (h)	12.1 ± 3.5	9.8 ± 2.5	11.0 ± 3.1
CL/F (L/h)	24.4 ± 7.6	22.2 ± 5.4	23.3 ± 6.7
V_d/F (L)	397.9 ± 83.5	306.9 ± 77.2	352.4 ± 91.2

a C_{max} and AUC parameters reflect freebase values (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; $T_{½}$ = terminal elimination half-life; CL/F = apparent plasma clearance after oral administration; V_d/F = apparent volume of distribution after oral administration.

Table 2.3.1.2.2. Mean PK Parameters in Young and Elderly Males and Females (Study # M116)

Pharmacokinetic Parameter[a]	*Young*		*Elderly*	
	Male Subjects (N = 4)	*Female Subjects (N = 4)*	*Male Subjects (N = 7)*	*Female Subjects (N = 7)*
	***d*-Milnacipran**			
C_{max} (ng/mL)	90.8 ± 15.1	94.5 ± 10.6	109.4 ± 19.1	133.4 ± 31.4
T_{max} (h)	2.6 ± 1.1	2.2 ± 0.6	1.7 ± 1.2	2.8 ± 1.4
AUC_{0-t} (ng•h/mL)	750 ± 131	762 ± 81	890 ± 114	1031 ± 158
$T_{½}$ (h)	10.4 ± 1.2	9.5 ± 1.3	11.5 ± 0.6	10.7 ± 1.1
CL/F (L/h)	29.6 ± 4.7	28.8 ± 3.1	24.8 ± 3.3	21.5 ± 3.4
CL_r (L/h)	14.8 ± 3.2	14.5 ± 1.8	11.7 ± 2.9	10.2 ± 2.0
	***l*-Milnacipran**			
C_{max} (ng/mL)	56.1 ± 14.1	69.4 ± 5.6	75.2 ± 15.1	97.6 ± 27.7
T_{max} (h)	2.2 ± 1.2	1.7 ± 0.3	1.7 ± 1.2	2.7 ± 1.4
AUC_{0-t} (ng•h/mL)	381 ± 101	485 ± 43	540 ± 99	664 ± 154
$T_{½}$ (h)	6.2 ± 0.7	6.5 ± 1.0	7.1 ± 0.9	7.5 ± 1.5
CL/F (L/h)	60.2 ± 15.9	45.1 ± 3.9	41.4 ± 7.2	34.0 ± 6.6
CL_r (L/h)	21.8 ± 3.9	21.7 ± 3.4	16.3 ± 4.4	14.3 ± 2.8

a C_{max} and AUC parameters reflect freebase values (conversion factor of 0.246 from nmol/L of HCl salt to ng/mL of 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 over the dosing interval at steady state; $T_{½}$ = terminal elimination half-life; CL/F = apparent total clearance of drug from plasma after oral administration; CL_r = renal clearance.

From this data, it appears that dose adjustment based on gender is not necessary.

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2.3.1.3 Effect of Renal Impairment

The effect of renal impairment on milnacipran PK was investigated in two studies: MLN-PK-02 and M045/M117. The first study (#MLN-PK-02) was conducted after a single 50 mg dose in patients with mild (n-8), moderate (n=8), and severe (n=5) renal impairment with matched healthy subjects (n=8). There was substantial increase in Cmax (~60%) and AUC (~200%) and half life (~120%) in patients with severe renal function compared to healthy subjects (**Tables 2.3.1.3.1 and 2.3.1.3.1 and Figure 2.3.1.3.1**). Corresponding with the plasma data, a reverse trend was seen in urinary excretion profiles (**Figure 2.3.1.3.2**).

Table 2.3.1.3.1. Mean Percent Change in PK Parameters in Patients with Renal Impairment Compared to Healthy Subjects (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.

Table 2.3.1.3.2. Mean PK Parameters in Patients with Renal Impairment Compared to Healthy Subjects (Study # MLN-PK-02).

Pharmacokinetic Parameter[a]	*Healthy Subjects (N = 7)*	*Subjects With Mild Renal Impairment (N = 8)*	*Subjects With Moderate Renal Impairment (N = 7)*	*Subjects With Severe Renal Impairment (N = 3)*
CrCL (mL/min)	98.4 ± 9.7	57.1 ± 6.0	44.7 ± 3.9	19.7 ± 8.5
C_{max} (ng/mL)	154.8 ± 29.0	173.8 ± 35.7	195.6 ± 87.3	246.4 ± 63.7
T_{max} (h)	3.8 ± 0.6	2.4 ± 0.9	4.2 ± 1.9	4.7 ± 2.3
AUC_{0-t} (ng•h/mL)	1543 ± 372	1787 ± 412	2374 ± 1060	4734 ± 1552
$AUC_{0-\infty}$ (ng•h/mL)	1646 ± 359	1912 ± 432	2501 ± 1054	4915 ± 1553
$T_{\frac{1}{2}}$ (h)	7.9 ± 1.7	10.9 ± 4.5	11.1 ± 3.5	17.5 ±3.2
CL_r (L/h)	15.0 ± 3.0	8.8 ± 2.3	7.1 ± 3.0	1.9 ± 0.9[b]
CL/F (L/h)	27.5 ± 5.8	23.6 ± 4.3	19.8 ± 7.2	9.5 ± 2.9
fe (%)	44.8 ± 5.9	30.8 ± 6.93	30.3 ± 12.0	18.7 ± 4.7[b]

a C_{max} and AUC parameters reflect freebase values

b N = 2.

CrCL = creatinine clearance; 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; CL_r = renal clearance; CL/F = apparent plasma clearance after oral administration; fe = fraction of dose excreted as unchanged drug in urine.

Table 2.3.1.3.1. Mean Plasma Concentration 24 hours Time Profiles of Milnacipran in Patients with Renal Impairment and Healthy Subjects (Study # MLN-PK-02).

B

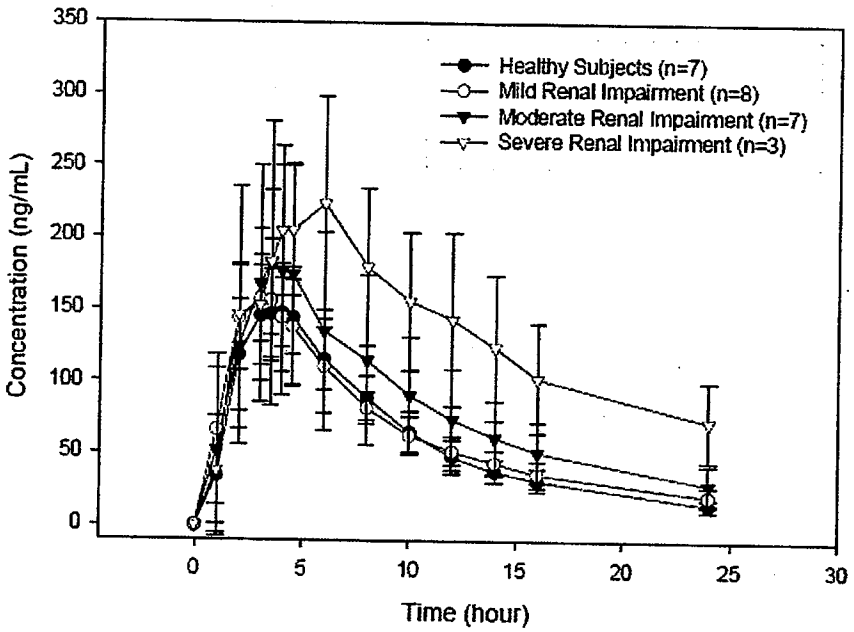
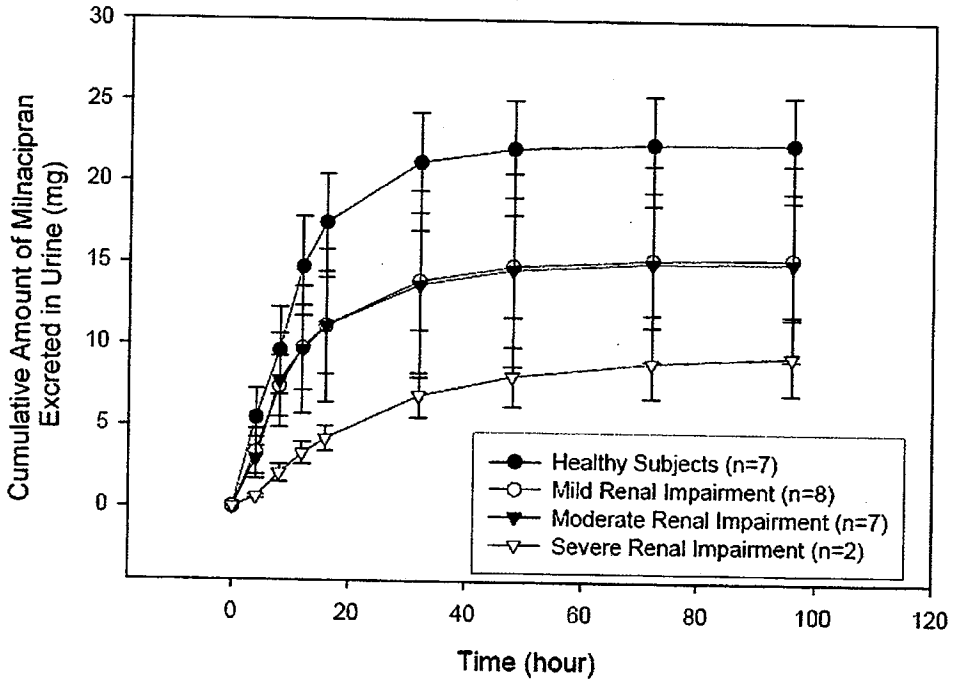


Figure 2.3.1.3.2. Cumulative Urinary excretion of Milnacipran (Study # MLN-PK-02).



In the second study (#M045/M117), the same single dose of 50 mg was administered to 7 healthy subjects and 7 patients with renal impairment (1 with mild, 1 with moderate, and 5 with severe renal impairment). The same trend of increase in exposure was also observed in this study but to a lesser extent for Cmax (21%) and AUC (110%) compared to healthy subjects (**Table 2.3.1.3.3 and 2.3.1.3.4**).

Table 2.3.1.3.3. Mean PK Parameters in Patients with Renal Impairment Compared to Healthy Subjects (Study # MO45-M117).

Pharmacokinetic Parameter[a]	*Healthy Subjects (N = 7)*	*Subjects With Severe Renal Impairment (N = 5)*
CrCL (mL/min)	116.5 ± 23.3	17.7 ± 7.8
C_{max} (ng/mL)	133.6 ± 26.3	161.3 ± 69.9
T_{max} (h)	1.9 ± 1.0	2.0 ± 1.9
AUC_{0-t} (ng•h/mL)	1110 ± 367	2568 ± 1265
$AUC_{0-\infty}$ (ng•h/mL)	1408 ± 649	2959 ± 1277
$T_{½}$ (h)	10.6 ± 6.5	15.3 ± 6.5
CLr (L/h)	17.7 ± 7.6	2.1 ± 0.7
CL/F	35.4 ± 11.9	16.7 ± 6.1
V_d/F	456 ± 84	357 ± 177
fe (%)	49 ± 8	13 ± 7

a C_{max} and AUC parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).
CrCL = creatinine clearance; 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; $T_{½}$ = terminal elimination half-life; CL_r = renal clearance; apparent total clearance of drug from plasma after oral administration ; V_d/F = apparent volume of distribution after oral administration; fe = fraction of dose excreted as unchanged drug in urine.

Table 2.3.1.3.4. Mean PK Parameters in Patients with Severe Renal Impairment Compared to Healthy Subjects (Study # MO45-M117).

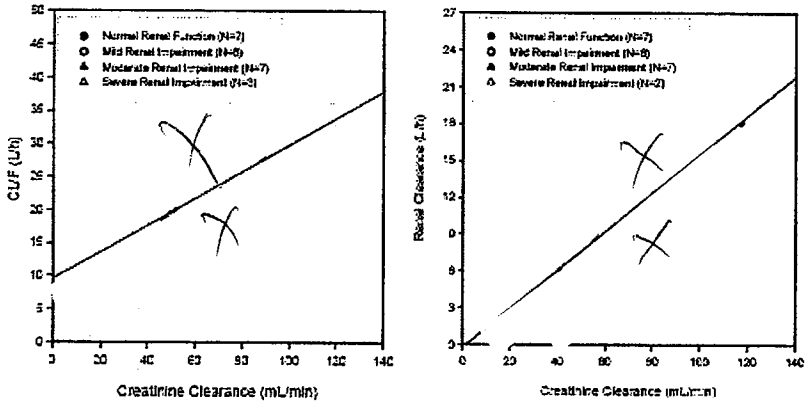
	Healthy Subjects (N = 3)			*Subjects With Severe Renal Impairment (N = 5)*		
Pharmacokinetic Parameter[a]	*d,l-Milnacipran*	*d-Milnacipran*	*l-Milnacipran*	*d,l-Milnacipran*	*d-Milnacipran*	*l-Milnacipran*
CrCL (mL/min)	128.0 ± 17.7			17.7 ± 7.8		
C_{max} (ng/mL)	97.3 ± 0.7	53.4 ± 3.1	46.0 ± 3.1	162.3 ± 82.2	80.5 ± 40.7	82.3 ± 41.8
T_{max} (h)	1.9 ± 1.1	5.0 ± 4.4	1.3 ± 0.9	1.6 ± 1.1	1.6 ± 1.1	1.6 ± 1.1
$AUC_{0-\infty}$ (ng•h/mL)	1168 ± 205	787 ± 67	407 ± 122	3070 ± 1823	1775 ± 866	1324 ± 974
$T_{½}$ (h)	7.7 ± 1.7	9.5 ± 0.6	6.2 ± 2.4	15.9 ± 4.3	19.5 ± 4.4	13.9 ± 5.7
CL/F	38.0 ± 6.1	27.8 ± 2.4	56.4 ± 14.8	18.3 ± 8.7	14.3 ± 5.7	25.1 ± 15.0

a C_{max} and AUC and parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).
CrCL = creatinine clearance; C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; $AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{½}$ = terminal elimination half-life; CL/F = apparent plasma clearance after oral administration.

