CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204168Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	*{See Appended Electronic Signature Page}*
From	Ni A. Khin, M.D. Lead Medical Officer Division of Psychiatry Products, HFD-130 Office of Drug Evaluation I, Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER)
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA#	NDA 204168
Applicant Name	Forest Laboratories Inc.
Date of Submission/Received Date	September 25, 2012
PDUFA Goal Date	July 25, 2013
Drug Name	Levomilnacipran
Dosage Forms / Strength	20, 40, 80 and 120 mg oral capsules; extended release formulation
Proposed Indication(s)	Major Depressive Disorder
Recommended Action:	Approval

1. INTRODUCTION

This NDA seeks a claim for levomilnacipran in the treatment of major depressive disorder (MDD). Levomilnacipran is a levo-enantiomer of milnacipran. Although the exact mechanism of action is unknown, its antidepressant effect is thought to be related to serotonin and norepinephrine reuptake inhibition (SNRI). It is available as 20 mg, 40 mg, 80 mg and 120 mg extended-release capsules. The recommended dose is 40 mg to 120 mg once daily.

Other antidepressant agents approved in the U.S. for MDD include tricyclics (such as imipramine, desipramine), monoamine oxidase inhibitors (tranylcypromine, isocarboxazid, and selegiline patch), selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline, paroxetine, citalopram, and escitalopram), serotonin and norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, duloxetine), and others (e.g. bupropion, trazodone).

This NDA contains efficacy and safety data from five short-term placebo-controlled clinical studies and one open-label extension safety study. Additionally, data from one longer-term, relapse prevention study and some safety data from a clinical study in (b) (4) were submitted with the NDA. The sponsor also included data from 19 clinical pharmacology and biopharmaceutic studies.

The review team consists of:

Material Reviewed/Consulted	Name of discipline reviewers
Clinical Reviewers*, DPP	Kavneet Kohli-Chhabra, M.D. Tiffany Farchione, M.D.
OB: Statistical Reviewer	Thomas Birkner, Ph.D.
Pharmacology Toxicology Reviewer, DPP	Arippa Ravindran, Ph.D.
ONDQA: CMC Reviewer Biopharmaceutics Reviewer	Pei-I Chu, Ph.D. Akm Khairuzzaman, Ph.D.
OCP: Clinical Pharmacology Reviewer	Kofi Kumi, Ph.D.

* Since Dr. Kohli-Chhabra was unable to complete the entire clinical review, Dr. Farchione was assigned to the team on June 4, 2013 to complete the safety review.

Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Consultants: Office of Scientific Investigations, GCP OSE/DMEPA QT consult OPDP consult PLT PMHT: Pediatrics PMHT: Maternal Health	 John Lee, M.D. Loretta Holmes, BSN, Pharm.D. Janice Brodsky, Ph.D., and IRT Susannah O'Donnell, MPH Twanda Scales, RN, MSN Amy Taylor, MD Carrie Ceresa, Pharm.D., MPH
Regulatory Health Project Manager, DPP	Juliette Toure, Pharm.D.

2. BACKGROUND

The IND development program of levomilnacipran (F2695) was initiated under IND#104,483 by Forest. F2695 is the levo isomer of the racemate milnacipran (F2207) which was approved in January 2009 for the treatment of fibromyalgia under the tradename Savella. The development program of levomilnacipran was focused on its use in the treatment of MDD in adults.

The Division held a number of meetings with the sponsor during the IND development including an end-of-phase 2 (EOP2) and pre-NDA meetings. During the EOP2 teleconference meeting (5/18/2009), the sponsor stated they would develop this drug as a sustained release formulation, not as an immediate release formulation. They also stated that they would use Sheehan Disability Scale as key secondary in the pivotal efficacy studies. (b) (4) At pre-NDA meetings (1/25/2012 and 5/4/2012), the sponsor sought to get the Division's agreement on the content and the format of this NDA submission.

(b) (4)

(b) (4)

3.0 CHEMISTRY, MANUFACTURING AND CONTROL (CMC)

Dr. Pei-I Chu conducted the CMC review of this NDA (see review dated 6/24/13 and amended review on 6/25/13). The drug product is a capsule, which contains extended-release beads with 23.0, 45.9, 91.8, or 137.8 mg of levomilnacipran HCl equivalent to 20, 40, 80, or 120 mg of levomilnacipran, respectively. Levomilnacipran (1S, 2R) is the more active form of the two enantiomers present in the racemate milnacipran. The sponsor selected common excipients for the capsule formulation. The drug substance has a good solubility. In February 2013, ONDQA sent an information request to the sponsor asking them to provide information on analytical methods used to accept drug substance, the stability protocol for the first 3 commercial batches and their justification on proposed dissolution acceptance criteria using IVIVC model. Dr. Chu noted that sponsor's response (including updated post-approval stability commitment) dated 3/6/13 was evaluated and found to be adequate. The sponsor's request for categorical exclusion was also found acceptable and is granted.

According to the Biopharmaceutic review by Dr. Khairuzzaman (dated 5/20/2013), the formulation development and the manufacturing process development are considered acceptable. Although the sponsor's initial proposed acceptance criteria for dissolution testing of the drug product were not found to be acceptable, the sponsor provided adequate justification regarding the dissolution acceptance criteria using IVIVC as outlined in the Agency's guidance for the in vitro/in vivo correlations of the ER oral dosage forms. Dissolution profile was found to be stable. Based on the compositionally proportional formulation of the drug products of different strengths and the linear pharmacokinetics of this drug, it was recommended that the bio-waiver request for the lower strength be granted. Regarding the alcohol dose dumping, the results of *in-vitro* study showed a pronounced drug release ((b) (4) dissolved at 30 minutes) with 40% v/v alcohol. The sponsor's in-vivo simulation was also evaluated and determined that the sponsor's request for the waiver for an in-vivo alcohol dose dumping is appropriate. The product label should convey a standard statement "as with other psychotropic medications, the use of alcohol by patients taking levomilnacipran is not recommended."

The Office of Compliance (inspections conducted by Office of Regulatory Affairs) found the manufacturing and testing facilities for the drug product to be acceptable.

Both CMC and Biopharmaceutics reviewers have recommended for an approval action.

