CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 July 2013

FROM: Mitchell V. Mathis, M.D.
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TO: File NDA 204168 [25 Sep 2012 submission]

SUBJECT: Approval recommendation for levomilnacipran ER (Fetzima) for the treatment of major depressive disorder (MDD)

Background and Summary
Levomilnacipran is a serotonin norepinephrine reuptake inhibitor (SNRI) approved in racemic form as milnacipran for the treatment of fibromyalgia. The sponsor (Forest Laboratories) submitted efficacy and safety data from five short-term placebo-controlled clinical studies and one open-label extension safety study to support this application. Data from an improperly designed randomized withdrawal study in patients with MDD, (b) (4) were also evaluated as part of the review. There were also 19 clinical pharmacology and biopharmaceutic studies submitted in support of the application.

Four of the five short-term controlled trials were positive at their primary endpoint and support approval. The maintenance trial was defective in design because patients were stable for only two weeks prior to randomization to continue drug or switch to placebo, and that trial failed to show a drug difference in preventing relapse.

Safety findings were as expected from an SNRI (elevated blood pressure/heart rate, mydriasis, urinary retention, sexual dysfunction).

Dose ranging was adequate and we have enough information to label the drug for safety and efficacy. The sponsor has agreed to multiple PMC/PMRs to add to our understanding of how to use the drug safely and effectively (see below).

Chemistry Manufacturing and Controls (CMC)
CMC and Biopharmaceutics reviewers determined the submission to be adequate and acceptable. The Office of Compliance found the manufacturing and testing facilities for the drug product to be acceptable.

Nonclinical Pharmacology/Toxicology
Dr. Ravindran reviewed this application. He determined that the preclinical assessment was adequate to conclude that there are no nonclinical barriers to approval. He has recommended a post-marketing juvenile animal study to assess safety in children less than 12 years old.

Office of Clinical Pharmacology (OCP)
There were 19 clinical pharmacology and biopharmaceutics studies. The sponsor assessed population PK, exposure response, bioavailability, bioequivalence between the different trial and to-be-marketed formulations, food effect, dose-proportionality, and drug-drug interactions. OCP concluded that there is no enantiomeric interconversion of levomilnacipran and that the no dose adjustments were needed based upon age, gender, hepatic impairment, or mild renal impairment and recommend dose adjustments for patients with moderate and severe renal impairment. These intrinsic factors have been forest plotted and included in labeling with the recommendation for reduced dose in patients mod/severe renal impairment.

A ketoconazole interaction study demonstrated an approximate 2-fold increase in levomilnacipran, and so the labeling recommendation is to not exceed 80 mg in these patients. The sponsor agreed with OCP and this information has been included in labeling (80 mg/day maximum when used with all strong 3A4 inhibitors).

Clinical
Dr. Kohli-Chhabra (clinical) and Dr. Birkner (statistics) conducted the efficacy review. The sponsor provided results from five short-term, double-blind, randomized, parallel-group, placebo-controlled, efficacy and safety trials and one longer-term maintenance trial. These studies evaluated levomilnacipran ER doses in adult outpatients with MDD in a range of 40-120 mg/day. The primary endpoint in the trials was change from baseline to endpoint in Montgomery Asberg Depression Rating Scale (MADRS) total score. The key secondary endpoint in the trials was change from baseline to endpoint in Sheehan Disability Scale (SDS) total scores. Three positive studies for the labeling efficacy claim were the focus of our review: 2 fixed-dose studies (LVM-MD-01 and LVM-MD-10) and 1 flexible-dose study (LVM-MD-03). The sponsor submitted their positive phase 2 non-US study (F02695 LP202) as a supportive study. In one other short-term flexible dose US study (LVM-MD-02) and the longer-term maintenance study (LVM-MD-05), the drug did not separate from placebo for efficacy. These two studies were reviewed, but not covered in detail. All short-term studies were 8 week placebo-controlled studies except for the non-US study which was a 10 week study. No active control was used in any of these studies. The clinical and statistical teams have reviewed these studies and have recommended approval.

LVM-MD-01
This was an 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter, outpatient study in adult patients (18-65 yrs) with MDD comparing three fixed doses of levomilancipran ER (40, 80 and 120 mg/day) vs. placebo. This was a US study. Primary efficacy results are presented below.