From these two studies, it can be stated that renal function plays a major role in the excretion of milnacipran. It should be noted that milnacipran renal clearance and apparent (oral) clearance (CL/F) increase linearly with increase creatinine clearance (**Figure**

2.3.1.2.3). Therefore, a dose reduction is recommended in patients with severe renal impairment and caution should be exercised in patients with moderate impairment.

Figure 2.3.1.3.3. Relationship Between Milnacipran Plasma and Renal Clearance (Study # MLN-PK-02).



b(4)

2.3.1.4 Effect of Liver Function (Hepatic Impairment)

The effect of hepatic impairment on milnacipran PK was investigated in two studies (MLN-PK-11 and M046). Both studies were conducted after a single 50-mg dose. In the first study (#Study MLN-PK-11) 8 patients with mild (Child-Pugh A), 8 patients with moderate (Child-Pugh B), and 5 patients with severe (Child-Pugh C) hepatic impairment were enrolled. In addition, 8 healthy subjects were enrolled as comparative control.

The Cmax was lower by approximately 16% in subjects with hepatic impairment compared with healthy subjects (**Table 2.3.1.4.1 and Figure 2.3.1.4.1**). In severe hepatic impairment patients the AUC was approximately 30% higher than that of healthy subjects. It should be noted that the reverse trend was observed in the urinary excretion data, in which the amount excreted in urine in patients with severe hepatic impairment was higher than that in healthy subjects (**Figure 2.3.1.4.2**). However, in mild hepatic impairment, the AUC was slightly higher and in moderate hepatic impairment subjects, the AUC was slightly lower. Overall, in this study only the severe hepatic impairment group showed an effect with a 30% higher AUC compared to healthy subjects.

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Table 2.3.1.4.1. Mean PK Parameters of Milnacipran in Healthy Subjects and Patients With Hepatic Impairment (Study # MLN-PK-11).

		Hepatic Impairment Group		
Pharmacokinetic Parameter	*Healthy Subjects (N = 7)*	*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)	1488 ± 467	1528 ± 729	1280 ± 621	1955 ± 573
$AUC_{0-\infty}$ (ng·h/mL)	1591 ± 455	1635 ± 762	1403 ± 655	2062 ± 588
$T_{½}$ (h)	8.0 ± 1.4	8.7 ± 1.7	8.4 ± 2.1	12.4 ± 1.1
Ae_{0-t} (mg)	19.02 ± 5.55	24.65 ± 6.59	19.1 ± 8.3	26.05 ± 5.33[b]
CL_r (L/h)	13.6 ± 5.7	17.9 ± 7.6	13.4 ± 5.3	14.7 ± 0.5[b]
fe (% dose)	43.7 ± 12.7	56.7 ± 15.1	44.0 ± 19.1	59.9 ± 12.2[b]

a C_{max} and AUC and parameters reflect freebase values

b N = 3; one subject was excluded because the subject had an unusually high value in Ae_{0-t} (ie, greater than 100% of administered dose).

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; $T_{½}$ = terminal elimination half-life; Ae_{0-t} = amount of drug excreted unchanged in urine from time 0 to t; CL_r = renal clearance; fe = fraction of dose excreted as unchanged drug in urine.

Figure 2.3.1.4.1. Mean Plasma Concentration 24 Hour Time Profiles of Milnacipran in Healthy Subjects and Patients With Hepatic Impairment (Study # MLN-PK-11).

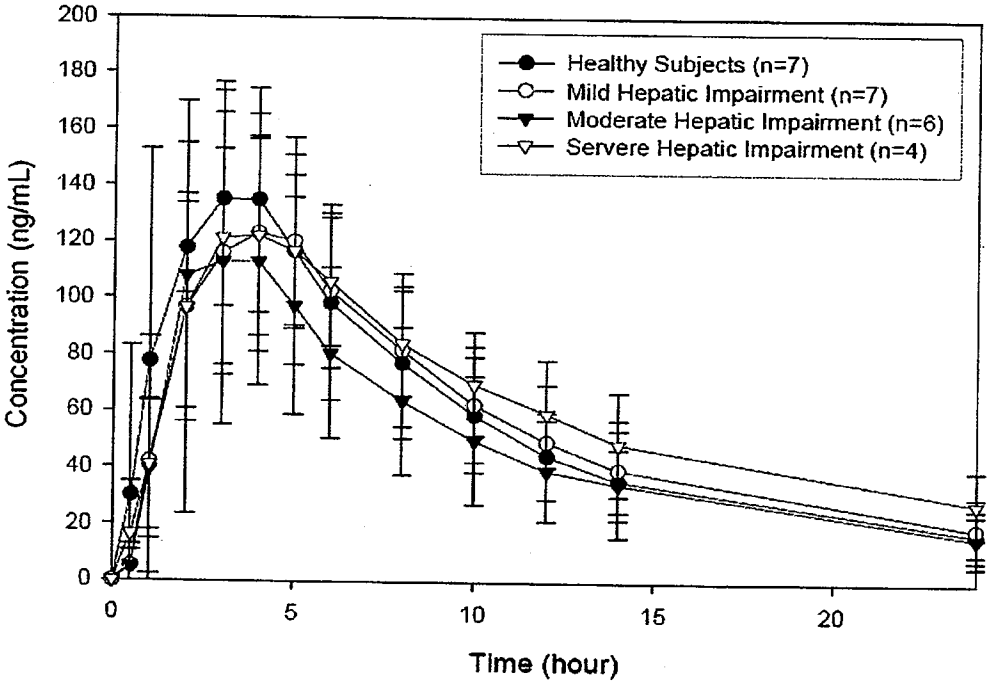
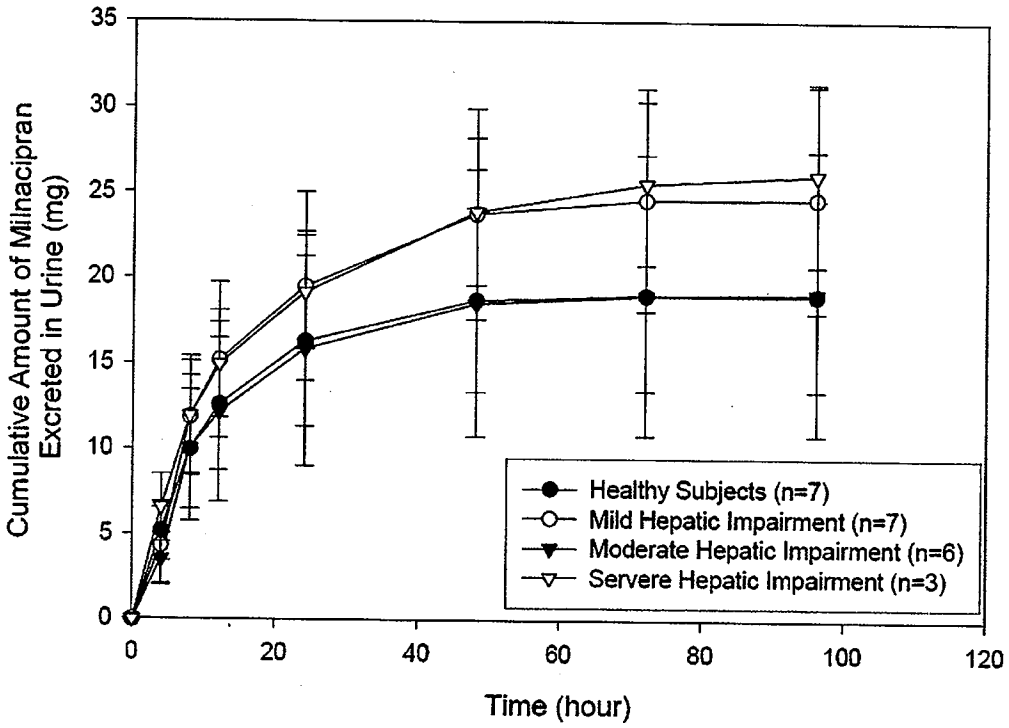


Figure 2.3.1.4.2. Cumulative Urinary excretion of Milnacipran (Study # MLN-PK-11).



In the second study (# M046) a single 50-mg IV dose and a single 50-mg oral dose of milnacipran were administered in a crossover manner with a washout period of 3 days. In this study 17 subjects were enrolled: 6 healthy, 1 mild (Group A), 6 moderate (Group B) and 4 severe (group C).

Following IV administration the AUC increased by approximately 13% and 30 % in moderate and severe hepatic impairment, respectively compared to healthy subjects. Similarly, following oral administration the AUC increased by approximately 46 and 60% in moderate and severe patients compared to control, respectively (**Table 2.3.1.4.2**). The Cmax after oral administration was slightly increased by 23% and 17% in moderate and severe patients, respectively, relative to healthy subjects.

The clearance decreased by 7% and 20% after IV and 17% and 35% after oral in moderate and severe groups, respectively, relative to control. It should be noted that the absolute bioavailability in this study was approximately 90% in healthy subjects and 110% in patients with hepatic impairment (**Table 2.3.1.4.2**).

Table 2.3.1.4.2. Mean PK Parameters of Milnacipran in Healthy Subjects and Patients With Hepatic Impairment (Study # M046).

Pharmacokinetic Parameter	*Control Subjects (N = 6)*	*Group B (N = 6)*	*Group C (N = 4)*
Intravenous Dose			
$AUC_{0-\infty}$ (ng·h/mL)	1324 ± 322	1496 ± 517	1732 ± 581
$T_{½}$ (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 Dose			
C_{max} (ng/mL)	117 ± 14	144 ± 55	137 ± 56
T_{max} (h)	2.2 ± 0.8	2.3 ± 1.2	3.8 ± 2.9
$AUC_{0-\infty}$ (ng·h/mL)	1189 ± 257	1733 ± 1202	1908 ± 547
$T_{½}$ (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 C_{max} and AUC parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

b N = 5; [c]N = 4; [d]N = 3

$AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{½}$ = 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.

Overall, the data from both studies indicates that in moderate and severe hepatic impairment, AUC increased by about 46% and 60% respectively. Caution should be exercised when administering milnacipran in patients with moderate and severe hepatic impairment.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Based on the data and discussion presented in the previous sections, milnacipran does not appear to be metabolized via any of the major CYP isozymes: CYP2C19, CYP2D6, CYP2C19, CYP1A2, and CYP3A4. Therefore, the potential interaction of milnacipran with drugs that may inhibit any of these major isozymes is minimal.

Therefore, most of the drug interaction studies conducted by the sponsor where part of the anti-depression program that the drug initially was developed for. Since most of these

studies are indirectly relevant to this indication and did not show clinically significant interaction they will be summarized briefly below. Only those with significant interaction (if any) will be discussed in more detail. In addition, some of the selected drugs are not marketed in the US. The drugs tested by the sponsor are: levomepromazine, carbamazepine, digoxin, warfarin, lithium, lorazepam, alcohol, fluoxetine or clomipramine.

Levomepromazine:

Levomepromazine is not marketed in the US. According to the sponsor, the drug is tested as CYP2D6 inhibitor. This was a crossover study at a dose of 50 mg milnacipran BID for 14 days given alone or in combination with 15 mg BID of levomepromazine. At steady state, the Cmax and AUC for milnacipran increased by only 10% to 20% when co-administered with levomepromazine compared when given alone (Study # M126). This data is expected based on the earlier discussion that CYP2D6 is not involved in the metabolism of milnacipran.

Carbamazepine:

Since carbamazepine is know as CYP3A4 and CYP1A2 inducer, the study was conducted at steady state following 200 BID of carbamazepine and 50 mg BID of milnacipran. The exposure (Cmax and AUC) to milnacipran decreased by <20% (18 and 19%) compared when milnacipran was administration alone (Study # M130). The data from this study is also expected as milnacipran is not metabolized by either CYP3A4 or CYP1A2.

Digoxin:

Digoxin is primarily excreted as unchanged in urine. It is also know as intestinal and renal P-glycoprotein (P-GP) substrate. The sponsor conducted a study to investigate the coadministration of milnacipran in three-way crossover, multiple dose in 30 healthy subjects as follows:

Treatment A:

Day 1:	0.2 mg digoxin BID
Days 2-8:	0.2 mg digoxin QAM
Day 9:	0.2 mg digoxin at AM

Treatment B:

Day 1:	12.5 mg milnacipran QAM and 25 mg milnacipran QPM
Day 2:	25 mg milnacipran BID
Day 3-5:	50 mg milnacipran BID
Days 6-8:	100 mg milnacipran BID
Day 9:	100 mg milnacipran at AM

Treatment C:

Day 1:	12.5 mg milnacipran + 0.2 mg digoxin at AM
	25 mg milnacipran + 0.2 mg digoxin at PM
Day 2:	25 mg milnacipran BID + 0.2 mg digoxin at AM
Day 3-5:	50 mg milnacipran BID + 0.2 mg digoxin QAM
Days 6-8:	100 mg milnacipran BID + 0.2 mg digoxin QAM
Day 9:	100 mg milnacipran single dose + 0.2 mg digoxin single dose at AM

The PK parameters of either milnacipran or digoxin did not change in this interaction study (Study # MLN-PK-08). In addition, no pharmacodynamic effects such as changes in blood pressure were noted.

Warfarin:

Warfarin is highly metabolized drug by several CYP450 enzymes. The effect on the prothrombin time (PT) and PK was tested in healthy subjects at steady-state following 100 mg BID doses of milnacipran and a single mega dose of warfarin (25 mg). No significant changes in either the PK parameter of warfarin or milnacipran or the PT were observed (Study # MLN-PK-07).

Lithium:

Lithium is predominantly excreted unchanged in urine. Lithium was administered at a dose of 375 mg BID concomitantly with 50 mg BID doses of milnacipran. There were no changes in the PK of either lithium or milnacipran (Study # M125).

Lorazepam:

No PK interaction was observed following a single dose of 50 mg milnacipran and 1.5 mg lorazepam (Study # M138).