4.0 NON-CLINICAL PHARMACOLOGY/TOXICOLOGY

In Dr. Ravindran's review dated 6/17/2013, he concluded that levomilnacipran was adequately assessed in nonclinical studies to support its approval. The findings with levomilnacipran in animal toxicity studies are summarized below:

General toxicities: Levomilnacipran did not appear to have significant toxicity up to one half of the dose that produced convulsions and/or death in rats and in monkeys. Exposure levels that resulted in convulsions and/or deaths in animals were above the levels in human at therapeutic doses.

Developmental and Reproductive toxicities: Reduced fetal body weights and delayed skeletal ossification were observed in both rats and rabbits at doses up to 2.4 times and 5 times the MHRD, respectively. Reduction in maternal body weight was also noted. Levomilnacipran was not found to have any teratogenic effects in either species.

Genotoxicity: Levomilnacipran was not found to be genotoxic in both *in-vitro* and *in-vivo* assays.

Carcinogenicity: Carcinogenicity studies were conducted in rats (2 years) and transgenic mice (6 months). No significant findings were reported in these studies.

The sponsor will be asked to submit a protocol to conduct a post-marketing juvenile animal study in rats to support the use of levomilnacipran in children less than 12 years of age.

5.0 CLINICAL PHARMACOLOGY

OCP review (dated 6/17/2013) noted that there were19 clinical pharmacology and biopharmaceutics studies, population PK, exposure response analyses, and 14 *in-vitro* studies in this submission. The evaluation included relative bioavailability (BA), bioequivalence (BE) between the clinical trial

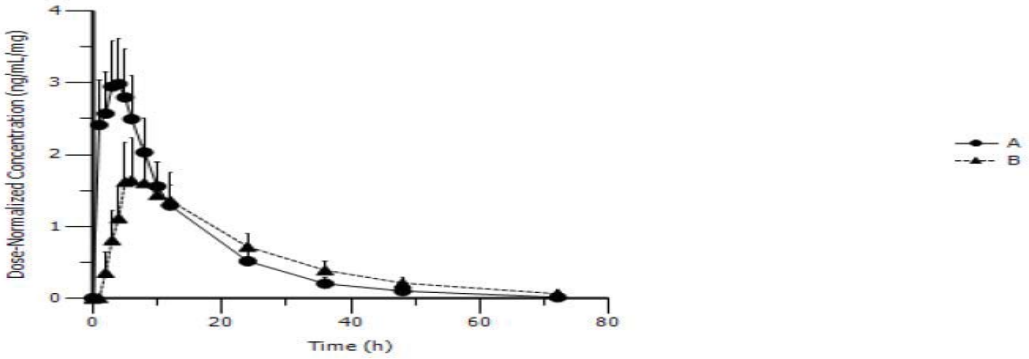
(CTM) and to be marketed (TBM) formulations, food effect, dose-proportionality, and drug-drug interaction studies.

A summary of ADME as presented by Dr. Kofi Kumi is excerpted below.

- Absorption
  - Relative BA 92% (oral solution as reference)
  - No significant effect of food
    - Levomilnacipran can be taken with or without food
  - Dose proportional
    - 25 to 120 mg after single dose
  - CTM bioequivalent to TBM
  - Levomilnacipran ER exhibits extended release characteristics
- Distribution
  - Widely distributed
  - 22% Protein binding
- Metabolism
  - CYP 3A4 primary enzyme
  - N-desethyl Levomilnacipran (F17400) major metabolite (inactive)
- Excretion
  - Renal (~94%), Feces (~4%)
  - ~ 58% of dose unchanged excreted in urine, 18% N-desethyl (F17400)
  - T ½ ~ 12 - 13 hours
- Interconversion
  - No interconversion observed in vivo

The following relative bioavailability figure illustrates the time-concentration profile for levomilnacipran.

Figure 1: Mean plasma concentration versus time profile following administration of a single dose 40 mg oral solution as compared 120 mg oral ER capsule formulation

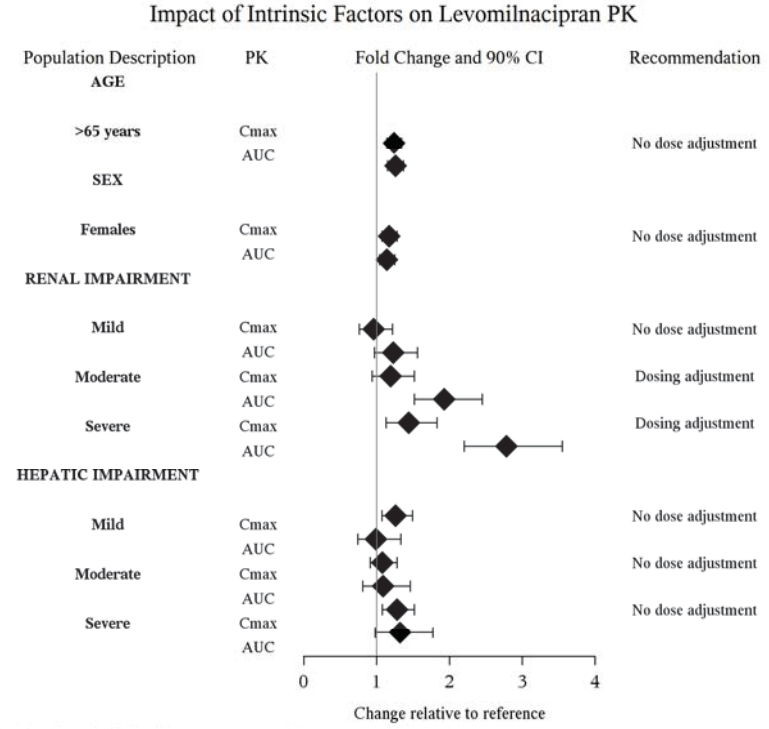


Note:
A: Levomilnacipran solution formulation, 40 mg
B: Levomilnacipran SR formulation, 120 mg
Subjects who experienced vomiting were excluded.

The effect of intrinsic and extrinsic factors on the PK of levomilnacipran was also reviewed by OCP. The sponsor provided change in Cmax and AUC values along with the proposed dosing recommendation, as can be seen in the following Forest plots.

