



Research Article

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Vomiting is a Potential Adverse Drug Reaction for Levomilnacipran

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ABSTRACT

Levomilnacipran is a drug used to treat depression. Micro Labs is a generic drug company which had developed an extended release formulation of Levomilnacipran 120 mg capsule. Two studies were conducted to assess the safety, tolerability and bioequivalence of the extended release formulation of 120 mg Levomilnacipran capsules. A total of 42 subjects had been included for each of the fasting and fed studies. Out of them, 30 subjects completed the fasting study and 28 subjects completed the fed study. Pharmacokinetic parameters like C_{max} , AUC_{0-t} , AUC_{0-inf} , T_{max} , K_{el} , $t_{1/2}$ and $\%AUC_{extra}$ were calculated for Levomilnacipran in order to compare the bioavailability of the test and reference formulations. The studies were conducted in healthy human volunteers in both fasting and fed conditions as per the US regulatory requirements for conduct of bioequivalence studies. The formulations were found to be bioequivalent to each other. Vomiting was observed as a major adverse reaction.

Keywords: Levomilnacipran, bioequivalence, vomiting, adverse reaction.

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INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Recently, extended release pharmaceutical products became a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. Extended release is also providing promising

way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. [1] Of all drug delivery systems, oral drug delivery remains the most preferred option for administration for various drugs. [2] Extended release formulations make the drug available over extended time period after oral administration. The extended release products optimize therapeutic effect and safety of a drug at the same time improves the patient convenience and compliance. [3]

According to the World Health Organization (WHO), depression is defined as a common mental disorder with symptoms of depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, decreased sleep or appetite, and poor concentration. [4]

Levomilnacipran (Fetzima®) has been approved by the US Food and Drug Administration for the treatment of major depressive disorder. It is a unique dual neurotransmitter reuptake inhibitor. In contrast with other selective serotonin norepinephrine reuptake inhibitors, including duloxetine, venlafaxine, and desvenlafaxine, it has greater selectivity for inhibiting norepinephrine reuptake than serotonin reuptake. [5] Levomilnacipran is the more active enantiomer of the serotonin and norepinephrine reuptake inhibitor (SNRI) milnacipran. It was recently approved in the US for the treatment of major depressive disorder (MDD). The drug was developed as an extended release (ER) capsule formulation to allow for once daily administration, thereby improving patient adherence. [6]

Bioavailability is used to describe the fraction of an administered dose of medication that reaches the systemic circulation, one of the principal properties of the drug. By definition, when the drug is administered intravenously, its bioavailability is 100%.

Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the innovator (reference) product, on the basis that if two formulations exhibit similar drug concentration time profile in the blood/plasma, they should exhibit similar therapeutic effects. Once bioequivalence has been established via bioavailability testing in a statistically significant manner subsequent batches of the same product are deemed bio-equivalent based on in-vitro measures such as drug dissolution. [7] Micro Labs Ltd. had developed a generic version of Levomilnacipran 120 mg ER capsule. It had been tested in healthy human volunteers in fasting and fed condition. The bioavailability, safety and tolerability were assessed along with Fetzima Levomilnacipran extended release capsules 120 mg of Forest Pharmaceuticals. Approval had been taken to conduct the studies from IBIOME Independent Ethics Committee and DCGI (Drug Controller General of India).

MATERIALS AND METHODS

An open label, randomised, balanced, two-treatment, two-period, two-sequence, single dose, two way crossover, oral bioequivalence study of Levomilnacipran extended release capsules 120 mg manufactured by Micro Labs Limited, India compared with that of Fetzima Levomilnacipran extended release capsules 120 mg of Forest Pharmaceuticals, Inc. Subsidiary Of Forest Laboratories, Inc. St. Louis, Mo 63045 USA in healthy, adult, human subjects under fasting and fed conditions.

The studies were conducted at Synchron Research Services Pvt. Ltd, Gujarat, India.