Fluoxetine:

Fluoxetine is inhibitor of CYP2D6 and CYP2C19. Therefore, the sponsor investigated the PK and tolerance of milnacipran by switching from 20 mg QD of fluoxetine to 50 mg BID milnacipran without a washout period. No changes were observed in the PK of milnacipran after a single dose on Day 1 or after multiple doses on Day 4 (Study # F2207 GE M212).

Clomipramine:

This is similar to fluoxetine study in which the sponsor investigating the PK of milnacipran by switching from clomipramine treatment to milnacipran without a washout period. No changes in the PK of milnacipran was noted in this study either (Study # F2207 GE M213).

Alcohol:

A double-blind, crossover, placebo controlled, and positive-controlled (amitriptyline) study in healthy male subjects was conducted after 0.6 g/L alcohol and 50 mg BID milnacipran. The PK and the PD (psychometric evaluations) of milnacipran was not affected in the presence of alcohol compared with placebo (Study # F2207 95 GE 103).

Conclusions:

The results from these studies are consistent with the primary excretion pathway of milnacipran (renal excretion of the unchanged drug and glucuronidation) and suggest a low potential of interaction between milnacipran and drugs that are substrates, inhibitors, or inducers of CYP450 enzymes.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class Classification for Milnacipran?

Milnacipran is classified as BCS class I drug substance (highly soluble and highly permeable). The supporting information were submitted and reviewed under IND # 63,736 (Study # PRD-RPT-EXP-00014). Based on this information, a bio-waiver request for the BE study for capsule (Phase I/III formulation) and tablets (the final to-be-marketed formulation) was granted by the Agency on December 12, 2006. The capsules and tablets exhibit similar *in vitro* dissolution profiles (detailed discussion later).

2.5.2.1 What is the Absolute Bioavailability of Milnacipran?

The absolute bioavailability of milnacipran capsule was determined in one formal study (Study # M038) and in another as part of the determination of the effect of hepatic impairment on the PK of milnacipran following oral and IV administration (Study #M046). The formal study was conducted in 12 healthy subjects following a single oral dose of 50 mg (2 x 25 mg) capsules (PF-C1) and IV infusion over 1 hour.

From this study the absolute bioavailability of milnacipran from the capsule was approximately 85% **(Figure 2.5.2.1.1 and Table 2.5.2.1.1)**. The Tmax occurred at approximately 2 hours. In addition, there was no difference in cumulative urinary excretion profiles between oral and IV administration **(Table 2.5.2.1.2 and 2.5.2.1.3 and Figure 2.5.2.1.2)**

Figure 2.5.2.1.1. Mean Plasma Concentration-Time Profile After 50 mg Oral and IV Doses of Milnacipran (Study # M038).

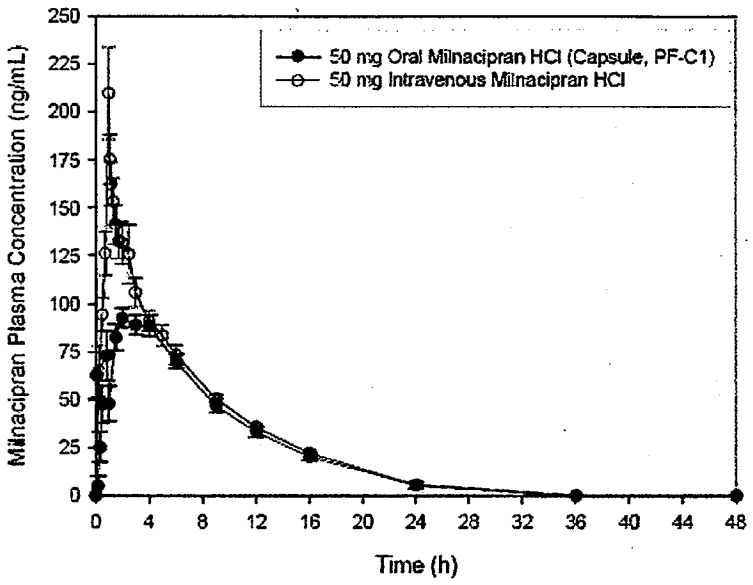


Table 2.5.2.1.1. Mean PK Parameters in Following 50 mg Oral and IV administration of Milnacipran (Study # M038).

Pharmacokinetic Parameter[a]	*50 mg Oral Milnacipran HCl (N=12)*	*50 mg Intravenous Milnacipran HCl (N=12)*
C_{max} (ng/mL)	97.4 ± 18.1	-
T_{max} (h)[b]	2 (0.7 - 6)	-
$AUC_{0-\infty}$ (ng•h/mL)	926 ± 133	1107 ± 172
F	0.85 ± 0.03	-
$T_{½}$ (h)	6.1 ± 1.4	6.4 ± 1.7
Ae_{0-t} (mg)	-	25.3 ± 4.4
CL (L/h)	-	40.2 ± 6.2

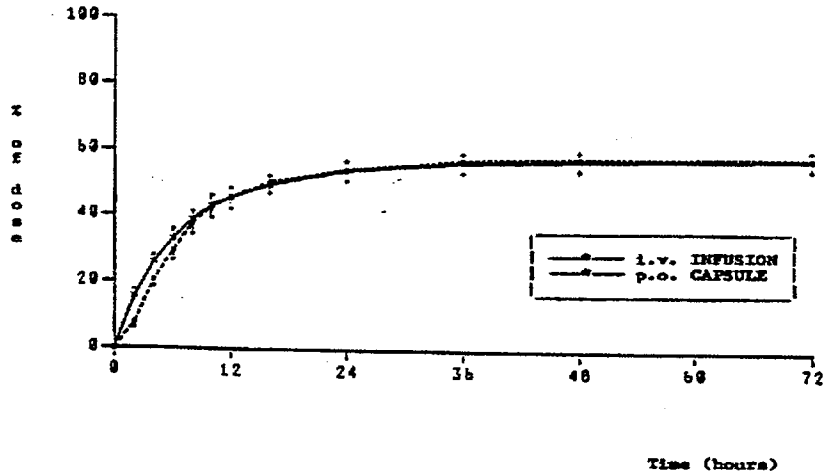
Table 2.5.2.1.2. Mean PK Parameters in Following 50 mg Oral and IV administration of Milnacipran (Study # M038).

Pharmacokinetic Parameter[a]	*50 mg Oral Milnacipran HCl (N=12)*	*50 mg Intravenous Milnacipran HCl (N=12)*
CLr (L/h)	-	23.7 ± 7.3
V_d (L)	-	367 ± 98

a C_{max}, AUC_∞ and Ae parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).
b Median (range).

Ae_{0-t} = amount of drug excreted unchanged in urine from time 0 to time t; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CL = apparent total clearance from plasma after intravenous administration; CLr = renal clearance; C_{max} = maximum plasma drug concentration; F = absolute bioavailability; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration; V_d = apparent volume of distribution.

Figure 2.5.2.1.2 Mean (± SEM) Urinary Elimination of Unchanged Milnacipran Following 50 mg Oral and IV administration (Study # M038, Source Study Report Page 65).



A similar conclusion was made from the hepatic impairment study in which the absolute bioavailability of milnacipran was 90% (**Table 2.5.2.1.3**).

Table 2.5.2.1.3. 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		
$AUC_{0-\infty}$ (ng·h/mL) (HCl salt)	1522 ± 370	1720 ± 595	1990 ± 668
$AUC_{0-\infty}$ (ng·h/mL) (freebase)[a]	1324 ± 322	1496 ± 517	1732 ± 581
$T_{½}$ (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 ± 11.3
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
$AUC_{0-\infty}$ (ng·h/mL) (HCl salt)	1367 ± 259	1992 ± 1382	2193 ± 628

Table 2.5.2.1.3 (continued).

$AUC_{0-\infty}$ (ng·h/mL) (freebase)[a]	1189 ± 257	1733 ± 1202	1908 ± 547
$T_{½}$ (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[c]
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

$AUC_{0-\infty}$ = area under the plasma concentration vs time curve from time 0 to infinity; $T_{½}$ = 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.

2.5.2 What is the Effect of Food on the BA of Milnacipran?

The sponsor conducted two studies to establish the effect of food on milnacipran (StudiesMLN-PK-04 and M124). In both studies, the effect of food was conducted using the capsule formulation; one used the clinical trial formulation (PF-C5, Study # MLN-PK-04) and the second using one of the prototype capsule formulations (PF-C3, M124). In both studies, food had no effect on the PK of milnacipran (**Figures 2.5.2.1 and 2.5.2.1 and Tables 2.5.2.1-2.5.2.3**).

Figure 2.5.2.1. Mean Plasma Concentration-Time Profile of Milnacipran in Fed and Fasted Conditions (Study # MLN-PK-04).

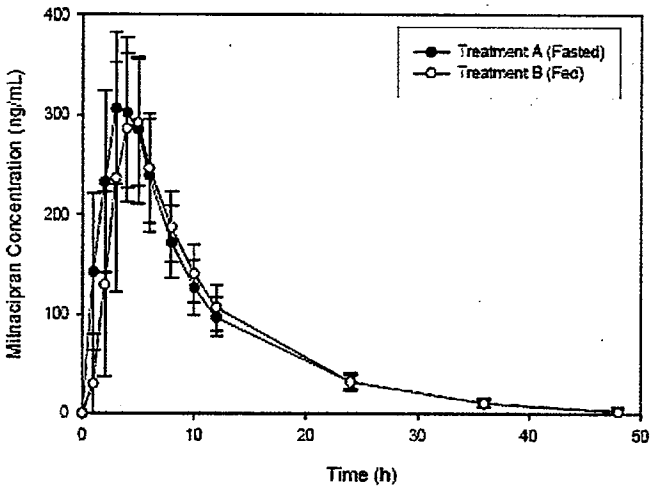


Figure 2.5.2.2. Mean Plasma Concentration-Time Profile of Milnacipran in Fed and Fasted Conditions After 50 mg Capsule (Study # M039/M124).

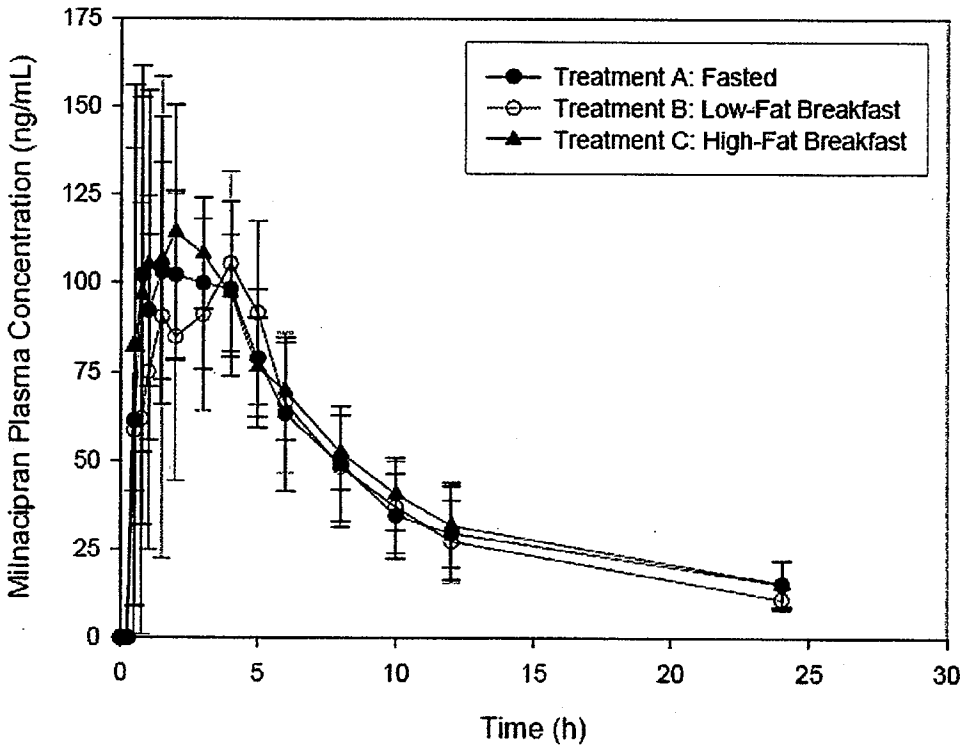


Table 2.5.2.1. Mean PK Parameters and 90% CI of Milnacipran in Fed and Fasted Conditions (Study # MLN-PK-04).

Pharmacokinetic Parameter	*Treatment A (fasting) (N=12)*	*Treatment B (fed) (N=12)*	*Ratio of Geometric Means (%)*	*90% CI*
C_{max} (ng/mL)[a]	332.8 ± 75.3	323.8 ± 64.3	98	91.3-104.2
T_{max} (h)	3.7 ± 1.0	4.2 ± 1.0	-	-
AUC_{0-t} (ng•h/mL)[a]	3403 ± 666	3231 ± 538	95	91.5-100.2
$AUC_{0-\infty}$ (ng•h/mL)[a]	3493 ± 682	3322 ± 544	96	91.8-100.3
$T_{½}$ (h)	7.6 ± 1.2	7.3 ± 1.1	-	-

a C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ parameters reflect freebase values

AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma drug concentration; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

Table 2.5.2.2. Mean PK Parameters and 90% CI of Milnacipran in Fed and Fasted Conditions Following Administration of 50 mg Capsule (Study # M039/M124).

Pharmacokinetic Parameter[a,b]	*Treatment A (fasting) n=8*[c]	*Treatment B (low-fat) n=11*[c]	*Treatment C (high-fat) n=12*[c]	*90% CIs*	
				B vs A	*C vs A*
C_{max} (ng/mL)	129.9 ± 40.3	135.2 ± 50.6	140.1 ± 43.6	88-118	93-125
T_{max} (h)	2.50 ± 1.43	2.98 ± 1.60	2.15 ± 1.08	-	-
AUC_{0-24} (ng•h/mL)	980 ± 249	911 ± 264	1040 ± 233	82-104	95-120

Table 2.5.2.3. Mean PK Parameters and 90% CI of Milnacipran in Fed and Fasted Conditions (Study # M039/M124).