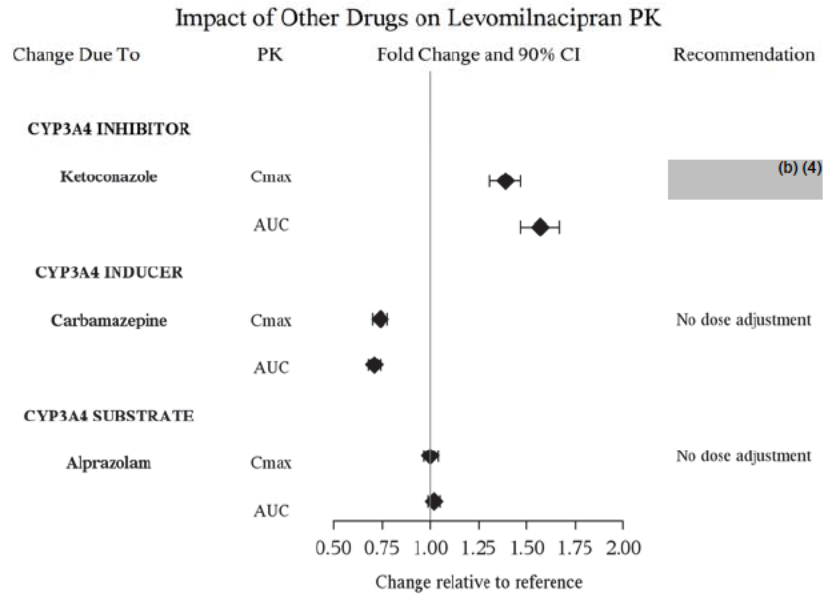
Regarding the effect of intrinsic factors, findings suggest that no dose adjustment is needed based on age, gender, hepatic impairment and mild renal impairment. OCP recommends dose adjustment for patients with moderate and severe renal impairment, not to exceed 60 mg and 40 mg, respectively.

Figure 2: The effect of Intrinsic Factors on Levomilnacipran PK



Regarding the effect of other drugs on levomilancipran (figure 3), the study revealed a concern for PK interaction with strong CYP3A4 inhibitors. Based on the finding with ketoconazole 80 mg, OCP asserts that the AUC (~ 1.5 - 2 fold) would further increase with the higher dose of levomilnacipran (e.g. 120 mg) when it is used concomitantly with strong 3A4 inhibitors. Therefore, OCP (b) (4) is recommending the dose of levomilnacipran should not exceed 80 mg with strong 3A4 inhibitors. No dose adjustment is needed with 3A4 inducers (e.g., carbamazepine) or 3A4 substrates (e.g., alprazolam).

Figure 3: Effect of Other Drugs on Levomilnacipran PK



The sponsor collected plasma PK in one fixed-dose efficacy study. The pharmacometrics reviewer conducted exposure-response analysis for that study (see figure 3 in OCP review).

Additionally, the sponsor conducted a randomized, placebo and active-controlled (moxifloxacin 400 mg), thorough QT study (LVM-PK-07) in which the effect of levomilnacipran (120 and 300 mg) on the QTc interval was evaluated in 170 healthy subjects. The maximum mean difference (upper bound of the 95% confidence interval), placebo-adjusted, baseline-corrected QTc interval was about the same, 7.3 (10.8) for the levomilnacipran 120 (therapeutic) and 7.5 (10.5) ms for the 300 mg (supratherapeutic) doses, based on the individual correction method (QTcI). Although this is slightly above the 10 ms threshold cut-off generally used for clinical concern, the QT-IRT noted that this modest QT prolongation has no apparent dose or exposure-response relationship. No subject was observed QTcI above 480 ms. There was one subject (1.2%) who experienced QTcI change greater than 60 ms with levomilnacipran 120 mg. An increase in heart rate with no dose or concentration dependency (~20 bpm) was observed for both doses. An increase in blood pressure (Systolic BP ~7 mm Hg, diastolic BP 12 mm Hg) was also noted. The QT-IRT recommended that changes to labeling language be made but the placement of the TQT description can stay in section 12.2.

6.0 CLINICAL MICROBIOLOGY

Not applicable.

7.0 CLINICAL/STATISTICAL - EFFICACY

7.1 Overview of Studies Pertinent to Efficacy

In this NDA, 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 was change from baseline to endpoint in Montgomery Asberg

Depression Rating Scale (MADRS) total score. The key secondary endpoint was change from baseline to endpoint in Sheehan Disability Scale (SDS) total scores. Three positive studies for labeling 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 failed to separate from placebo in efficacy. These two failed studies were reviewed, but not covered in detail. All short-term studies were 8 week placebo-controlled studies except that the non-US study was a 10 week study. No active control was used in any of these studies. I would briefly describe each of these studies in the subsection below. I would refer to Dr. Birkner's statistical review dated 6/14/13 for details.

7.2 Summary of Studies Pertinent to Efficacy Claim in Treatment of MDD

7.2.1 Study 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. After one week of single-blind placebo run-in period, eligible subjects who were randomized to levomilnacipran ER was given 20 mg for the first two days and titrated to the target doses of 40, 80 (Day 4) or 120 mg (Day 7) over a 7-day period. Patients were evaluated at week 1, 2, 4, 6 and 8 of the double-blind treatment period, followed by a two week of double-blind down-taper period.

The study was conducted in 38 U.S. study sites. A total of 724 subjects were randomized. Of 713 who received at least one dose of study medication, 704 had at least one post-baseline assessment for efficacy in the intent-to treat (ITT) population (176, 177, 176 and 175 in the levomilnacipran ER 40, 80, 120 mg and the placebo groups, respectively). 506 subjects (130 in 40 mg, 121 in 80 mg, 117 in 120 mg and 138 in placebo) completed the study and 207 discontinued. The overall discontinuation rate was slightly higher for the three levomilnacipran ER groups; 27%, 32%, 35% vs. 21.6% in placebo. The common reasons for discontinuation included withdrawal of consent (7.7%), adverse events (7.6%), lost to follow up (6.6%) and protocol violation (4.6%). For lack of efficacy, it was slightly higher in placebo; 4% vs. approx. 2% for the drug groups.

The mean (SD) age of all subjects was 41 years. The majority of subjects were female (63%) and Caucasian (74%). The mean baseline scores of efficacy parameters were around 36 for MADRS total score and 21 for SDS total scores. Demographic characteristics and baseline disease rating scale total scores were similar among the treatment groups in the ITT population.

The primary efficacy endpoint was change from baseline to end of study (week 8) of the MADRS total score. The primary efficacy analysis was performed using a Mixed Model Repeated Measures (MMRM) model with treatment group, pooled study center, visit, and treatment group by visit interactions as fixed effects and the baseline score and baseline-by-visit interaction as covariates. The Hochberg multiple-comparison procedure was used to control the family-wise error rate. Two sensitivity analyses were conducted: LOCF-ANCOVA and a pattern-mixture model. Dr. Birkner confirmed the sponsor's study results. Primary efficacy results are summarized in table below.