Volunteers selected were healthy young adults within 18-45 years age and having no history of smoking or drug abuse. Informed consent was obtained from each volunteer before screening.

Fasting and fed study dosing

In each period, a single oral dose of one capsule of either test formulation (T) or reference formulation (R), both containing 120 mg of Levomilnacipran, was administered with about 240 mL drinking water at ambient temperature in fasting condition (at least 10.00 hours before dosing) and fed condition (30 minutes after start of a high calorie and high fat breakfast) as per randomisation schedule in the morning.

PK Blood Draw Time Points (Fasting)

Pre-dose (within 1.00 hour prior to dosing) and at 0.50, 1.00, 2.00, 3.00, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.33, 6.67, 7.00, 7.33, 7.67, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours post-dose.

PK Blood Draw Time Points (Fed)

Pre-dose (within 1.00 hour prior to dosing) and at 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.33, 7.67, 8.00, 8.33, 8.67, 9.00, 9.50, 10.00, 11.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours post-dose.

Healthy adult human volunteers having a BMI between 18.5 and 24.9 Kg/m² without a history of smoking or drug abuse were included in the studies.

Vital signs like Blood Pressure (B.P.), pulse rate, temperature and respiratory rate were measured at regular intervals. Subjects were asked about their well-being status from time to time.

There were forty two (42) healthy, adult, eligible human subjects enrolled in the fasting study. Out of forty two (42) enrolled subjects, thirty (30) subjects were completed both the periods of the study.

There were forty two (42) healthy, adult, eligible human subjects planned and enrolled with their consent for fed study. Out of them, twenty eight (28) subjects had completed both the periods of the study.

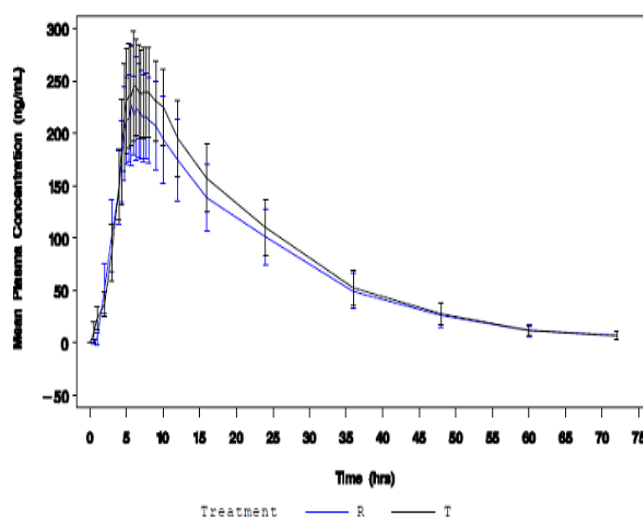


Fig. 1: Mean plasma concentration of Levomilnacipran Test and Reference formulations under fasting condition

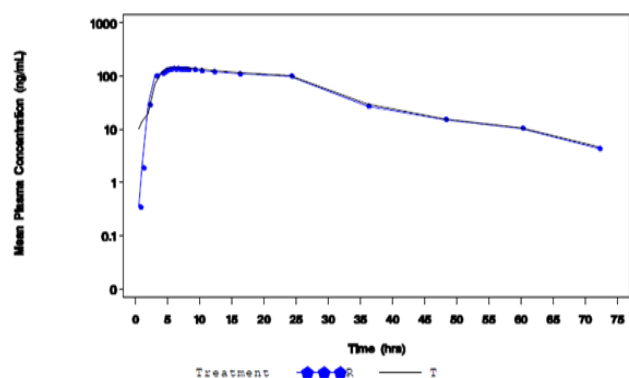


Fig. 2: Semi Logarithmic plot of Levomilnacipran Test and Reference formulations under fasting condition