Pharmacokinetic Parameter[a,b]	*Treatment A (fasting) n=8*[c]	*Treatment B (low-fat) n=11*[c]	*Treatment C (high-fat) n=12*[c]	*90% CIs*	
				B vs A	*C vs A*
$AUC_{0-\infty}$ (ng•h/mL)	1088 ± 318	981 ± 306	1149 ± 282	77-105	91-124
$T_{½}$ (h)	6.52 ± 2.29	5.43 ± 1.90	6.50 ± 1.94	-	-
Ae_{0-24} (mg)	24.39 ± 2.21	24.43 ± 3.91	24.47 ± 4.83	89-110	89-110
Clr (L/h)	26.3 ± 7.0	29.0 ± 10.5	24.4 ± 6.2	92-125	80-108

a C_{max}, AUC, and Ae_{0-24} parameters reflect milnacipran freebase values (conversion factor of 0.87 from HCl salt to freebase).

b Based on Report M124.

c Subjects who did not vomit.

Ae_{0-24} = amount of drug excreted unchanged in urine from time 0 to 24 hours; AUC_{0-24} = area under the plasma concentration versus time curve from time 0 to 24 hours; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; CLr = renal clearance; C_{max} = maximum plasma drug concentration; fe = fraction of dose excreted as unchanged drug in urine; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

2.5.3 Was the to-be-Marketed Formulation Used in the Clinical Trials?
Background:

The drug was originally developed as 25, 50, and 100 mg capsules (25 mg, 50 mg, and 100 mg). I

b(4)

The 50 mg dibasic calcium phosphate-based tablet formulation developed was found to be bioequivalent to the [ ] capsule formulation (PF-C4) in Study M048, **Figure 2.5.3.1 and Table 2.5.3.1**). However, Cmax (but not AUC) for half of the 100 mg scored tablet (i.e., 50 mg dose) of dibasic calcium phosphate–based formulation was approximately 17% higher than that of the [ ] capsule formulation PF-C3 (Study # 141, **Figure 2.5.3.1 and Table 2.5.3.2**).

b(4)

Figure 2.5.3.1. Mean Plasma Concentration-Time Profile of Milnacipran After 50 mg Capsule and Tablet Formulations (Study # M048).

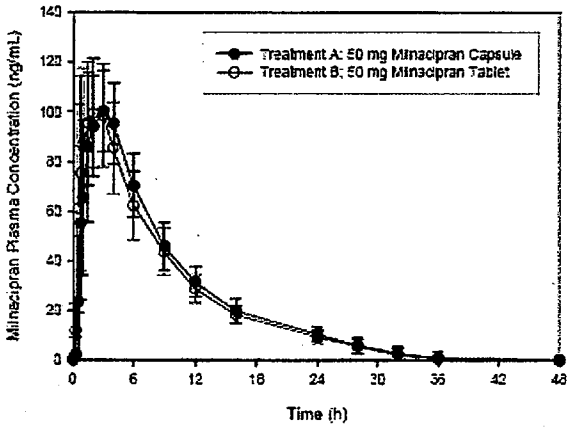


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Table 2.5.3.1. Mean PK Parameters of Milnacipran Following Administration of 50 mg Capsule and Tablet Formulations (Study # M048).

	TREATMENT A (capsule dosed at 50 mg)	TREATMENT B (tablet dosed at 50 mg)	STATISTICS Westlake interval
Cmax ($ng.ml^{-1}$)	125.76 (20.35)	126.18 (27.90)	NS (1) (11.99 %)
tmax (h)	2.75 (0.84)	1.83 (1.02)	NS (2)
$AUC_{0-24\ h}$ ($ng.ml^{-1}.h$)	1131.34 (161.48)	1094.95 (201.69)	NS (1) (11.18 %)
$AUC_{0-\infty}$ ($ng.ml^{-1}.h$)	1266.43 (183.21)	1208.45 (226.25)	NS (1) (13.60 %)
T1/2 (h)	7.60 (1.26)	7.36 (0.93)	NS (1) (12.99 %)
MRT (h)	10.64 (1.67)	9.94 (0.92)	NS (1) (13.59 %)

(1) : ANOVA 2 ways

(2) : Wilcoxon test

Figure 2.5.3.2. Mean Plasma Concentration-Time Profile of Milnacipran After One-Half of a 100 mg Scored Tablet (Test) and 50 mg Capsule (PF-C3 (Reference) (Study # M141).

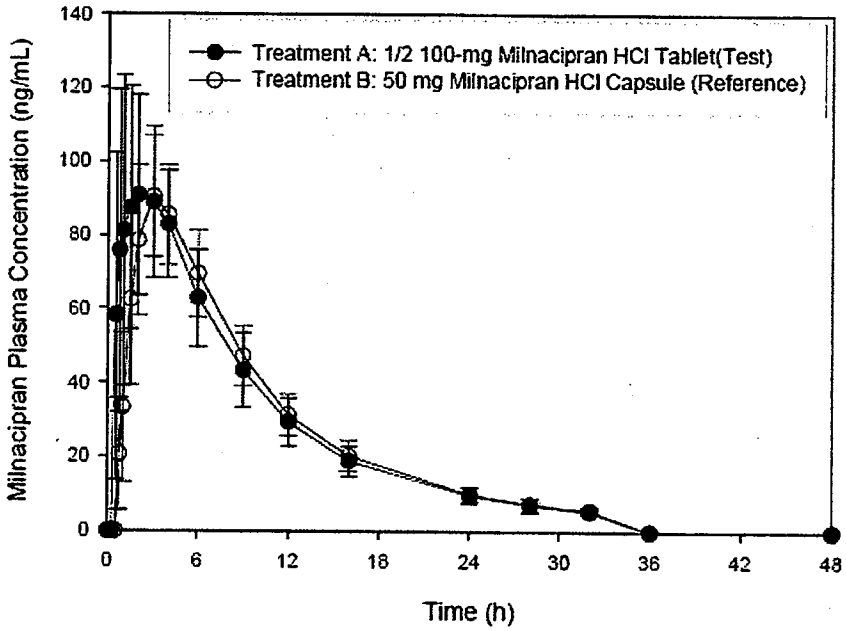

Table 2.5.3.2. Mean PK Parameters of Milnacipran Following One-Half of a 100 mg Scored Tablets and 50 mg Capsule (PF-C3 (Reference) (Study # M141).

Pharmacokinetic Parameter[a]	*Treatment A ½ 100-mg Tablet (N=24)*	*Treatment B 50-mg Capsule (N=24)*
C_{max} (ng/mL)	109.7 ± 29.1	93.5 ± 17.6
T_{max} (h)	2.08 ± 1.27	3.42 ± 1.02
AUC_{0-t} (ng•h/mL)	986 ± 184	972 ± 147
$AUC_{0-\infty}$ (ng•h/mL)	1047 ± 186	1033 ± 146
$T_{½}$ (h)	7.91 ± 0.93	8.10 ± 1.00
Ae_{0-24} (mg)	19.5 ± 4.0	18.9 ± 3.9
fe (%)	44.8 ± 9.2	43.4 ± 8.8

a C_{max}, AUC, and Ae_{0-24} parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

Ae_{0-24} = amount of drug excreted unchanged in urine from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t hours; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; C_{max} = maximum plasma drug concentration; fe = fraction of dose excreted as unchanged drug in urine; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

In addition, the capsule and tablet formulations based on dibasic calcium phosphate (PF-C5 and PFM) were also found to be bioequivalent to the [ ] formulation PF-C3 (Study # M112/M113, **Figure 2.5.3.3 and Table 2.5.3.3**). Based on these data, the sponsor chose the dibasic calcium phosphate based capsule formulation (PF-C5) for further clinical development. Additional lower strength of 12.5 mg capsule was later developed by the sponsor. b(4)

Figure 2.5.3.3. Mean Plasma Concentration-Time Profile of Milnacipran After 50 mg Capsule and Tablet Formulations (Study # M112/M113).

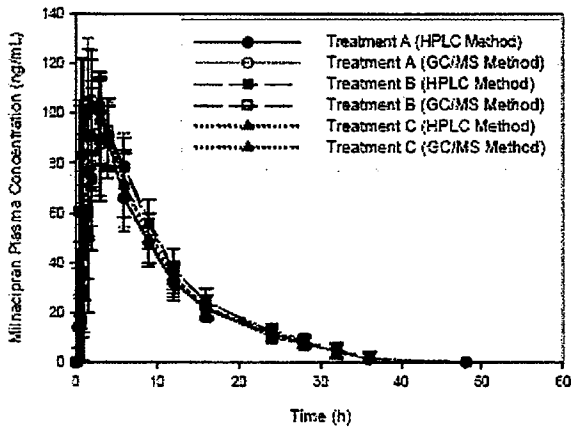

Table 2.5.3.3. Mean PK Parameters of Milnacipran Following Administration of 50 mg Capsules and Tablet Formulations (Study # M112/M113).

	HPLC Method			*GC/MS Method*		
Pharmacokinetic Parameter[a]	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*
C_{max} (ng/mL)	117.1 ± 14.8	99.1 ± 15.3	102.7 ± 17.4	121.0 ± 14.1	100.0 ± 14.4	104.1 ± 17.5
T_{max} (h)	1.8 ± 0.9	3.6 ± 1.1	2.6 ± 1.0	1.7 ± 1.0	3.4 ± 1.2	2.6 ± 0.9
AUC_{0-t} (ng•h/mL)	1082 ± 181	1076 ± 174	1057 ± 179	1095 ± 150	1071 ± 158	1054 ± 157
$AUC_{0-\infty}$ (ng•h/mL)	1137 ± 186	1134 ± 179	1114 ± 184	1189 ± 179	1176 ± 183	1149 ± 174
$T_{½}$ (h)	7.2 ± 0.7	7.3 ± 0.6	7.2 ± 0.7	7.9 ± 0.8	7.9 ± 0.7	7.9 ± 0.8
Ae_{0-24} (mg)	19.4 ± 4.5	20.2 ± 3.2	20.8 ± 3.8	-	-	-

In the later stages of drug development, the sponsor developed tablet dosage form using [redacted] as the final capsules containing diabasic calcium phosphate for marketing in the U.S. As stated earlier in Section 2.5.1, a bio-waiver request, based on data supporting milnacipran as BCS Classification I drug, for the bioequivalence of the capsule and tablet formulations was previously submitted to the IND 63,736 and was granted by the Agency on December 13, 2006. b(4)

A summary of all the bioavailability and bioequivalent studies submitted with this NDA is shown in **Table 2.5.3.4.**

Table 2.5.3.4. Synopsis of all Bioavailability and Bioequivalent Studies

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M038 (1988) France	Study of the absolute bioavailability of F2207 in the healthy subject by comparison of the capsule form with an intravenous infusion at the dose of 50 mg	To assess the absolute bioavailability of milnacipran To define the pharmacokinetics of milnacipran and evaluate its urinary excretion	Open label, randomized, two-way crossover with a 15-day washout period	12 healthy male subjects 26 years (21-29)	50-mg IV infusion over 1 hour Two 25-mg oral capsules (PF-C1)	Absolute bioavailability was 85%. T½ was similar for the two treatments (around 6 hours). For IV treatment, renal clearance accounted for 59% of total clearance. Volume of distribution following IV administration was 367 L.	Module 5.3.1.1.1
MLN-PK-04 (2007) USA	A single-center, randomized, open-label, single-dose, two-way crossover study comparing the effect of food on the oral bioavailability of 100 mg milnacipran HCl capsules	To evaluate the effect of food on the oral bioavailability of milnacipran HCl capsules	Open label, randomized, two-way crossover with 1-week washout period between treatments	31 healthy subject (21M/10F) 27 years (19-44)	Treatment A: Single dose of 100-mg milnacipran HCl capsule (PF-C5) under fasting conditions Treatment B: Single dose of 100-mg milnacipran HCl capsule (PF-C5) under fed conditions	The 90% CIs for the ratio of Cmax and AUC for fed and fasting states were within the 80%-125% range, indicating no significant food effect.	Module 5.3.1.1.2

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M039 and Addednum M124 (1988) France	Influence of food on the pharmacokinetics of F2207	To evaluate the effect of food on the bioavailability of milnacipran and to determine whether food reduces the incidence of side effects	Open-label, randomized, three-way crossover	12 healthy male subjects 23 years (20-25)	Treatment A: one 50-mg capsule (PF-C3), fasting Treatment B: one 50-mg capsule (PF-C3) with a low-fat breakfast Treatment C: one 50-mg capsule (PF-C3) with a high-fat breakfast	There was no food effect. Gastrointestinal tolerability appeared to be poorer in the fasting subjects.	Module 5.3.1.1.3
M048 (1989) France	Study on relative bioavailability of two F2207 oral formulations after single administration in twelve healthy volunteers	To compare the bioavailability of two 50- mg formulations after single administration	Open label, randomized, two-way crossover with 1-week washout between treatments	12 male subjects 23 years (18-30)	Treatment A: one 50-mg [redacted] capsule Treatment B: one 50-mg dibasic calcium phosphate–based tablet	The pharmacokinetics of milnacipran following administration of the tablet and capsule formulations were similar.	Module 5.3.1.2.1

b(4)

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M112 and Addendum M113 (1994) France	Comparative bioavailability study of three F2207 formulations (milnacipran) after single 50-mg oral administration in 24 healthy volunteers	To evaluate the relative bioavailability and tolerability of three different milnacipran formulations	Randomized, open-label, three-way crossover study with a 7-day washout period between treatments	24 healthy male subjects 23 years (18-27)	Treatment A: one 50-mg milnacipran test tablet (dibasic calcium phosphate–based formulation) with a standard breakfast Treatment B: one 50-mg milnacipran test capsule (dibasic calcium phosphate–based formulation, PF-C5) with a standard breakfast Treatment C: one 50-mg milnacipran reference [redacted] formulation with a standard breakfast	Bioequivalence was demonstrated between Treatments A and C and Treatments B and C. Plasma levels of milnacipran were similar following analyses using the HPLC and GC-MS methods. The *d*-isomer (F2695) had higher exposure than the *l*-isomer (F2696). Mean C_{max} values of F2695 were 5%–12% higher than for F2696; mean $AUC_{0-\infty}$ parameters were 70%–74% higher for F2695 than F2696. $T_{\frac{1}{2}}$ was 8.5 h for F2695 and 5.4 h for F2696.	Module 5.3.1.2.2

b(4)