Table 1: 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=176)	36±4.5	-14.8 (1)	-3.2 (-5.9, -0.5)	0.0186
Levomilnacipran ER 80 mg (N=177)	36.1±3.9	-15.6 (1)	-4.0 (-6.7, -1.3)	0.0038
Levomilnacipran ER 120 mg (N=176)	36±3.9	-16.5 (1)	-4.9 (-7.6, -2.1)	0.0005
Placebo (N=175)	35.6± 4.5	-11.6 (1)		

The key secondary efficacy parameter was change from baseline to week 8 in Sheehan Disability total score. Results showed statistically superiority for levomilnacipran 80 and 120 mg, placebo-subtracted difference around -2.5 for both doses. Dr. Birkner noted in his statistical review that 27% of SDS baseline scores for the ITT population were missing for this study.

Comment: The review team considered this a positive study for levomilnacipran ER, and I agree with them.

7.2.2 Study 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 three fixed doses of levomilancipran ER (40 and 80 mg/day) vs. placebo. After one week of single-blind placebo run-in period, patients who were randomized to levomilnacipran ER was given 20 mg for the first two days and then titrated to the target doses of 40 (Day 3) or 80 mg (Day 6). Patients were evaluated at week 1, 2, 4, 6 and 8 of the double-blind treatment period, followed by a two week of double-blind down-taper period.

The study was conducted in 47 U.S. and 4 Canadian centers. A total of 568 patients were randomized. Of 562 who received at least one dose of study medication, 557 had at least one post-baseline assessment for efficacy in the intent-to treat (ITT) population (185, 187 and 185 in the levomilnacipran ER 40, 80 mg and the placebo groups, respectively). 441 subjects (145 in 40 mg, 142 in 80 mg, and 154 in placebo) completed the study and 124 discontinued. The overall discontinuation rate was slightly higher for the 80 mg levomilnacipran ER group, 25% compared to 22% in the 40 mg and 17% in placebo. The common reasons for discontinuation included withdrawal of consent (8%), lost to follow up (7%), and adverse events (6%). For lack of efficacy, the rate was around 2% for all treatment groups.

The mean age of all subjects was 42.8 years. The majority of subjects were female (64%) and Caucasian (74%). The mean baseline scores of efficacy parameters were around 31 for MADRS total score and approximately 17 for SDS total scores. Demographic characteristics and baseline disease rating scale total scores were similar among the treatment groups in the ITT population.

The primary efficacy endpoint was change from baseline to end of study (week 8) of the MADRS total score. The primary efficacy analysis was performed using a Mixed Model Repeated Measures (MMRM) model. The statistical analysis methods were identical to study LVM-MD-01. Dr. Birkner confirmed the sponsor's study results. Primary efficacy results are summarized in table below.

Table 2: 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)		

The key secondary efficacy parameter was change from baseline to week 8 in Sheehan Disability total score, which showed statistical superiority of levomilnacipran 40 and 80 mg, with placebo-subtracted difference of -1.8 and -2.7, respectively.

Comment: The review team considered this a positive study for levomilnacipran ER, and I agree with them.

7.2.3 Study LVM-MD-03

This was an 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter, outpatient study in adult patients (18-80 yrs) with MDD comparing flexible dose levomilancipran ER (40 -120 mg/day) vs. placebo. After one week of single-blind placebo run-in period, subjects who were randomized to levomilnacipran ER in the 8 weeks of double-blind treatment period was first given 20 mg for two days and increased the dose to 40 mg per day. Based on response (<50% improvement in MADRS total) and tolerability, investigators could make possible dose increases to 80 mg at week 1 and 2, and up to 120 mg at week 4 during the double-blind treatment. No dose increase was allowed after week 4. Patients were evaluated at week 1, 2, 4, 6 and 8 of the double-blind treatment period, followed by a two week of double-blind down-taper period.

The study was conducted in 23 U.S. centers. A total of 442 patients were randomized. Of 434 who received at least one dose of study medication, 429 had at least one post-baseline assessment for efficacy in the intent-to treat (ITT) population (215 in the levomilnacipran ER 40-120 mg and 214 the placebo group). 335 subjects (163 in the drug group, and 172 in placebo) completed the study and 99 discontinued. The overall discontinuation rate was 25% for the levomilnacipran ER group and, 21% for the placebo. The common reasons for discontinuation included lost to follow up (7%), and adverse events (6%) in which a higher proportion of patients discontinued due to adverse events with levomilnacipran (8% vs. 3% in placebo). For lack of efficacy, the rate was around 2% for both treatment groups.

The mean age of all subjects was around 45 years. The majority of subjects were female (65%) and Caucasian (83%). The mean baseline scores of efficacy parameters were around 35 for MADRS total score and approximately 20 for SDS total scores. Demographic characteristics and baseline disease rating scale total scores were similar among the treatment groups in the ITT population.

The primary efficacy endpoint was change from baseline to end of study (week 8) of the MADRS total score. The primary efficacy analysis was performed using a Mixed Model Repeated Measures (MMRM) model. The statistical methods used to analyze data from this study were the same as studies 01 and 10. Dr. Birkner confirmed the sponsor's study results. Primary efficacy results are summarized in table below.

Table 3: 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 efficacy parameter, change from baseline to week 8 in Sheehan Disability total score, also showed statistical superiority for levomilnacipran, as compared to placebo (-2.6, p=0.001).

Comment: The review team considered this a positive study for levomilnacipran ER, and I agree with them.

7.2.4 Study F02695 LP2 02

This was a 10-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter, outpatient study in adult patients with MDD comparing flexible dose levomilancipran ER (75-100 mg/day) vs. placebo. At randomization, subjects were stratified each center based on the MADRS total score at baseline (<30 Stratum 1 vs. ≥30 Stratum 2). Patients who were randomized to levomilnacipran ER in the 10 weeks of double-blind treatment period were forced titrated with 25 mg for 3 days, 50 mg from Day 4 to 7, and then 75 mg from Day 8 to 11. Based on patient tolerability as judged by investigator, patient was continued on 75 mg or increased up to 100 mg at Day 12 during the double-blind treatment. No dose increase was allowed after week 4. Patients were evaluated at Day 14, 21, 28 and 42 of the double-blind treatment period, followed by one week of down-taper period.