Change from baseline to endpoint of MADRS total score: ITT population

Treatment (N)	Baseline Mean $\pm$ SD	LS mean change from baseline (SE)	Placebo-subtracted difference (CI)	p-value (vs. placebo)
Levomilnacipran ER 40 mg (N=176)	36$\pm$4.5	-14.8 (1)	-3.2 (-5.9, -0.5)	0.0186
Levomilnacipran ER 80 mg (N=177)	36.1$\pm$3.9	-15.6 (1)	-4.0 (-6.7, -1.3)	0.0038
Levomilnacipran ER 120 mg (N=176)	36$\pm$3.9	-16.5 (1)	-4.9 (-7.6, -2.1)	0.0005
Placebo (N=175)	35.6$\pm$ 4.5	-11.6 (1)		

The Sheehan Disability total score was the key secondary efficacy variable and it too was positive at 80 mg and 120 mg.

LVM-MD-10
This was an 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter, outpatient study in adult patients (aged 18-75 yrs) with MDD comparing fixed doses of levomilancipran ER (40 and 80 mg/day) vs. placebo and was conducted in 47 US and 4 Canadian centers. Primary efficacy results are presented below.

Change from baseline to endpoint of MADRS total score: ITT population

Treatment (N)	Baseline Mean ± SD	LS mean change from baseline (SE)	Placebo-subtracted difference (CI)	p-value (vs. placebo)
Levomilnacipran ER 40 mg (N=185)	30.8±3.4	-14.6 (0.8)	-3.3 (-5.5, -1.2)	0.0027
Levomilnacipran ER 80 mg (N=187)	31.2±3.5	-14.4 (0.8)	-3.1 (-5.3, -1.0)	0.0043
Placebo (N=185)	31± 3.8	-11.3 (0.8)		

LVM-MD-03
This was an 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter (23 US centers), outpatient study in adult patients (18-80 years old) with MDD comparing flexible dose levomilancipran ER (40 -120 mg/day) vs. placebo. Primary efficacy results are presented below.

Change from baseline to endpoint of MADRS total score: ITT population

Treatment (N)	Baseline Mean ± SD	LS mean change from baseline (SE)	Placebo-subtracted difference (CI)	p-value (vs. placebo)
Levomilnacipran ER 40-120 mg (N=215)	35±3.6	-15.3 (0.8)	-3.1 (-5.3, -0.9)	0.005
Placebo (N=214)	35.2± 3.8	-12.2 (0.8)		

The key secondary Sheehan Disability total score was also statistically superior to placebo.

F02695 LP2 02
This was a 10-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter (68 non-US centers), outpatient study in adult patients with MDD comparing flexible dose levomilancipran ER (75-100 mg/day) vs. placebo. Primary efficacy results are below.

Change from baseline to endpoint of MADRS total score: ITT population

Treatment (N)	Baseline Mean ± SD	LS mean change from baseline (SE)	Placebo-subtracted difference	p-value (vs. placebo)
Levomilnacipran ER 75-100 mg (N=276)	30.7±4	-18.7 (0.6)	-4.2	<0.0001
Placebo (N=277)	30.5±4	-14.5 (0.6)		

The Sheehan Disability total score was also statistically significant.

LVM-MD-02
This study was an 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter, outpatient, 24 center US study in adult patients with MDD comparing flexible dose

levomilancipran ER (40 -120 mg/day) vs. placebo. This was a negative study, likely due to smaller sample size. Primary efficacy results are presented below.

Change from baseline to endpoint of MADRS total score: ITT population

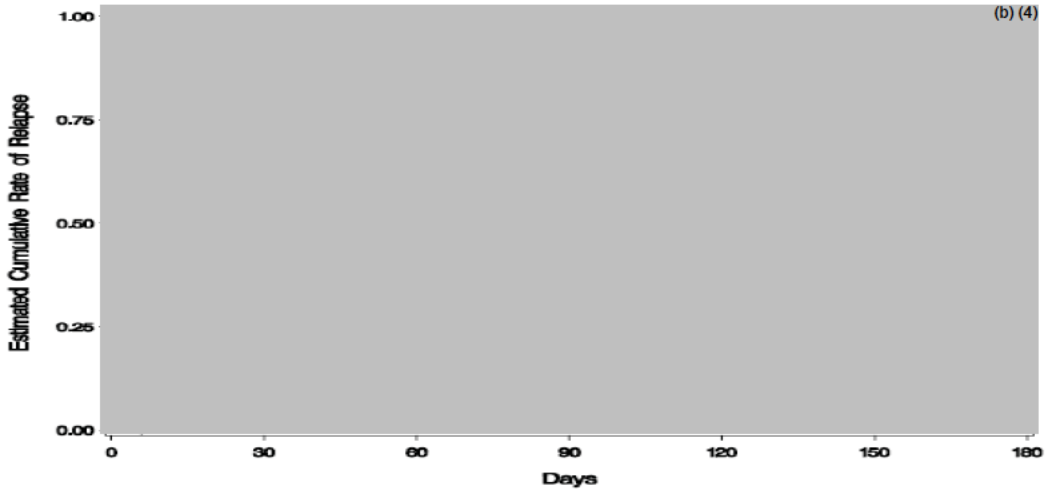
Treatment (N)	Baseline Mean + SD	LS mean change from baseline (SE)	Placebo-subtracted difference	p-value (vs. placebo)
Levomilnacipran ER 40-120 mg (N=135)	(b) (4)			
Placebo (N=153)	35.5± 0.3	-14.2 (0.8)		