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M140 (1997) France	Bioequivalence study of a new milnacipran oral formulation: 100 mg score tablet after single administration - 1/2 score tablet (50 mg) versus 50 mg milnacipran tablet in twelve normal healthy volunteers-100 mg scored tablet versus 100 mg milnacipran tablet in twelve normal healthy volunteers	To test the bioequivalence of a 100-mg scored tablet formulation relative to 50-mg and 100-mg tablet (reference) formulations	Open label, randomized, two-way crossover study in 3 groups of subjects with a 1-week washout between treatments	37 healthy male subjects (one subject was a replacement) 22 years (18-30)	Group A: - a half 100-mg scored tablet with a standard breakfast - one 50-mg tablet with a standard breakfast Group B: - one 100-mg scored tablet with a standard breakfast - one 100-mg tablet with a standard breakfast Group C: - one 100-mg scored tablet with a modified breakfast - one 100-mg tablet with a modified breakfast	Within each group, there were no differences in mean PK parameters between test and reference formulations. Milnacipran C_{max} and AUC parameters were about 2-fold higher following administration of a 100-mg oral dose compared to administration of a 50-mg oral dose, indicating dose proportionality.	Module 5.3.1.2.3

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M141 (1995) USA	Comparative bioavailability study of two F2707 formulations (milnacipran) after single 50-mg oral administration in healthy volunteers	To compare the bioavailability of two different milnacipran oral formulations following a single 50 mg oral administration	Single-dose, open-label, randomized, two-way crossover study with a 1-week washout between treatments	24 healthy male subjects 24 years (20-31)	Treatment A: a half 100-mg milnacipran scored dibasic calcium phosphate–based tablet (test) with a standard breakfast Treatment B: one 50-mg milnacipran [illegible] reference) with a standard breakfast	Mean Cmax was 17% greater for the test formulation. There were no differences in AUC.	Module 5.3.1.2.4

AUC = area under the plasma concentration versus time curve; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; GC = gas chromatography; HPLC = high performance liquid chromatography; IV = intravenous; MS = mass spectrometry; PK = pharmacokinetic; $T_{½}$ = terminal elimination half-life.

b(4)

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

Originally, milnacipran product was developed in France by Pierre Fabre Medicament (PFM) as an immediate release capsule, in 25 mg, 50 mg and 100 mg strengths and approved for marketing for the treatment of depression in many countries of Europe in 1998. These formulations contain [illegible]

b(4)

[ ] These new formulations had [ ] of shelf-life. In 1998, the capsule formulation PF-C5 was approved and marketed in Europe at 25, 50 and 100 mg strengths. b(4)

In 2001, Cypress Bioscience, Inc. (Cypress) licensed milnacipran from PFM and submitted IND # 63,736 for the treatment of the FMS, and introduced a new 12.5 mg strength capsule. In 2004, Forest and Cypress started the co-development of milnacipran drug product in the United States for the treatment of FMS. The capsule formulation marketed in Europe was used in the FMS pivotal clinical trials. The sponsor opted to develop an oral tablet dosage form [ ] as the capsules currently marketed in Europe. b(4)

As stated earlier, the sponsor utilized PF-C3 and PF-C5 capsules in Phase 1 and pivotal Phase 3 studies. In a PK/BE study (Study # M112), the capsules of formulation PF-C5 (the marked capsule in Europe), the tablets (containing dibasic calcium phosphate [ ]) and capsules of the [ ] formulation PF-C3 were found to be bioequivalent (see earlier Section). b(4)

For the marketing in US, Forest opted to develop a commercial immediate release (IR) tablets containing dibasic calcium phosphate [ ] at 12.5 mg, 25 mg, 50 mg, and 100 mg strengths. No new data was obtained using these tablets. Instead, Forest submitted data to support that milnacipran is a BCS class I drug subtance and that both the capsules formulation (PF-C5) and the to-be-marketed tablets are rapidily dissolving and requested a biowaiver for the tablets. Based on the data showing high permeability and high solubility and similarity in the dissolution data for the capsules (PF-C5 formulation) and tablets a bio-waiver for the tablet was granted by the Agency on December 13, 2006 (IND 63,736). Therefore, the proposed final-to-be marketed formulation in the US for the treatment of FMS will be IR, film-coated tablet in 12.5 mg, 25 mg, 50 mg and 100 mg strengths. b(4)

2.5.5 Are the method and dissolution specifications supported by the data provided by the sponsor?

The *in vitro* dissolution testing was conducted for marketed capsule formulation (# PF-C5) and the proposed commercial tablets (12.5, 25, 50, and 100 mg strengths). In addition, a dissolution equivalence study was conducted to compare the [ ] based capsule used in the majority of the PK studies with the dibasic calcium phosphate–based capsules (PF-C5). b(4)

All strengths of capsules and tablets of milnacipran demonstrated rapid dissolution (> [ ] in 30 minutes) and similar dissolution profiles in all media (Study # PRD-RPT-00014). Example of dissolution profiles for 100 mg strengths of capsule and tablet are shown in **Tables 2.5.5.1 and 2.5.5.2.** b(4)

Table 2.5.5.1. Mean Percent dissolved for 100 mg Capsule (Study # PRD-RPT-EXP-00014

Condition	Time	Mean	%RSD	Min.	Max.
0.1 N HCl	10	100	1.7	97	104
	15	100	1.7	98	105
	30	100	1.6	98	104
	45	100	1.4	98	104
Acetate Buffer pH 4.5	10	85	10.2	69	99
	15	101	1.1	100	104
	30	102	1.2	100	105
	45	103	1.1	101	105
Phosphate Buffer pH 6.8	10	65	20.3	47	93
	15	82	12.3	64	99
	20	90	7.9	80	101
	30	96	5.3	90	104
	45	100	3.2	95	107

Table 2.5.5.2. Mean Percent dissolved for 100 mg Tablet (Study # PRD-RPT-EXP-00014

Condition	Time	Mean	%RSD	Min.	Max.
0.1 N HCl	10	86	6.1	74	94
	15	96	3.4	90	101
	30	96	3.5	90	101
	45	96	3.7	89	101
Acetate Buffer pH 4.5	10	85	7.9	74	96
	15	96	4.8	85	101
	30	97	4.3	88	102
	45	97	4.2	88	102
Phosphate Buffer pH 6.8	10	62	14	43	72
	15	87	10.9	67	102
	20	93	7.3	76	105
	30	97	5.8	88	109
	45	98	5.3	92	111

The method proposed for *in vitro* dissolution is summarized below:

Apparatus: 1I (Paddles)
Media: 0.1N HCl
Speed: 50 RPM
Volume: 900 mL
Sampling Time Points: 10, 15, 30, 45 min, and 60 min.
Q = [redacted] % in 30 min

b(4)

ONDQA will assess the adequacy of the final method and specifications.

2.6 Analytical Section

The plasma and urine concentrations of milnacipran and its isomers (*d* and *l*) were determined by two main methods; LC-MS or GC-MS and fluorometric HPLC. Overall, the lower limit of quantitation (LLOQ) of the assays for both the parent drug and its isomers in plasma and urine ranges from approximately 0.1 to 5 ng/mL. The assay validation data are satisfactory. The inter- and intra-day assay %CV for all methods in plasma and urine is <10% **(Tables 2.6.1 and 2.6.2)**

Table 2.6.1. Accuracy and Precision For Plasma Milnacipran Analytical Method

Method Validation	*Observation*	*QC.1 (300 ng/mL)*	*QC.2 (2500 ng/mL)*	*QC.3 (8000 ng/mL)*
Accuracy (% deviation)	Intraday	within ± 1.6	within ± 1.0	within ± 2.2
	Interday	1.3	0.5	-1.1
Precision (% CV)	Intraday	≤ 2.3	≤ 1.5	≤ 2.0
	Interday	1.7	1.4	2.0

CV = coefficient of variation; QC = quality control.

Table 2.6.2. Method Accuracy and Precision For *d*- and *l*- Milnacipran in Plasma and Urine

Protocol No.	*d-milnacipran*				*l-milnacipran*			
	Standards		*QC Samples*		*Standards*		*QC Samples*	
	% CV	% dev	% CV	% dev	% CV	% dev	% CV	% dev
Plasma Samples								
PFM Study M126 (BA Report M127)	≤ 9.4	within ± 3.7	≤ 4.8	within ± 2.7	≤ 7.4	within ± 6.2	≤ 5.1	within ± 3.8
PFM Study M130 (BA Report M132)	≤ 9.4	within ± 7.7	≤ 6.3	within ± 1.1	≤ 9.4	within ± 10.1	≤ 7.4	within ± 3.8
PFM Study M135 (BA Report M136)	≤ 4.7	within ± 5.7	≤ 6.3	within ± 2.3	≤ 6.9	within ± 4.7	≤ 6.8	within ± 1.0
Urine Samples								
PFM Study M126 (BA Report M127)	≤ 11.9	within ± 9.4	≤ 5.5	within ± 8.7	≤ 9.8	within ± 9.8	≤ 5.6	within ± 8.9
PFM Study M135 (BA Report M136)	≤ 9.0	within ± 9.2	≤ 7.5	within ± 6.9	≤ 10.6	within ± 7.7	≤ 6.9	within ± 6.5

CV = coefficient of variation; % dev = percent deviation of the mean concentration from its nominal concentration; QC = quality control.

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_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2 Selected Individual Study Review:

This section contains detailed reviews of selected studies that are most relevant from the clinical pharmacology perspective.

Biopharmaceutics Studies:

Background:

The drug was originally developed as 25, 50, and 100 mg capsules (25 mg, 50 mg, and 100 mg). [ ] b(4)

The 50 mg dibasic calcium phosphate-based tablet formulation developed was found to be bioequivalent to the [ ] capsule formulation (Study # M048). However, Cmax (but not AUC) for half of the 100 mg scored tablet (i.e., 50 mg dose) of dibasic calcium phosphate–based formulation was approximately 17% higher than that of the [ ] capsule (Study # 141). b(4)

In addition, the capsule and tablet formulations based on dibasic calcium phosphate were also found to be bioequivalent to the [ ] formulation (Study # M112 and addendum # M113). Based on these data, the sponsor chosen the dibasic calcium phosphate–based capsule formulation (PF-C5) for further clinical development. Additional lower strength of 12.5 mg capsule was later developed by the sponsor. b(4)

In the later stage of drug development, the sponsor developed an oral tablet dosage form [ ] as the final capsules containing diabasic calcium phosphate. A biowaiver request for the bioequivalence of the capsule and tablet formulations was previously submitted to the IND 63,736 and was granted by the Agency on December 13, 2006. b(4)

A summary of all bioavailability and bioequivalent studies conducted by the sponsor are listed in **Table 4.2.1.**

Table 4.2.1. List of all Bioavailability and Bioequivalent Studies

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M038 (1988) France	Study of the absolute bioavailability of F2207 in the healthy subject by comparison of the capsule form with an intravenous infusion at the dose of 50 mg	To assess the absolute bioavailability of milnacipran To define the pharmacokinetics of milnacipran and evaluate its urinary excretion	Open label, randomized, two-way crossover with a 15-day washout period	12 healthy male subjects 26 years (21-29)	50-mg IV infusion over 1 hour Two 25-mg oral capsules (PF-C1)	Absolute bioavailability was 85%. T½ was similar for the two treatments (around 6 hours). For IV treatment, renal clearance accounted for 59% of total clearance. Volume of distribution following IV administration was 367 L.	Module 5.3.1.1.1
MLN-PK-04 (2007) USA	A single-center, randomized, open-label, single-dose, two-way crossover study comparing the effect of food on the oral bioavailability of 100 mg milnacipran HCl capsules	To evaluate the effect of food on the oral bioavailability of milnacipran HCl capsules	Open label, randomized, two-way crossover with 1-week washout period between treatments	31 healthy subject (21M/10F) 27 years (19-44)	Treatment A: Single dose of 100-mg milnacipran HCl capsule (PF-C5) under fasting conditions Treatment B: Single dose of 100-mg milnacipran HCl capsule (PF-C5) under fed conditions	The 90% CIs for the ratio of Cmax and AUC for fed and fasting states were within the 80%-125% range, indicating no significant food effect.	Module 5.3.1.1.2

Table 4.2.1 (continued)

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M039 and Addendum M124 (1988) France	Influence of food on the pharmacokinetics of F2207	To evaluate the effect of food on the bioavailability of milnacipran and to determine whether food reduces the incidence of side effects	Open-label, randomized, three-way crossover	12 healthy male subjects 23 years (20-25)	Treatment A: one 50-mg capsule (PF-C3), fasting Treatment B: one 50-mg capsule (PF-C3) with a low-fat breakfast Treatment C: one 50-mg capsule (PF-C3) with a high-fat breakfast	There was no food effect. Gastrointestinal tolerability appeared to be poorer in the fasting subjects.	Module 5.3.1.1.3
M048 (1989) France	Study on relative bioavailability of two F2207 oral formulations after single administration in twelve healthy volunteers	To compare the bioavailability of two 50- mg formulations after single administration	Open label, randomized, two-way crossover with 1-week washout between treatments	12 male subjects 23 years (18-30)	Treatment A: one 50-mg capsule (PF-C4) Treatment B: one 50-mg dibasic calcium phosphate–based tablet	The pharmacokinetics of milnacipran following administration of the tablet and capsule formulations were similar.	Module 5.3.1.2.1

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Table 4.2.1 (continued)