The study was conducted in 68 non-US centers including 11 sites in France, 5 in Bulgaria, 5 in Czech Republic, 4 in Estonia, 7 in Finland, 7 in Germany, 8 in India, 2 in Latvia, 5 in Lithuania, 6 in Sweden and 8 in South Africa. A total of 563 patients were randomized. Of 557 who received at least one dose of study medication, 553 had at least one post-baseline assessment for efficacy in the intent-to treat (ITT) population (276 in the levomilnacipran ER 75-100 mg [71.6% on 100 mg dose] and 277 the placebo group). 426 subjects completed the study and 127 discontinued. The overall discontinuation rate was 20% for the levomilnacipran ER group and, ~25% for the placebo. The common reasons for discontinuation included consent withdrawal (12%), and therapeutic failure (11%) in which a higher proportion of patients discontinued due to treatment failure in placebo (14% vs. 8% in drug).

The mean age of all subjects was 44 years. The majority of subjects were female (67%) and Caucasian (91%). The mean baseline scores of efficacy parameters were 30.6 for MADRS total score (around 27 for the Stratum 1, 33 for the Stratum 2) and 26 for SDS total scores. Demographic characteristics were similar between the drug and placebo groups. Baseline disease rating scale total scores were also similar between the two strata as well as between the drug and placebo groups in the ITT population.

The primary efficacy endpoint was change from baseline to end of study (Day 70) of the MADRS total score. The primary efficacy analysis was performed using a Mixed Model Repeated Measures (MMRM) model. The model included treatment, center and visit as main effects, baseline MADRS

total score as covariate, and treatment-by-visit and baseline-by-visit interactions. Dr. Birkner confirmed the sponsor's study results. Primary efficacy results are summarized in table below.

Table 4: 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 secondary efficacy parameter, change from baseline to week 10 in Sheehan Disability total score, also showed statistically significant result for levomilnacipran, as compared to placebo (-3.4, $p<0.0001$).

Comment: Although it was a positive study, the sponsor considered this as supportive and did not wish to describe efficacy results as part of the clinical study section in the label. Their approach seemed fine with me. Although the doses used in this study fall within the ranges used in the three positive studies, the relevance in clinical practice seemed limited. Perhaps, it may be confusing for prescribers, as these doses were different (75-100 mg) than the to-be-marketed doses (40-120 mg).

7.2.5 Study LVM-MD-02

This study was another 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.

Table 5: 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)		

Comment: This is a failed study. No active control for assay sensitivity was included in this study. Although the design was similar to the other positive flexible dose study (study 03), the sample size for each treatment arm in this study was smaller. The placebo response in this study was somewhat larger.

7.2.6 Study LVM-MD-05

This study consisted of a 12 week open-label treatment with levomilnacipran 40-120 mg in which patients who were stable to meet responder criteria at week 10 and 12, were randomized into a 24 week double-blind treatment period to continue treatment with levomilnacipran (40-120 mg/day) or placebo and observed for relapse. Response criteria included MADRS total score ≤12 and CGI-I ≤ 2 study on weeks 10 and 12 of the open-label period. Relapse criteria were one of the following: MADRS total score ≥22 at 2 consecutive visits, ≥2points increase in CGI-I score at consecutive visit as compared to randomization visit (Visit 9), discontinuation from the study because of an insufficient response or MADRS item 10 score ≥4.

This study was conducted as an outpatient study in 30 sites in the US and 6 centers in Canada. A total of 734 subjects were enrolled into the 12-week open-label treatment with levomilnacipran ER 40-120 mg/day. Of these, 724 patients had at least one MADRS assessment; 494 patients completed the open-label treatment period. Responders (N=348) were then randomized 2:1 into a double blind treatment with levomilnacipran 40-120 mg/day (n=235) or placebo (n=113). There was one subject who had no post-baseline efficacy assessment. The Intent-to-treat (ITT) population for the primary efficacy analysis was 348 subjects: levomilnacipran 40-120 mg/day (n=235) or placebo (n=113).

Treatment groups were comparable on the demographic variables. Mean age was 43 years. The majority of patients were females (58%) and Caucasians (75%) in this study. Mean (SD) and median doses of levomilnacipran during the open label treatment were 79 (26.3) mg and 80 mg, respectively. Regarding the proportion of stable patients randomized into the double-blind treatment, a slightly higher trend for earlier stability was observed for those assigned to placebo (35% at week 4) as compared to the drug group (25%).

The primary efficacy endpoint was time to relapse during the double-blind treatment. The primary analysis compared the time from randomization to relapse using the Cox proportional hazards regression model. Dr. Birkner confirmed the sponsor's results. As Dr. Birkner noted, the estimated hazard ratio of (b) (4), which indicated a reduced risk of relapse for the levomilnacipran group; yet, the result was found to be not statistically significant (Table 6).

The Kaplan-Meier curves for cumulative rates of relapse were also compared (see figure extracted from sponsor's submission below).

Figure 4: Kaplan-Meier Curve for cumulative rate of relapse, ITT Population

Table 6: Primary efficacy parameter: Time to relapse in the double-blind period (ITT population)

Time to relapse	Levomilnacipran ER 40-120 mg (N = (b) (4)	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		

Comment: This study was considered a failed study. Dr. Birkner noted in his statistical review, as one of the conjectures, why he thinks this study failed was that, the sample size was calculated with an expectation of higher relapse rates in both treatment groups (38% for placebo and (b) (4) for drug), while the actual relapse rates observed in this study were much lower, in particular, for placebo (20.5% for placebo and (b) (4) for drug).

The longer-term maintenance efficacy of antidepressants is usually assessed in post-marketing studies. In our recent exploratory analysis of maintenance efficacy studies for approved antidepressant products, we have observed that, despite various definitions of responder and relapse criteria were used, almost all MDD maintenance studies with other approved antidepressants were successful†. In these studies, mean relapse rate of placebo was around 37% (SD=11) and for the study drug groups was (b) (4) Of note, the Division's requirement for a12-week stabilization in responder status criteria is fairly recent, and therefore, only one trial included this requirement.

As stated in both clinical and statistical reviews, the short-term study data provide sufficient evidence for the efficacy of levomilnacipran in treatment of MDD. We will be asking the sponsor to conduct a longer-term maintenance study with an adequate period of stabilization, as part of their post-marketing commitment.