LVM-MD-05

This study was (b) (4): after 12 week open-label treatment with levomilnacipran 40-120 mg in which patients who meet responder criteria at week 10 and 12 were randomized to a 24 week double-blind treatment period to continue treatment with levomilnacipran (40-120 mg/day) or placebo and observed for relapse. This was an outpatient study in 30 US and 6 Canadian sites. Primary efficacy was time to relapse and the data are presented below.

Time to relapse in the double-blind period (ITT population)

Time to relapse	Levomilnacipran ER 40-120 mg (N = 230)	Placebo (N = 112)
Number of patients relapsed, n (%)	(b) (4)	23 (20.5)
Number of patients censored, n (%)		89 (80)
Hazard ratio (95% CI)		
p-value		



Note: Day to relapse was calculated as date of relapse – date of randomization + 1.
ITT – intent to treat; SR – sustained release.

Comment: It is very unusual for an antidepressant with multiple positive short-term studies to not demonstrate a difference from placebo in a maintenance study. I believe the primary reason this study was negative is because the patients were only stable for 2 weeks prior to randomization. We have asked the sponsor to repeat this study with a better design post-marketing and they have agreed. Labeling will have our usual advice about continuing treatment past the initial response.

Comments on Efficacy
The clinical and statistical teams have concluded that the sponsor has provided sufficient evidence of efficacy, and I agree with them. We have negotiated a PMC to repeat the randomized withdrawal trial with a more standardized design and the sponsor has agreed to comply.

Dose response is evident from the fixed dose studies in the range of 40 mg to 120 mg. OCP concurred with the sponsor that doses below 40 are not likely to confer efficacy based upon model extrapolation from exposure/efficacy data collected in the fixed dose studies. The 20 mg dose is used as the dose for treatment initiation only, and that has been made clear in labeling.

Study	Primary efficacy/method	Levomilnacipran 40 mg	Levomilnacipran 80 mg	Levomilnacipran 120 mg
LVM-MD-01	MADRS (MMRM)	-3.2 (-5.9, -0.5)	-4.0 (-6.7, -1.3)	-4.9 (-7.6, -2.1)
LVM-MD-10	MADRS (MMRM)	-3.3 (-5.5, -1.2)	-3.1 (-5.3, -1.0)	N/A

There were no differential effects identified from subgroup analyses excepting that males had a larger treatment effect in study 10 and Whites had a larger response than other races (majority of the study population was Caucasian).

The key secondary endpoint, the Sheehan Disability Scale, was positive in several trials, and so we will include a description of this in labeling. We have negotiated labeling to say that the scale measures dysfunction, and that the score improved on drug, (b) (4)

Safety
Dr. Farchione completed the safety review. A total of 2655 patients/subjects were exposed to drug in the MDD development program; 1583 in the short-term trials; 691 for at least 24 weeks; 324 for at least 48 weeks. Total exposure correlates to approximately 900 patient-years.

Serious Adverse Events (SAE)
There were two deaths that cannot be reasonably attributed to drug and 35 non-fatal SAEs reported in 25 patients. Eleven patients experienced SAEs in the controlled portion of the short-term trials and 4 of these events were determined by the investigators to be drug-related: aggression, suicidal ideation, hypertension, non-cardiac chest pain, premature infant, and small for dates pregnancy. Six of these 11 patients were discontinued from the study due to the SAE.

Class Safety
Relevant safety issues for the SNRI class include suicidal thoughts and behavior, serotonin syndrome, abnormal bleeding, activation of mania, discontinuation syndrome, hyponatremia, and mydriasis. These are all described and discussed in the clinical safety review and have been included in labeling.

Hypertension
SNRIs are known to increase blood pressure as a class. The mean increase (from the short-term controlled trials, measured as change from baseline to the end of treatment) in levomilnacipran-treated patients for systolic blood pressure (SBP) was 3.0 mm Hg (as compared to 0.4 mm Hg decrease in placebo) and diastolic blood pressure (DBP) was 3.2 mm Hg (no change in DBP in

placebo-treated patients). No dose-dependent relationship of blood pressure changes was observed among patients in the levomilnacipran 40 mg, 80 mg, and 120 mg groups in the fixed-dose studies.