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M112 and Addendum M113 (1994) France	Comparative bioavailability study of three F2207 formulations (milnacipran) after single 50-mg oral administration in 24 healthy volunteers	To evaluate the relative bioavailability and tolerability of three different milnacipran formulations	Randomized, open-label, three-way crossover study with a 7-day washout period between treatments	24 healthy male subjects 23 years (18-27)	Treatment A: one 50-mg milnacipran test tablet (dibasic calcium phosphate–based formulation) with a standard breakfast Treatment B: one 50-mg milnacipran test capsule (dibasic calcium phosphate–based formulation, PF-C5) with a standard breakfast Treatment C: one 50-mg milnacipran reference capsule [redacted] formulation with a standard breakfast	Bioequivalence was demonstrated between Treatments A and C and Treatments B and C. Plasma levels of milnacipran were similar following analyses using the HPLC and GC-MS methods. The *d*-isomer (F2695) had higher exposure than the *l*-isomer (F2696). Mean C_{max} values of F2695 were 5%-12% higher than for F2696; mean $AUC_{0-\infty}$ parameters were 70%-74% higher for F2695 than F2696. $T_{½}$ was 8.5 h for F2695 and 5.4 h for F2696.	Module 5.3.1.2.2

b(4)

Table 4.2.1 (continued)

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M140 (1997) France	Bioequivalence study of a new milnacipran oral formulation: 100 mg score tablet after single administration - 1/2 score tablet (50 mg) versus 50 mg milnacipran tablet in twelve normal healthy volunteers-100 mg scored tablet versus 100 mg milnacipran tablet in twelve normal healthy volunteers	To test the bioequivalence of a 100-mg scored tablet formulation relative to 50-mg and 100-mg tablet (reference) formulations	Open label, randomized, two-way crossover study in 3 groups of subjects with a 1-week washout between treatments	37 healthy male subjects (one subject was a replacement) 22 years (18-30)	Group A: - a half 100-mg scored tablet with a standard breakfast - one 50-mg tablet with a standard breakfast Group B: - one 100-mg scored tablet with a standard breakfast - one 100-mg tablet with a standard breakfast Group C: - one 100-mg scored tablet with a modified breakfast - one 100-mg tablet with a modified breakfast	Within each group, there were no differences in mean PK parameters between test and reference formulations. Milnacipran C_{max} and AUC parameters were about 2-fold higher following administration of a 100-mg oral dose compared to administration of a 50-mg oral dose, indicating dose proportionality.	Module 5.3.1.2.3

Table 4.2.1 (continued)

Study No (Report Year) Country	*Protocol Title*	*Objectives*	*Design*	*Number of Subjects Mean Age (range)*	*Dosage*	*Results and Conclusion*	*Study Report Location*
M141 (1995) USA	Comparative bioavailability study of two F2707 formulations (milnacipran) after single 50-mg oral administration in healthy volunteers	To compare the bioavailability of two different milnacipran oral formulations following a single 50 mg oral administration	Single-dose, open-label, randomized, two-way crossover study with a 1-week washout between treatments	24 healthy male subjects 24 years (20-31)	Treatment A: a half 100-mg milnacipran scored dibasic calcium phosphate–based tablet (test) with a standard breakfast Treatment B: one 50-mg milnacipran [redacted] capsule (reference) with a standard breakfast	Mean Cmax was 17% greater for the test formulation. There were no differences in AUC.	Module 5.3.1.2.4

b(4)

AUC = area under the plasma concentration versus time curve; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; GC = gas chromatography; HPLC = high performance liquid chromatography; IV = intravenous; MS = mass spectrometry; PK = pharmacokinetic; T½ = terminal elimination half-life.

4.2.1. Study # M038 (Absolute Bioavailability Study)

Objective:

The primary objective of this study was to determine the absolute bioavailability of milnacipran capsule and its urinary elimination

Study Design:

This was a single dose, two-way crossover design in 12 healthy subjects as follows:

Treatment A: Oral administration: a single dose of two 25-mg (50 mg) milnacipran capsules (PF-C1)

Treatment B: Intravenous administration: a single 50-mg intravenous dose of milnacipran as 1-hour infusion

Blood and urine samples were collected at appropriate time points over 48 hours for the for PK analysis.

Results:

- A typical plasma concentration-time profiles were obtained following oral and IV administration (**Figure 4.2.1.1**).
- The absolute bioavailability of milnacipran from the capsule was approximately 85%.
- The Tmax occurred at approximately 2 hours.
- The elimination half-life was short approximately 6 hours following oral and IV administration (**Table 4.2.1.1**)
- The renal clearance after IV administration accounted for 59% of total drug clearance (**Tables 4.2.1.1.and 4.2.1.2**)
- There was no difference in cumulative urinary excretion profiles between oral and IV administration (**Figure 4.2.1.2.**)

Figure 4.2.1.1. Mean Plasma Concentration-Time Profile After 50 mg Oral and IV Doses of Milnacipran (Study # M038).

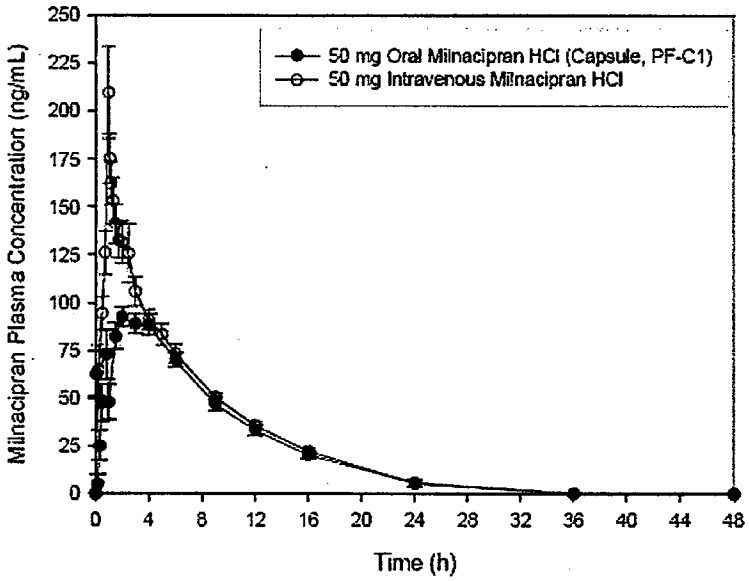

Table 4.2.1.1. Mean PK Parameters Following 50 mg Oral and IV administration of Milnacipran (Study # M038).

Pharmacokinetic Parameter[a]	*50 mg Oral Milnacipran HCl (N=12)*	*50 mg Intravenous Milnacipran HCl (N=12)*
C_{max} (ng/mL)	97.4 ± 18.1	-
T_{max} (h)[b]	2 (0.7 - 6)	-
$AUC_{0-\infty}$ (ng•h/mL)	926 ± 133	1107 ± 172
F	0.85 ± 0.03	-
$T_{½}$ (h)	6.1 ± 1.4	6.4 ± 1.7
Ae_{0-t} (mg)	-	25.3 ± 4.4
CL (L/h)	-	40.2 ± 6.2

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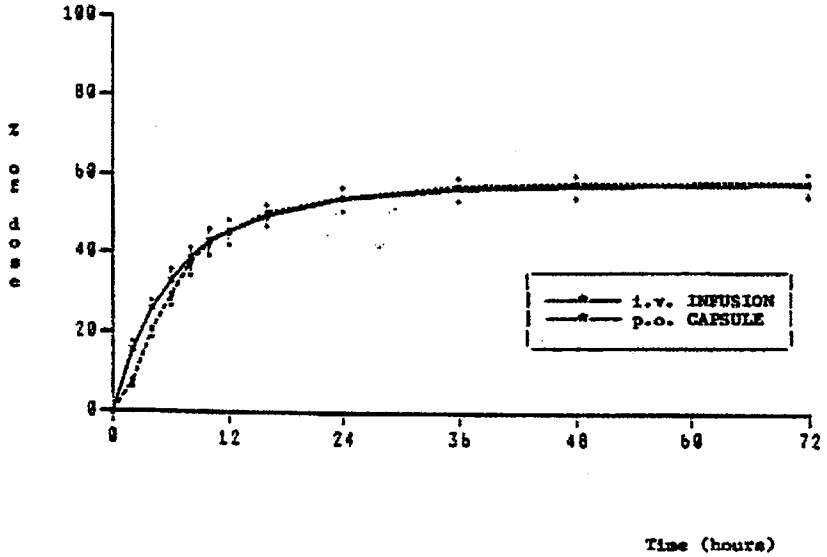
Table 4.2.1.2. Mean PK Parameters Following 50 mg Oral and IV administration of Milnacipran (Study # M038).

Pharmacokinetic Parameter[a]	*50 mg Oral Milnacipran HCl (N=12)*	*50 mg Intravenous Milnacipran HCl (N=12)*
CLr (L/h)	-	23.7 ± 7.3
V_d (L)	-	367 ± 98

a C_{max}, AUC, and Ae parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).
b Median (range).

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

Figure 4.2.1.2. Mean (± SEM) Urinary Elimination of Unchanged Milnacipran Following 50 mg Oral and IV administration (Study # M038, Source Study Report Page 65).



Reviewer's Comments:

This is straight forward study to determine the absolute bioavailability of milnacipran following moderate 50 mg dose. The study design and data analysis are acceptable.

Conclusions:

The main conclusion from this study is that the absolute bioavailability of milnacipran is approximately 85% when administered as capsule formulation.

4.2.2. Study # MLN-PK-04 (Effect of Food Study)

Objective:

The primary objective of this study was to determine the effect of food on the PK of milnacipran after oral administration of capsule formulation (**PF-C5**)

Study Design:

This was a single dose, two-way crossover design in 31 healthy subjects as follows:

Treatment A: Oral administration: a single dose of 100 mg milnacipran capsules (**PF-C5**) under **fasting** conditions.

Treatment B: Oral administration: a single dose of 100 mg milnacipran capsules (**PF-C5**) under **fed** conditions.

Blood samples were collected at appropriate time points over 48 hours for the for PK analysis.

Results:

- The mean plasma concentration-time profiles of milnacipran were almost identical in the presence or absence of food (**Figure 4.2.2.1**)

- The 90% CIs for the ratio of geometric means of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Treatment B versus Treatment A were within the equivalence limits of 80% to 125%, indicating that food intake did not affect the PK of milnacipran capsule (**Table 4.2.2.1**)

Figure 4.2.2.1. Mean Plasma Concentration-Time Profile of Milnacipran in Fed and Fasted Conditions (Study # MLN-PK-04).

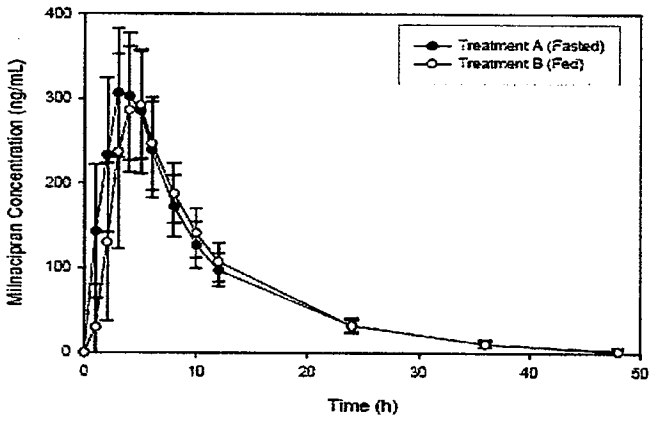


Table 4.2.2.1. Mean PK Parameters and 90% CI of Milnacipran in Fed and Fasted Conditions (Study # MLN-PK-04).

Pharmacokinetic Parameter	*Treatment A (fasting) (N=12)*	*Treatment B (fed) (N=12)*	*Ratio of Geometric Means (%)*	*90% CI*
C_{max} (ng/mL)[a]	332.8 ± 75.3	323.8 ± 64.3	98	91.3-104.2
T_{max} (h)	3.7 ± 1.0	4.2 ± 1.0	-	-
AUC_{0-t} (ng•h/mL)[a]	3403 ± 666	3231 ± 538	95	91.5-100.2
$AUC_{0-\infty}$ (ng•h/mL)[a]	3493 ± 682	3322 ± 544	96	91.8-100.3
$T_{½}$ (h)	7.6 ± 1.2	7.3 ± 1.1	-	-

a C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ parameters reflect freebase values

AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma drug concentration; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

Reviewer's Comments:

This is straight forward study that was conducted to determine the effect of food on milnacipran 100 mg capsule strength. The study design and data analysis are acceptable.

Conclusions:

The main conclusion from this study is that food had no effect on the absorption or the PK of milnacipran.

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4.2.3. Study # M039 and Addendum M124 (Effect of Food Study, Capsule PF-C3)

Objective:

The primary objective of this study was to determine the effect of food (low and high fat) on the PK of milnacipran after oral administration of capsule formulation (**PF-C3**).

Study Design:

This was a single dose, three-way crossover design in 12 healthy subjects as follows:

Treatment A: Oral administration: a single dose of **50 mg** milnacipran capsules (**PF-C3**) under **fasting** conditions.

Treatment B: Oral administration: a single dose of **50 mg** milnacipran capsules (**PF-C3**) under fed conditions (**low fat breakfast**).

Treatment B: Oral administration: a single dose of **50 mg** milnacipran capsules (**PF-C3**) under fed conditions (**high fat breakfast**).

Blood samples were collected at appropriate time points over 24 hours for the for PK analysis.

Results:

- There was wide variability in the data. Therefore, there was no real trend in the mean plasma concentration-time profiles of milnacipran when given with or without food. (**Figure 4.2.3.1**).

- The 90% CIs for the ratio of geometric means of C_{max} and AUC_{0-t} for Treatment were within the equivalence limits of 80% to 125% (**Table1 4.2.3.1 A & B**). The 90% CI for $AUC_{0-\infty}$ was slightly lower than 80% (77%). This is not clinically significant.

Figure 4.2.3.1. Mean Plasma Concentration-Time Profile of Milnacipran in Fed and Fasted Conditions After 50 mg Capsule (Study # M039/M124).