7.3 Comments on Other Important Efficacy Issues

7.3.1 Subgroup Analyses: Clinical Predictors of Response

The sponsor conducted exploratory analyses based on the following subgroups:

- Sex (Male, Female)
- Age (<55 or ≥55 yrs)
- Race (Caucasians, Other races)

Treatment effect was observed in both males and females in all studies except that males showed a larger effect in Study 10. For the age subgroups, it did not reveal any differential effect. Regarding race, the reduction in the MADRS total score was larger for Whites (-3 to -4.6) as compared to other races (0.3 to -2.5) across the studies. Given the majority of the study population was Caucasian and the size of all other races was too small, it is difficult to have a meaningful interpretation of such data.

7.3.2 Dose Response Relationship

As can be seen in the table below, in study LVM-MD-01, there appeared to show a good dose response numerically. However, there seemed no difference between the two doses (40 and 80 mg) in study LVM-MD-10.

Table 7– LS mean difference (95% CI) in change from baseline to primary efficacy endpoint total score in short-term, fixed Dose, MDD Trials

† Borges, S. FDA Review of Maintenance Trials for Major Depressive Disorder: A 25 year perspective. Regulatory Plenary Presentation, NCDEU meeting, 2012.

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

The sponsor has not studied the efficacy of doses less than 40 mg. We will request that the sponsor agrees to conduct a study for lower effective dose(s) as a post-marketing commitment.

7.3.3 Size of Treatment Effect

The treatment effect sizes observed in these short-term trials with levomilnacipran were similar to those observed in trials with other approved antidepressant drugs at effective doses.

7.3.4 Duration of Treatment

The short-term efficacy studies were 8-10 week studies. Their longer-term study (LVM-MD-05) was designed to have stabilization at week 10 and 12 of the 12-week open-label treatment. The patient enrollment in the open label phase and randomization to double-blind treatment was already completed when the Division communicated with the sponsor about the requirement of a 12 week stabilization period. It seemed the number of events observed in this study was insufficient to have a meaningful interpretation of data. We should get an agreement from the sponsor, as a post-marketing commitment, a longer-term maintenance study with an adequate period of stabilization would be conducted.

7.3.5 Secondary Efficacy Variable

The Sheehan Disability Scale (SDS) was pre-specified as key secondary efficacy variable. In 3 positive studies, the SDS results favored for the study drug. These results are sufficient to support inclusion of a statement that the drug showed superiority over placebo based on this key secondary endpoint in labeling.

7.4 Conclusions Regarding Efficacy Claim in Treatment of MDD

The sponsor has provided sufficient data to support the efficacy claim of milnacipran in the acute treatment of MDD.

8.0 SAFETY

8.1 General Safety Considerations

The clinical safety review completed by Dr. Farchione focused on safety data from 5 short-term placebo-controlled MDD studies (study LVM-MD-01, 02, 03, 10 and F02695 LP2 02**)**. Safety data from open-label extension study (study LVM-MD-04) and other patient population (b) (4) was reviewed. Additional safety data from clinical pharmacology studies in normal volunteers and MDD relapse prevention study (LVM-MD-05) was also reviewed.

A total of 2655 subjects were exposed to levomilnacipran in the MDD clinical development program. In the controlled short-term trials, 1583 patients were exposed to levomilnacipran. Six

hundred ninety-one patients were exposed for at least 24 weeks, with 324 patients exposed for at least 48 weeks. The total exposure in clinical studies was 899.5 patient-years.

The 120-day safety update data was also considered. The clinical review (section 7.7) covered the safety findings from an additional 46 patients.

8.2 Major Safety Findings and Issues of Particular Interest

8.2.1 Serious Adverse Events (SAE)

There were two deaths. One patient died reportedly from accidental drowning after screening visit with no exposure to study drug. Another patient who received open label treatment of levomilnacipran for 224 days died 42 days after she discontinued from the study from gastric adenocarcinoma.

In short-term trials, there were 35 non-fatal SAEs reported in a total of 25 individual patients (0.07% levomilnacipran vs. 1.3% of patients receiving placebo). Of the 11 patients on levomilnacipran who experienced SAEs in the double-blind period, four experienced events that were deemed drug-related by the sponsor which included aggression, suicidal ideation, hypertension, non-cardiac chest pain, premature baby, and small for dates baby. Six of these 11 patients were discontinued from the study; and additional two temporarily discontinued treatment. Additional SAE cases observed in the longer-term open-label study, the relapse prevention study and the clinical pharmacology studies were also reviewed (refer to section 7.3.2 of clinical review).

8.2.2 Important class-related safety issues

The sponsor's evaluation of the relevant safety issues for this class of antidepressants regarding suicidal thoughts and behavior, serotonin syndrome, abnormal bleeding, activation of mania, discontinuation syndrome, hyponatremia, and mydriasis, are described and discussed in the clinical safety review. The proposed product label seems to adequately address these issues including the standard boxed warning for antidepressants and the class language in the warnings and precautions. We would just need to reorder the subsections based on the level of clinical concerns with this drug. I would briefly describe some issues of particular interest in this memo.

8.2.3 Hypersensitivity Reactions

Two patients (0.1%) experienced AEs of hypersensitivity on levomilnacipran compared to one (0.1%) on placebo. Six patients (0.4%, n= 6/1583) discontinued in the levomilnacipran treatment group secondary to skin rash, two of these patients had a history of hypersensitivity, no patients listed in the AE dropout due to skin rash for placebo. Most of the rashes were considered mild or moderate, and no cases of Stevens-Johnson Syndrome or angioedema were reported. Select cases are described briefly the clinical safety review (refer to section 7.3.3 of clinical review).

Hypersensitivity to both levomilnacipran and milnacipran including any excipients in the formulation will be included as part of contraindication in the product label.

8.2.4 Elevated Blood Pressure

As expected for an SNRI, in the short-term controlled studies, the mean increases, as measured by change from baseline to the end of treatment, in levomilnacipran-treated patients for systolic blood pressure (SBP) of 3.0 mm Hg (as compared to 0.4 mm Hg decrease in placebo) and diastolic blood pressure (DBP) of 3.2 mm Hg (no change in DBP in placebo-treated patients). No dose-dependent relationship to 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: as defined, by a relatively broader criteria, in terms of SBP $\geq$ 140 mm Hg and increase $\geq$ 15 mm Hg "OR" DBP $\geq$ 90 mm Hg and increase $\geq$ 10 mm Hg for at least 3 visits (1.8% in drug vs. 1.2% in placebo); and for a stricter criteria, SBP $\geq$ 140 mm Hg and increase $\geq$ 15 mm Hg "AND" DBP $\geq$ 90 mm Hg and increase $\geq$ 10 mm Hg for at least 3 visits (0.3% in drug vs. 0.1% in placebo). In the fixed-dose studies, the incidence of sustained hypertension among levomilnacipran-treated patients did not suggest any dose relationship.