Based on BP readings at the end of the double-blind treatment period, 10.4% of the levomilnacipran-treated patients who had normal or prehypertensive BP readings at baseline had a hypertensive reading at the end of the treatment period compared with 7.1% of placebo patients.

The proportion of patients who met the sustained hypertension criteria was slightly greater with levomilnacipran than with placebo. In the fixed-dose studies, the incidence of sustained hypertension among levomilnacipran-treated patients did not suggest a dose relationship.

Six levomilnacipran-treated patients were discontinued for BP increase or hypertension. In the placebo group, two patients were prematurely discontinued for BP increased (one reported as SAE).

Labeling has addressed increases in blood pressure in Warnings and Precautions and states that blood pressure should be monitored prior to and during treatment.

Elevated Heart Rate
SNRIs cause increased heart rate as a class. The mean increase in heart rate at endpoint in levomilnacipran-treated patients was 7.4 bpm compared to a mean decrease of 0.3 bpm in placebo patients. The mean increase in heart rate at endpoint in levomilnacipran-treated patients was 7.4 bpm compared to a mean decrease of 0.3 bpm in placebo patients. In the fixed-dose studies, a greater mean increase in heart rate was observed in the levomilnacipran 120-mg dose group (9.1±10.6 bpm, n=177) relative to lower-dose levomilnacipran groups 7.2±10.2 bpm (n=363) and 7.2±11.5 bpm (n=367) increases in the 40 mg and 80 mg dose groups, respectively [0.0±9.0 bpm in the placebo group (n=360)].

Labeling has addressed elevations in heart rate in Warnings and Precautions and physicians are instructed to monitor their patients prior to and during treatment.

Urinary Retention
Urinary Hesitation or Retention (noradrenergic effect) was seen in the short-term controlled trials (7.9% on drug compared to 0.9 percent on placebo). The sponsor has included this in Warnings and Precautions and we agree that it should be prominently labeled.

Sexual Dysfunction
Spontaneous reports revealed a higher percentage of levomilnacipran treated patients had treatment-emergent sexual dysfunction. The sponsor included the Arizona Sexual Experiences Scale (ASEX) in one short-term trial, but there was no positive control in that study (b) (4) .

Elevated Liver Enzymes
There were no patients who met Hy's Law criteria for potential drug-induced liver injury or who had ALT or AST above 3 times the upper limit of normal and bilirubin higher than 1.5 times the upper limit of normal. There were slight increases in AST/ALT in levomilnacipran treated patients compared to placebo, but these were not clinically significant. The milnacipran label identifies an association between drug and liver enzyme elevation and even mentions postmarketing cases of severe liver injury, but the cases were confounded by underlying illness and use of multiple

concomitant medications. Because levomilnacipran is different from milnacipran and does not convert isomeric form, it is possible that even if the severe cases of liver injury seen with milnacipran are related to drug, they could be due to the other isomer and not levomilnacipran.

Common AEs
The most frequently reported drug-related AEs (≥ 5% and twice the rate of placebo) in short term controlled studies were nausea (17.1% in levomilnacipran vs. 4.1% in placebo), constipation (8.5% vs. 3.0%), hyperhidrosis (8.5% vs. 1.1%), erectile dysfunction (5.7% vs. 2.2%), heart rate increased (5.7% vs. 0.8%), tachycardia (5% vs. 1.7%), palpitations (5% vs. 0.8%), and vomiting (5% vs. 0.6%). These events are identified in labeling and included in the Highlights of Prescribing section.

Long-term safety
Results from the longer-term open label safety data are consistent with the short-term controlled studies and no additional safety issues were identified by the clinical team.

Safety Conclusions
Levomilnacipran is an SNRI and has a safety profile consistent with its pharmacology.

Inspections
OSI has concluded that data from the 6 sites they audited are reliable and acceptable.

Labeling
Labeling is in PLR format and has been negotiated to current Division standards.

Postmarketing Requirements/Commitments
The sponsor has agreed to conduct several studies postmarketing. These include:

- Maintenance of efficacy trial with an adequate period of stabilization (PMC)
- Pediatric development program (two safety and efficacy studies covering the age ranges as well as supportive pharmacology/toxicology and PK studies) (PMR)

Conclusions and Recommendations
Sufficient information has been submitted to conclude that levomilnacipran ER is safe and effective for the treatment of MDD. The review team has recommended approval and I agree.

The labeling and Medication Guide have been negotiated to current Division standards.

The sponsor has agreed to labeling and PMC/PMRs, and I anticipate that this application will be approved by the PDUFA date.

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/s/

MITCHELL V Mathis
07/25/2013