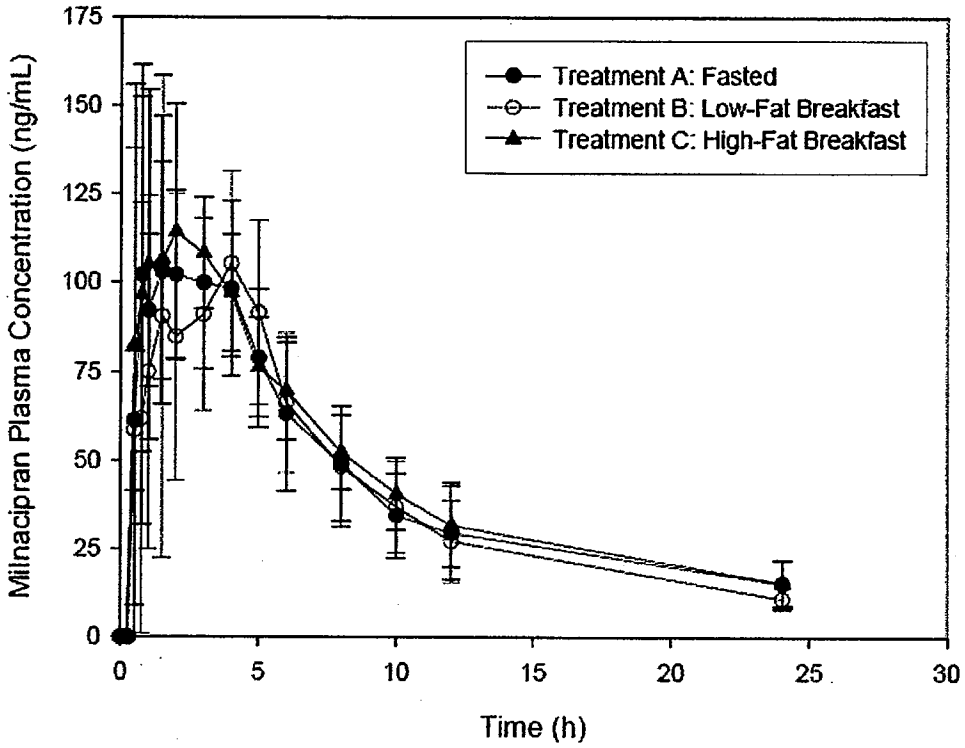

Table 4.2.3.1 A. Mean PK Parameters and 90% CI of Milnacipran in Fed and Fasted Conditions Following Administration of 50 mg Capsule (Study # M039/M124).

Pharmacokinetic Parameter[a,b]	*Treatment A (fasting) n=8*[c]	*Treatment B (low-fat) n=11*[c]	*Treatment C (high-fat) n=12*[c]	*90% CIs*	
				B vs A	*C vs A*
C_{max} (ng/mL)	129.9 ± 40.3	135.2 ± 50.6	140.1 ± 43.6	88-118	93-125
T_{max} (h)	2.50 ± 1.43	2.98 ± 1.60	2.15 ± 1.08	-	-
AUC_{0-24} (ng•h/mL)	980 ± 249	911 ± 264	1040 ± 233	82-104	95-120

Table 4.2.3.1 B. Mean PK Parameters and 90% CI of Milnacipran in Fed and Fasted Conditions (Study # M039/M124).

Pharmacokinetic Parameter[a,b]	*Treatment A (fasting) n=8*[c]	*Treatment B (low-fat) n=11*[c]	*Treatment C (high-fat) n=12*[c]	*90% CIs*	
				B vs A	*C vs A*
$AUC_{0-\infty}$ (ng•h/mL)	1088 ± 318	981 ± 306	1149 ± 282	77-105	91-124
$T_{½}$ (h)	6.52 ± 2.29	5.43 ± 1.90	6.50 ± 1.94	-	-
Ae_{0-24} (mg)	24.39 ± 2.21	24.43 ± 3.91	24.47 ± 4.83	89-110	89-110
Clr (L/h)	26.3 ± 7.0	29.0 ± 10.5	24.4 ± 6.2	92-125	80-108

a C_{max}, AUC, and Ae_{0-24} parameters reflect milnacipran freebase values (conversion factor of 0.87 from HCl salt to freebase).

b Based on Report M124.

c Subjects who did not vomit.

Ae_{0-24} = amount of drug excreted unchanged in urine from time 0 to 24 hours; AUC_{0-24} = area under the plasma concentration versus time curve from time 0 to 24 hours; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; CLr = renal clearance; C_{max} = maximum plasma drug concentration; fe = fraction of dose excreted as unchanged drug in urine; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

Reviewer's Comments:

This is straight forward study to determine the effect of food on milnacipran 50 mg capsule strength. The study design and data analysis are acceptable.

Conclusions:

The main conclusion from this study is that the food had no effect on the absorption or the PK of milnacipran. This study confirms the previous study (Study # MLN-PK-04).

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4.2.4. Study # M048 (Relative Bioavailability Between Capsule and Tablets)

Objective:

The primary objective of this study was to determine the relative bioavailability and bioequivalence of milnacipran after oral administration of capsule formulation [ ] **PF-C4)** and tablet (dibasic calcium phosphate) b(4)

Study Design:

This was a single dose, two-way crossover design in 12 healthy subjects as follows:

Treatment A: Oral administration: a single dose of **50 mg** milnacipran [ ] containing **capsules (PF-C4).** b(4)

Treatment B: Oral administration: a single dose of **50 mg** milnacipran diabasic calcium phosphate containing **tablets.**

Blood samples were collected at appropriate time points over 48 hours for the for PK analysis.

Results:

- The mean plasma concentration-time profiles of milnacipran after capsule and tablets are almost identical **(Figure 4.2.4.1).**
- There was virtually no difference in Cmax and AUC between capsule and tablets **(Table1 4.2.4.1)**

Figure 4.2.4.1. Mean Plasma Concentration-Time Profile of Milnacipran After 50 mg Capsule and Tablet Formulations (Study # M048).

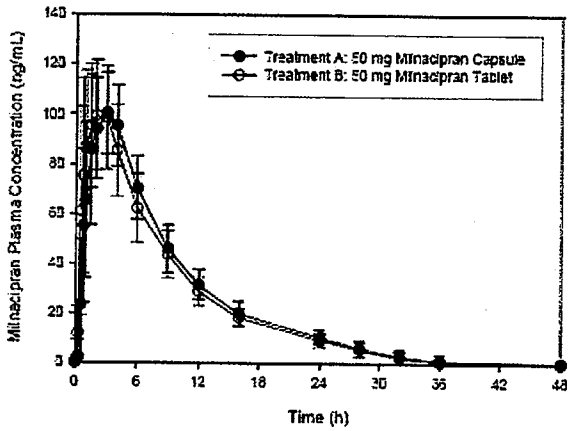

Table 4.2.4.1. Mean PK Parameters of Milnacipran Following Administration of 50 mg Capsule and Tablet Formulations (Study # M048).

	TREATMENT A (capsule dosed at 50 mg)	TREATMENT B (tablet dosed at 50 mg)	STATISTICS Westlake interval
Cmax ($ng.ml^{-1}$)	125.76 (20.35)	126.18 (27.90)	NS (1) (11.99 %)
tmax (h)	2.75 (0.84)	1.83 (1.02)	NS (2)
$AUC_{0-24\ h}$ ($ng.ml^{-1}.h$)	1131.34 (161.48)	1094.95 (201.69)	NS (1) (11.18 %)
$AUC_{0-\infty}$ ($ng.ml^{-1}.h$)	1266.43 (183.21)	1208.45 (226.25)	NS (1) (13.60 %)
T1/2 (h)	7.60 (1.26)	7.36 (0.93)	NS (1) (12.99 %)
MRT (h)	10.64 (1.67)	9.94 (0.92)	NS (1) (13.59 %)

(1) : ANOVA 2 ways

(2) : Wilcoxon test

Reviewer's Comments:

This study demonstrates no difference in absorption of milnacipran when administered as capsule or tablet.

Conclusions:

The main conclusion from this study is that the capsule and table showed no difference in absorption profiles (rate and extent).

4.2.5. Study # M112 and Addendum M113 (Relative Bioavailability for Three Formulations: Two Capsules (diabasic and [ ], and Tablet (diabasic) b(4)

Objective:

The primary objective of this study was to determine the relative bioavailability of three formulations: Two capsules, one with diabasic calcium phosphate (**PC-5**) and the other with [ ] **PC-3**) and tablet with dibasic calcium phosphate. b(4)

Study Design:

This was a single dose, three-way crossover design in 24 healthy subjects as follows:

Treatment A: Oral administration: a single dose of **50 mg** milnacipran dibasic calcium phosphate containing **tablet**

Treatment B: Oral administration: a single dose of **50 mg** milnacipran dibasic calcium phosphate containing **capsule (PF-C5).**

Treatment C: Oral administration: a single dose of **50 mg** milnacipran [ ] containing **capsule (PF-C3)** b(4)

Blood and urine samples were collected at appropriate time points over 48 and 24 hours for the PK analysis, respectively. Milnacipran plasma concentration and its *d* and *l* enantiomers were determined by HPLC and GC/MS Methods.

Results:

- The mean plasma concentration-time profiles of milnacipran after capsule and tablets were almost identical irrespective of the analytical method used **(Figure 4.2.5.1).**
- There was virtually no difference in Cmax and AUC data between capsules and tablet formulations, irrespective of the method used **(Table1 4.2.5.1).** The same was true for the % of unchanged drug excreted in urine **(Table 4.2.5.1 and 4.2.5.2).**
- The 90% CIs for all treatments were within 80% to 125% limits, indicating bioequivalence between formulations **(Table 4.2.5.3)**
- Similarly, for *d* and *l* enantiomers the profiles and the data are comparable after the three treatments and irrespective of the method used **(Figure 4.2.5.2 and Table 4.2.5.4).** It should be noted that the level of *d* enantiomer was consistently higher than that of *l* enantiomer in all treatments. For Cmax, the *d* enantiomer was approximately 5% to 10% higher than *l* enantiomer. However, the AUC of *d* enantiomer was much higher by approximately 70 to 74% than *l* enantiomer **(Table 4.2.5.4)**

Figure 4.2.5.1. Mean Plasma Concentration-Time Profile of Milnacipran After 50 mg Capsule and Tablet Formulations (Study # M112/M113).

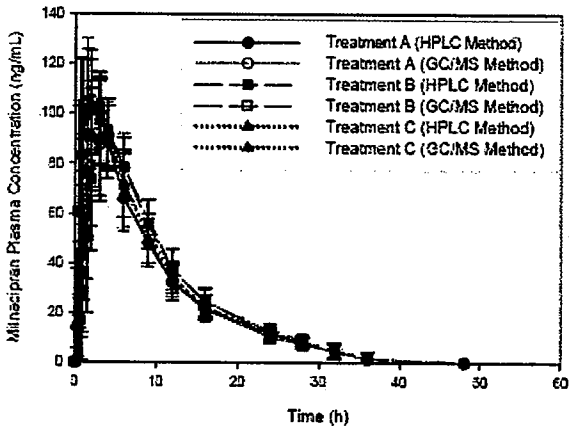

Table 4.2.5.1. Mean PK Parameters of Milnacipran Following Administration of 50 mg Capsules and Tablet Formulations (Study # M112/M113).

	HPLC Method			*GC/MS Method*		
Pharmacokinetic Parameter[a]	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*
C_{max} (ng/mL)	117.1 ± 14.8	99.1 ± 15.3	102.7 ± 17.4	121.0 ± 14.1	100.0 ± 14.4	104.1 ± 17.5
T_{max} (h)	1.8 ± 0.9	3.6 ± 1.1	2.6 ± 1.0	1.7 ± 1.0	3.4 ± 1.2	2.6 ± 0.9
AUC_{0-t} (ng•h/mL)	1082 ± 181	1076 ± 174	1057 ± 179	1095 ± 150	1071 ± 158	1054 ± 157
$AUC_{0-\infty}$ (ng•h/mL)	1137 ± 186	1134 ± 179	1114 ± 184	1189 ± 179	1176 ± 183	1149 ± 174
$T_{½}$ (h)	7.2 ± 0.7	7.3 ± 0.6	7.2 ± 0.7	7.9 ± 0.8	7.9 ± 0.7	7.9 ± 0.8
Ae_{0-24} (mg)	19.4 ± 4.5	20.2 ± 3.2	20.8 ± 3.8	-	-	-

Table 4.2.5.2. % Excreted Unchanged in Urine Following Administration of 50 mg Milnacipran Capsules and Tablet Formulations (Study # M112/M113).

	HPLC Method			*GC/MS Method*		
Pharmacokinetic Parameter[a]	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*
fe (%)	44.7 ± 10.3	46.4 ± 7.3	47.9 ± 8.7	-	-	-

a C_{max}, AUC, and Ae_{0-24} parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

Ae_{0-24} = amount of drug excreted unchanged in urine from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; C_{max} = maximum plasma drug concentration; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

Table 4.2.5.3. 90% CI Parameters of Milnacipran Following Administration of 50 mg Capsules and Tablet Formulations (Study # M112/M113).

Parameter	*Treatment A vs. Treatment C*	*Treatment B vs. Treatment C*
C_{max} (ng/mL)	108 - 120	91 - 102
AUC_{0-t} (ng•h/mL)	98 - 106	98 - 106
$AUC_{0-\infty}$ (ng•h/mL)	98 - 106	98 - 106

a Comparison of parameters based on HPLC method (Study Report M112)

AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t hours; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma drug concentration.

Figure 4.2.5.2. Mean Plasma Concentration-Time Profile of Milnacipran Enantiomers After 50 mg Capsules and Tablet Formulations (Study # M112/M113).