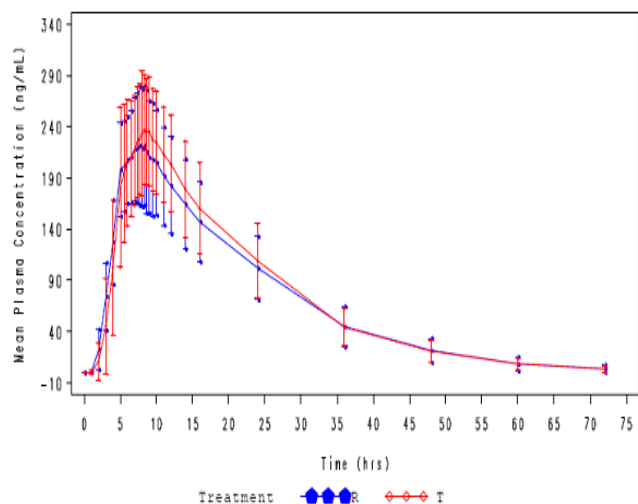


Fig. 3: Mean plasma concentration of Levomilnacipran Test and Reference formulations under fed condition

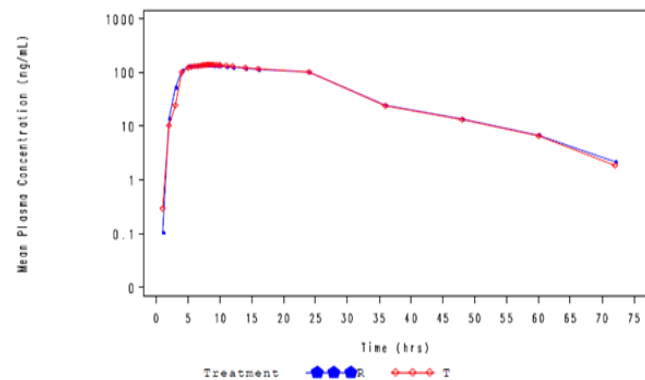


Fig. 4: Semi Logarithmic plot of Levomilnacipran Test and Reference formulations under fed condition

RESULTS AND DISCUSSION

The bioequivalence assessment between the formulation manufactured by Micro Labs and Fetzima is presented below in fasting and fed conditions:

Table 1: Bioavailability assessment for Levomilnacipran 120 mg ER capsule in fasting condition

PK Parameters	Ratio of Geometric Means (%)	90% C.I.	Intra-Subject %CV
AUC _(0-t) (ng.h/mL)	109.85%	104.39% to 115.61%	11.66%
AUC _(0-∞) (ng.h/mL)	109.75%	104.24% to 115.54%	11.75%
C _{max} (ng/mL)	111.72%	104.31% to 119.65%	15.71%

Table 2: Bioavailability assessment for Levomilnacipran 120 mg ER Capsule in fed condition

PK Parameters	Ratio of Geometric Means (%)	90% C.I.	Intra-Subject %CV
AUC _(0-t) (ng.h/mL)	102.09%	94.73% to 110.03%	16.54%
AUC _(0-∞) (ng.h/mL)	102.11%	94.77% to 110.02%	16.47%
C _{max} (ng/mL)	105.18%	96.62% to 114.50%	18.79%