The proportion of patients who met orthostatic hypotension criteria (reduction in SBP of $\geq$ 20 mm Hg or reduction in DBP of $\geq$ 10 mm Hg while changing from the supine to standing position) was also slightly higher in the levomilnacipran arm (11.6%) relative to placebo (9.7%). The incidences of patients who met either the SBP or DBP criterion for orthostatic hypotension were higher in all levomilnacipran dose-levels compared to placebo. For the fixed dose studies, the percentage of patients with orthostatic hypotension was higher in all three levomilnacipran dose groups relative to placebo but there was no clear trend suggesting a dose-dependent increase.

Regarding the dropouts due to abnormal blood pressure category, 6 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).

8.2.5 Elevated Heart Rate

In the short-term controlled studies, 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 among 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 among 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$\pm$10.6 bpm, n=177) relative to lower-dose levomilnacipran groups 7.2$\pm$10.2 bpm (n=363) and 7.2$\pm$11.5 bpm (n=367) increases in the 40 mg and 80 mg dose groups, respectively [0.0$\pm$9.0 bpm in the placebo group (n=360)].

Nine patients in the levomilnacipran group were prematurely discontinued for TEAEs of tachycardia or heart rate increase. In the placebo group, one patient was prematurely discontinued for tachycardia.

8.2.6 Narrow-Angle Glaucoma

The incidence rate of adverse reactions related to mydriasis in the levomilnacipran-treated patients was 0.9% as compared to none in the placebo group. The fixed dose studies did not suggest any dose dependency. None of the events were reported as SAEs and no levomilnacipran-treated patients were discontinued from the study for AEs related to mydriasis. All mydriasis cases were considered either mild or moderate in severity. None of levomilnacipran-treated patients developed narrow angle glaucoma. Of note, patients with a history of narrow angle glaucoma were excluded from all short-term trials.

The sponsor's proposal to include a contraindication in patients with uncontrolled narrow angle glaucoma and a warning and precaution for controlled narrow-angle glaucoma along with the findings of mydriasis in the levomilnacipran treated patients seemed non-objectionable. Within this class of SNRI antidepressants, the level of warning language in product labels varies in regard to this issue. The Division's safety team is working this as a class issue in consultation with the Ophthalmology Division. Additional labeling change will likely be made for consistency when that review is complete.

8.2.7 Urinary Retention

As noted by Dr. Farchione in the clinical review, adverse event rates of obstructive uropathies in the short-term studies were higher in the levomilnacipran arm (7.9%) compared to the placebo arm (0.9%). In fixed-dose trials, dose dependent increases were seen for the TEAE of urinary hesitation (3.6% in 40 mg/day; 4.9% in 80 mg/day; 6.1% in 120 mg/day). Almost all events of dysuria and urinary hesitation had occurred in male patients. A total of 6/63 (9.5%) patients with TEAE of urinary hesitation and 5/24 (20.8%) patients with TEAEs of dysuria were prematurely discontinued from the study. The sponsor's proposal to include this category under the warnings and precautions is reasonable.

8.2.8 Liver Function Tests

In the short term studies, no patients met Hy's law criteria for potential drug-induced liver injury or had ALT or AST ≥ 3 times upper limit of normal (UNL) and total bilirubin ≥ 1.5 x UNL. A higher percentage of patients with potentially clinically significant values observed in the levomilnacipran-treated group for the following liver function test parameters:

Table 8: The percentage of patients with PCS values for LFTs in short-term controlled studies

	ALT		AST		ALT or AST		Total Bilirubin		Alkaline Phosphatase	
	≥3UNL	≥5UNL	≥3xUNL	≥5xUNL	≥3xUNL	≥5xUNL	1.5ULN	2ULN	1.5ULN	3ULN
Levomilnacipran 40-120 mg/day	0.6%	0.2%	0.7%	0.2%	0.7%	0.4%	0.2%	0.2%	0.3%	0
Placebo	0	0	0.1%	0	0.1%	0	0.1%	0	0	0

A slight increase in mean change from baseline to endpoint was observed for ALT of 2.6 U/L in levomilancipan, as compared to 0.5 U/L for placebo. Similar mean change for AST of 2.3 U/L in levomilnacipran vs. 0.2 for placebo was observed.

One subject discontinued due to abnormal LFT. This 33 yr old patient with no significant medical history showed elevated ALT 133 U/L and AST 73 U/L on Day 27 of double-blind treatment with levomilancipran, in the flexible dose study (study 02), of 40-120 mg/day (the actual dose for this

patient was not provided in case narrative). Both alkaline phosphatase and total bilirubin were within normal limit. With drug discontinuation on Day 32, AST returned to normal within a week, and ALTs were decreasing (but remained slightly elevated 61 U/L) at end of study follow up.

8.2.9 Sexual Dysfunction

Based on spontaneous reports of SD in short-term controlled trials, a higher percentage of levomilnacipran-treated male patients reported treatment-emergent adverse reactions associated with sexual dysfunction compared with placebo-treated patients, erectile dysfunction, ejaculation disorder, and testicular pain of 5.9%, 4.7%, and 3.8% respectively. In fixed-dose trials, the incidence of erectile dysfunction was found to be dose-dependent: 5.5% in the 40 mg group, 8.3% in the 80 mg group, 9.5% in the 120 mg group, and 2.2% in the placebo group.

The sponsor included the Arizona Sexual Experiences Scale (ASEX) only in one short-term trial (LVM-MD-02). A major limitation of interpreting the ASEX data is that there was no positive control in the study. In addition, the sponsor presented the ASEX results based on their analysis on mean change data. The ASEX is designed for a categorical, not continuous, fashion.

8.2.10 Common Adverse Reactions

The most frequently reported AEs (≥ 5% and twice the rate of placebo) of levomilacipran 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%).

8.2.11 Longer-term safety data

In general, the longer-term open label safety data seemed to be consistent with short-term placebo-controlled studies. No additional concern identified.

8.3 Conclusion Regarding Safety Data

The safety profile of levomilnacipran, as reported in both short-term and longer term studies, seemed similar to the overall safety profile observed in other SNRIs. These safety findings should be adequately described in the product labeling.