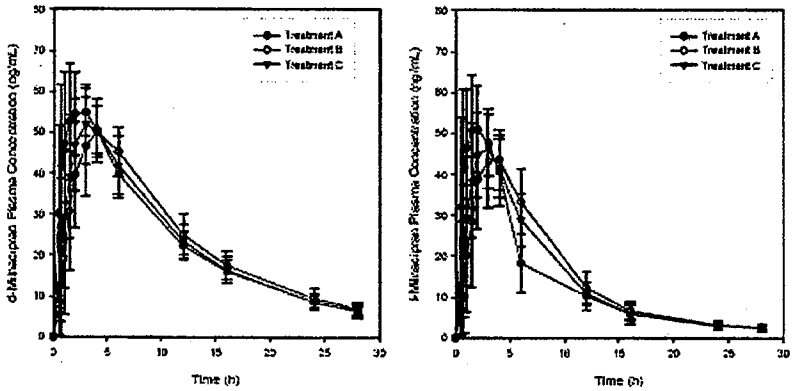

Figure 4.2.5.4. Mean Plasma PK Parameters of Milnacipran Enantiomers After 50 mg Capsules and Tablet Formulations (Study # M112/M113).

	F2695 (d-Milnacipran)			*F2696 (l-Milnacipran)*		
Pharmacokinetic Parameter[a]	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*	*Treatment A (N=24)*	*Treatment B (N=24)*	*Treatment C (N=24)*
C_{max} (ng/mL)	62.1 ±7.0	53.0 ± 7.1	54.7 ± 8.5	59.2 ± 8.0	47.4 ± 7.7	50.1 ± 9.4
T_{max} (h)	1.78 ± 0.92	3.85 ± 1.30	2.94 ± 1.01	1.63 ± 0.91	3.35 ± 1.27	2.27 ± 0.91
AUC_{0-t} (ng•h/mL)	669 ± 77	655 ± 85	648 ± 94	419 ± 93	410 ± 92	398 ± 83
$AUC_{0-\infty}$ (ng•h/mL)	747 ± 96	742 ± 105	728 ± 109	439 ± 98	430 ± 98	418 ± 86
$T_{½}$ (h)	8.43 ± 0.72	8.59 ± 0.82	8.54 ± 0.86	5.37 ± 0.94	5.45 ± 0.97	5.41 ± 1.08

a C_{max} and AUC parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t hours; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; C_{max} = maximum plasma drug concentration; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

Reviewer's Comments:

This study demonstrated the PK profile of the parent drug, milnacipran and its *d* and *l* enantiomers after administration of capsules or tablet formulation. In addition, the study validated the robustness of the analytical methods used during the development of the drug.

Conclusions:

The main conclusion from this study is that milnacipran formulated as capsule (with dibasic calcium or [ ]) or tablet (with dibasic calcium phosphate) showed no difference in absorption profiles (rate and extent). b(4)

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4.2.6. Study # M140 (BE of 100 mg Scored vs 50 and 100 mg un-scored Tablets)

Objective:

The primary objective of this study was to determine the relative bioavailability of 100 mg scored tablets (test) to 50 and 100 mg un-scored tablets (reference).

Study Design:

This was a single dose, in three groups (crossover within the same group) in 12 healthy subjects in each group as follows:

Group A (100 scored vs 50 un-scored):

Treatment A: Oral administration: a single dose of **50 mg** milnacipran as **one half** tablet of 100 mg **scored tablet** (test)

Treatment B: Oral administration: a single dose of **50 mg** milnacipran as 50 mg **un-scored** tablet (reference)

Group B (100 mg scored vs 100 mg un-scored tablets):

Treatment A: Oral administration: a single dose of **100 mg scored** tablet (test)

Treatment B: Oral administration: a single dose of **100 mg** milnacipran as **un-scored** ablets (reference)

Group C (Repeat of Group B, 100 mg scored vs 100 mg un-scored tablets):

Due to the excessive vomiting in group B, group C was added as a replacement/ additional subjects.

Treatment A: Oral administration: a single dose of **100 mg scored** tablet (test)

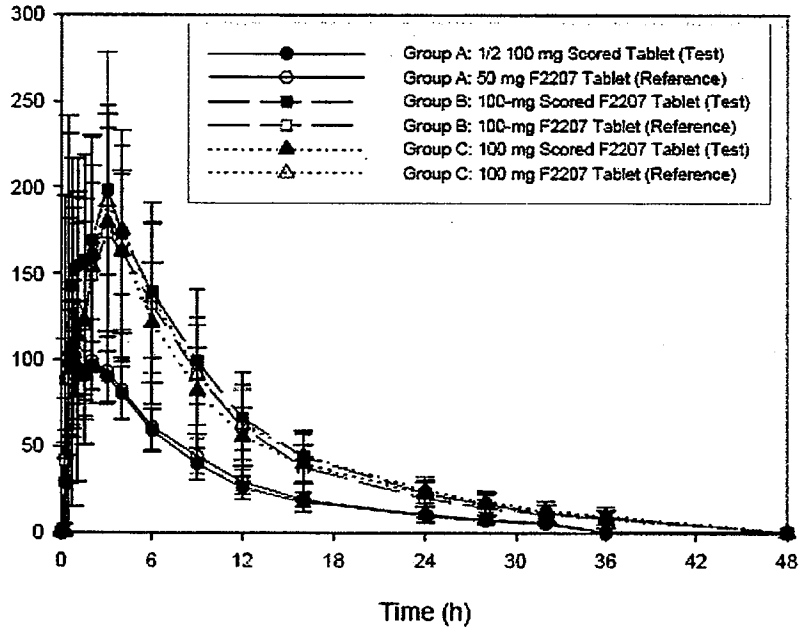
Treatment B: Oral administration: a single dose of **100 mg** milnacipran as **un-scored** tablets (reference)

Blood samples were collected at appropriate time points over 48 hours for the for PK analysis.

Results:

- The mean plasma concentration-time profiles of milnacipran after each respective dose/group were almost identical (**Figure 4.2.6.1).**

Figure 4.2.6.1. Mean Plasma Concentration-Time Profile of Milnacipran After Scored (Test) and un-scored Tablets (Reference) (Study # M140).



- There was virtually no difference in Cmax within each dose group. However, there was some minor difference in AUC in Group B and Group C (**Table1 4.2.6.1**). The 100 mg scored tablet (test) show slightly higher mean AUC value than the 100 mg non-scored tablet (reference). Conversely, the AUC was slightly lower after 100 mg scored tablet (test) than the non-scored tablet in group C (**Table 4.2.6.1**). The difference may not be clinical significant.

Table 4.2.6.1. Mean PK Parameters of Milnacipran Following Scored and un-scored Tablets (Study # M140).

	Group A		*Group B*		*Group C*	
Pharmacokinetic Parameter[a]	*½ 100-mg Scored Tablet (test) (N=12)*	*50-mg Tablet (reference) (N=12)*	*100-mg Scored Tablet (test) (N=12)*	*100-mg Tablet (reference) (N=12)*	*100-mg Scored Tablet (test) (N=12)*	*100-mg Tablet (reference) (N=12)*
C_{max} (ng/mL)	110.1 ± 24.2	115.4 ± 33.5	222.4 ± 51.0	191.8 ± 44.3	210.4 ± 93.7	224.5 ± 62.6
T_{max} (h)	1.46 ± 0.83	1.69 ± 1.01	1.85 ± 1.11	2.75 ± 1.56	2.42 ± 2.31	2.31 ± 1.31
$AUC_{0-\infty}$ (ng•h/mL)	1029 ± 230	1079 ± 228	2325 ± 564	2065 ± 808	2037 ± 590	2234 ± 658
$T_{½}$ (h)	8.07 ± 1.69	7.88 ± 0.69	8.42 ± 1.38	8.66 ± 1.19	8.36 ± 1.35	8.79 ± 1.56

a C_{max} and AUC parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).
$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; C_{max} = maximum plasma drug concentration; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

- It was noted that the Cmax and AUC values after 100 mg doses are approximately twice as after 50 mg doses (**Table 4.2.6.1**). This indicates dose proportionality within these dosage strengths.

Reviewer's Comments:

The study showed comparable PK profiles for the 100 mg scored tablet (test) compared to 50 mg and 100 mg strengths un-scored tablets (reference). However, the sponsor did not conduct a formal bioequivalence analysis of the data to obtain the 90% CI. Therefore, without the 90% CI values the bioequivalence between the test and the references cannot be declared.

Conclusions:

The main conclusion from this study is that milnacipran PK profiles after the administration of scored and un-scored tablets are comparable. However, no statistical analysis was provided by the sponsor to confirm bioequivalence among formulations.

4.2.7. Study # M141 (Relative Bioavailability for 50 mg Formulations with Breakfast)

Objective:

The primary objective of this study was to determine the relative bioavailability of 100 mg tablet (one-half tablet, 50 mg dose) to 50 mg capsule when administered with breakfast.

Study Design:

This was a single dose, two-way crossover in 24 healthy subjects as follows:

Treatment A: Oral administration: a single dose of **50 mg** milnacipran as **one half** tablet of 100 mg **scored tablet** (Test)

Treatment B: Oral administration: a single dose of **50 mg** milnacipran of [ ] capsule (Reference)

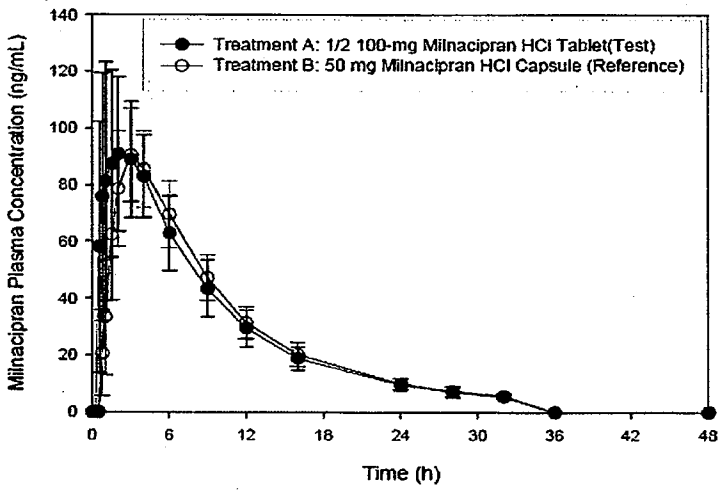
b(4)

Blood samples were collected at appropriate time points over 48 hours for the for PK analysis. In addition, urine was collected at 0-4, 4-12, and 12-24 hours intervals.

Results:

- From the mean plasma concentration-time profiles the rate of absorption of milnacipran after the tablet appears to be faster than that after the capsule (**Figure 4.2.7.1).**

Figure 4.2.7.1. Mean Plasma Concentration-Time Profile of Milnacipran After One-Half of a 100 mg Scored Tablet (Test) and 50 mg Capsule (PF-C3 (Reference) (Study # M141).



- The Cmax was approximately 17% higher following the test tablet than the reference capsule (**Table 4.2.7.1**). The same trend was seen in urinary excretion of the drug after the first collection period of 0-4 hours (**Figure 4.2.7.2**). However, the AUC values following both treatments were comparable (**Table 4.2.7.1**).

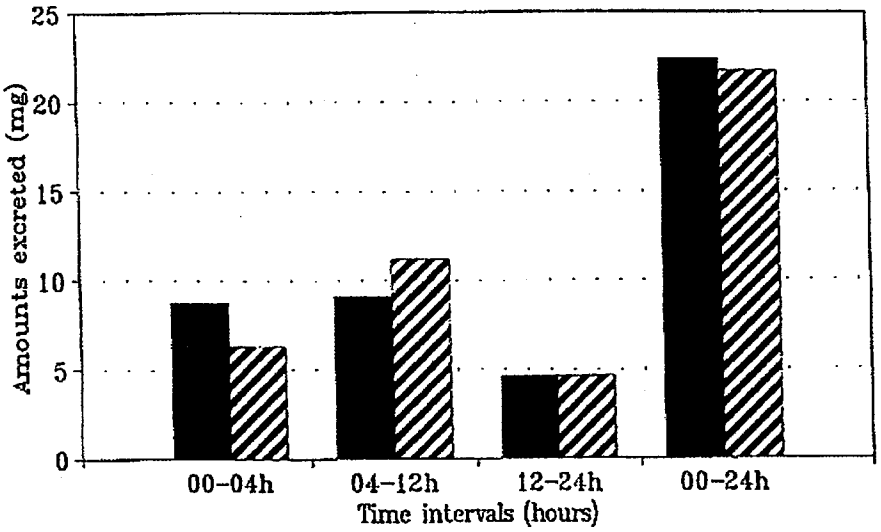
Table 4.2.7.1. Mean PK Parameters of Milnacipran Following One-Half of a 100 mg Scored Tablets and 50 mg Capsule (PF-C3 (Reference) (Study # M141).

Pharmacokinetic Parameter[a]	*Treatment A ½ 100-mg Tablet (N=24)*	*Treatment B 50-mg Capsule (N=24)*
C_{max} (ng/mL)	109.7 ± 29.1	93.5 ± 17.6
T_{max} (h)	2.08 ± 1.27	3.42 ± 1.02
AUC_{0-t} (ng•h/mL)	986 ± 184	972 ± 147
$AUC_{0-\infty}$ (ng•h/mL)	1047 ± 186	1033 ± 146
$T_{½}$ (h)	7.91 ± 0.93	8.10 ± 1.00
Ae_{0-24} (mg)	19.5 ± 4.0	18.9 ± 3.9
fe (%)	44.8 ± 9.2	43.4 ± 8.8

a C_{max}, AUC, and Ae_{0-24} parameters reflect freebase values (conversion factor of 0.87 from HCl salt to freebase).

Ae_{0-24} = amount of drug excreted unchanged in urine from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to t hours; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; C_{max} = maximum plasma drug concentration; fe = fraction of dose excreted as unchanged drug in urine; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration.

Figure 4.2.7.2. Mean Urine Excretion Data of Milnacipran After One-Half of a 100 mg Scored Tablet (Test) and 50 mg Capsule (PF-C3 (Reference) (Study # M141).



Reviewer's Comments:

The study showed comparable PK profiles in terms of AUC for the 100 mg scored tablet (test) compared to 50 mg capsule (reference). However, the Cmax is approximately 17% higher after the test tablet than the capsule. This also suggests that the rate of absorption after the tablet is faster than after the capsule.

Conclusions:

The main conclusion from this study is that milnacipran Cmax after the test tablet is approximately 17% higher than the reference capsule. However, the AUCs are comparable.