Table 3: Summary of pharmacokinetic parameters in fasting study

PK Parameters	Geometric Mean (%CV)	
	Arithmetic Mean ± SD	
	Test Formulation (T) [n = 30]	Reference Formulation (R) [n = 30]
C _{max} (ng/mL)	263.517 (19.14)	235.880 (25.13)
AUC _(0-t) (ng.h/mL)	267.930 ± 51.280	242.249 ± 60.883
AUC _(0-∞) (ng.h/mL)	5515.270 (18.83)	5020.549 (22.96)
AUC _(0-∞) (ng.h/mL)	5613.849 ± 1057.031	5142.955 ± 1180.732
AUC _(0-∞) (ng.h/mL)	5636.373 (19.34)	5135.843 (23.64)
AUC _(0-∞) (ng.h/mL)	5742.618 ± 1110.472	5268.622 ± 1245.419
%AUC _{extra}	1.893 (52.13)	1.980 (59.82)
Kel _(λ_z) (1/h)	2.142 ± 1.117	2.236 ± 1.337
Kel _(λ_z) (1/h)	0.0580 (13.72)	0.0580 (13.56)
t _{1/2} (h)	0.0585 ± 0.0080	0.0586 ± 0.0079
t _{1/2} (h)	11.95 (13.83)	11.94 (16.32)
t _{1/2} (h)	12.06 ± 1.67	12.08 ± 1.97
T _{max} (h)	6.67 (4.33 - 10.00)	6.00 (4.67 - 9.00)

Table 4: Summary of pharmacokinetic parameters in fed study

PK Parameters	Geometric Mean (%CV)	
	Arithmetic Mean ± SD	
	Test Formulation (T) [n = 28]	Reference Formulation (R) [n = 28]
C _{max} (ng/mL)	251.538 (22.84)	239.147 (22.11)
AUC _(0-t) (ng.h/mL)	259.462 ± 59.263	244.547 ± 54.063
AUC _(0-∞) (ng.h/mL)	4929.344 (24.68)	4828.324 (23.12)
AUC _(0-∞) (ng.h/mL)	5112.519 ± 1261.737	4960.779 ± 1146.987
AUC _(0-∞) (ng.h/mL)	4994.490 (24.93)	4891.227 (23.62)
AUC _(0-∞) (ng.h/mL)	5182.592 ± 1292.218	5030.521 ± 1188.193
%AUC _{extra}	1.024 (75.52)	0.989 (78.06)
Kel _(λ_z) (1/h)	1.300 ± 0.981	1.281 ± 1.000
Kel _(λ_z) (1/h)	0.0777 (19.46)	0.0766 (22.94)
t _{1/2} (h)	0.0792 ± 0.0154	0.0786 ± 0.0180
t _{1/2} (h)	8.92 (19.64)	9.05 (22.94)
t _{1/2} (h)	9.08 ± 1.78	9.28 ± 2.13
T _{max} (h)	8.00 (5.00 - 14.00)	7.17 (5.00 - 12.00)

The safety assessment in the fasting and fed conditions is presented below:

Fasting study

Total thirteen (13) AEs (Adverse Events) were reported by eleven (11) subjects during the study. All thirteen (13) AEs had possible relationship with the IPs. Out of thirteen (13) AEs, seven (07) AEs were mild in nature and six (06) AEs were moderate in nature. All thirteen (13) AEs were resolved.

Out of forty two (42) enrolled subjects,

- Bradycardia was observed in one (01) subject
- Hypertension was observed in one (01) subject
- Tachycardia was observed in one (01) subject
- Vomiting was observed in nine (09) subjects

Fed study

Total ten (10) AEs were reported by ten (10) subjects during the study. All ten (10) AEs had possible relationship with the IPs. Out of ten (10) AEs, seven

(07) AEs were mild in nature and three (03) AEs were moderate in nature. All ten (10) AEs were resolved.

Out of forty one (41) dosed subjects,

- Hypertension was observed in one (01) subject.
- Vomiting was observed in nine (09) subjects.

There was no death or other serious adverse event reported during either of the study.

Bioequivalence

The statistical results indicated that “Test/Reference” ratio of geometric means for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} were within the bioequivalence range of 80.00% to 125.00%.

From the above information, it can be concluded that Levomilnacipran extended release capsules 120 mg of Micro Labs is bioequivalent to Fetzima levomilnacipran extended release capsules 120 mg under fasting and fed condition.

Safety and tolerance

From the assessment of safety presented above, it may be concluded that Levomilnacipran has an adverse drug reaction of vomiting as a total of 18 subjects (9 in fasting and 9 in fed) experienced the same in the studies. Hence, caution should be exercised while using the drug product.

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