9.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

During the review cycle, the review team discussed and determined not to take it to the PDAC given this NDA did not identify new efficacy or safety concern as levomilnacipran is another SNRI in this class of approved drugs.

10.0 PEDIATRICS

The sponsor has requested for a pediatric waiver (age 0-6 yrs) and a deferral (age 7-17 yrs) in MDD with this NDA as the adult studies are completed and ready for approval. The sponsor's pediatric

plan includes two controlled efficacy and safety MDD studies. The first fixed-dose adolescent study (12-17 yrs) will utilize simulation and PK modeling from adult data for dose selection. Upon completion of at least 50% of adolescent patients from the first study, the sponsor also plans to do simulation and PK modeling to select the dosing regimen for children (b) (4) in the second pediatric study (7-17 yrs). We discussed the sponsor's proposal with the FDA's Pediatric Review Committee (PeRC) on 6/5/13. The committee recommended that the Division ask the sponsor to move up on their proposed protocol submission and the study report submissions dates. We will obtain the sponsor's agreement to conduct these controlled efficacy and safety studies in children and adolescents with MDD as part of post-marketing PREA requirements. We will also get an agreement with the sponsor to conduct a juvenile animal study to support the use in pediatric population (<12 yrs).

11.0 OTHER RELEVANT REGULATORY ISSUES

11.1 OSI Clinical Site Inspections

The following clinical investigator sites were selected for inspection based on the fact that these sites enrolled a relatively large number of subjects with significant contribution to overall product efficacy and multiple studies were conducted at the same site.

Investigator Name	Site #	Study #	Number of subjects
N. Vatakis	32	LVM-MD-01	19
Z. Benzar	51 04	LVM-MD-03 LVM-MD-10	28 12
A. Horwitz	58 17	LVM-MD-03 LVM-MD-10	31 24
A. Khan	33	LVM-MD-10	33

According to OSI clinical inspection summary report dated 5/23/13, it was concluded that all audited study data appeared reliable.

11.2 Other Outstanding Regulatory Issues

According to Dr. Kohli-Chhabra, there seemed no major financial disclosure issue (except for 4 with incomplete report was identified) with this NDA.

11.3 World Literature

The sponsor reported that they conducted a comprehensive literature review covering the period through 12/10/12 utilizing Ovid MEDLINE, BIOSIS Previews, and EMBASE. Publications (including posters and abstracts) reported were based on data from the sponsor's clinical studies. The literature review did not seem to show findings that would adversely affect their conclusions regarding the efficacy and safety profile of levomilnacipran.

11.4 Other Discipline Consults

11.4.1 Professional Promotion and Drug Advertisement

Both Office of Prescription Drug Promotion and Office of Medical Policy/Patient Labeling Team reviewed the proposed product labeling (including Med Guide) with the Division's edits. Their comments were discussed at the labeling meeting on 6/24/13, and the relevant issues, as pointed by them, are addressed in the label.

11.4.2 Labeling Team

The review team followed the labeling guidance provided by the SEALD. The proposed trade name, Fetzima, is acceptable per DMEPA.

12.0 LABELING

All disciplines provided their labeling comments. Some modifications to the sponsor's proposed language were made. Additional editorial changes were made to the sponsor's proposed label to reflect current labeling format guidelines according to the Physician Labeling Rule (PLR). I would reiterate some points, which were already mentioned in the summary of our FDA labeling changes in the clinical review, below.

Boxed Warning:
The language related to suicidal thoughts and behavior has been updated in content and format to match current class labeling. The content, however, has not been changed
Indications and Usage

- (b) (4)
- To meet requirements of the single enantiomer exclusivity, a limitation of use statement was added noting that efficacy and safety of this product in fibromyalgia have not been established.

Dosage and Administration

- Under *Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant [2.5]*, the recommendation to allow (b) (4) days after stopping this product before starting an MAOI was changed to 7 days (b) (4)
- Dosing recommendations for concomitant use with strong inhibitors of CYP3A4 were added.

Warnings & Precautions

- Subsections were reordered to reflect decreasing order of clinical concern.
- Language under *Suicidal Thoughts and Behavior [5.1]* and *Serotonin Syndrome [5.2]* was modified to reflect current class language.
- Data pertaining to mean increases in SBP and DBP, and to orthostatic hypotension was added to *Elevated Blood Pressure [5.3]*.

Adverse Reactions

- The list of common adverse reactions was reordered to reflect decreasing incidence.
- The sponsor was asked to group similar event terms for 1) palpitation, heart rate increased, and tachycardia; 2) increased blood pressure and hypertension. The sponsor was asked to recalculate the percent of patients experiencing these events for Table 3, and to insert a footnote which terms were combined.
- Language related to the thorough QT study was modified to reflect our view that QTc prolongation, although modest, was observed.

Drug Interactions

- Recommendations regarding dose adjustment when this product is co-administered with inhibitors of CYP3A4 were added, and the rest of *Potential for Other Drugs to Affect TRADENAME* was expanded and reformatted.
- *Potential forTRADENAME to Affect Other Drugs* was similarly expanded and reformatted.
- The sponsor was asked to modify the forest plot presented in Figure 1 to reflect the revised dosing recommendations by OCP.
- The sponsor was asked to include an additional forest plots to describe the study results based on alprazolam or carbamazepine.
- *Central Nervous System (CNS)-Active Agents* was combined with *Alcohol*.

Use in Specific Populations

- This section was updated to be more consistent in content and format with other SNRIs.
- (b) (4)
- The sponsor was asked to include recommended dose adjustments under *Renal Impairment [8.7]*.

Clinical Pharmacology

- *Mechanism of Action [12.1]* was updated with current class language.
- QT information with revised language was moved to *Pharmacodynamics [12.2]*.

Clinical Studies

- Information presented in the primary efficacy table was removed from the text.
- (b) (4)

How Supplied/Storage and Handling

- Titration pack information was removed.

We have sent the label with our edits to the sponsor on 06/27/13. Labeling negotiations are underway.

13.0 RECOMMENDATION/RISK BENEFIT ASSESSMENT

In my view, the sponsor has submitted sufficient data to support the conclusion that levomilnacipran is effective and acceptably safe in the treatment of MDD in adults. I recommend the approval of this NDA once we reach agreement on final labeling with the sponsor.

cc: HFD-130/Mathis/Kohli-Chhabra/Farchione/Grewal/Toure
File: NK/NDA204138/Memo_N204138_07012013.doc

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

/s/

NI A KHIN
07/02/2013