CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 25, 2013
Reviewer:	Somya Dunn, M.D. Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D., DRISK
Division Director	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Fetzima (levomilnacipran hydrochloride) F2695
Therapeutic Class:	Antidepressant
Dosage and Route:	20 mg, 40 mg, 80 mg, and 120 mg oral capsules
Application Type/Number:	NDA/204-168
Submission Number:	Supporting Document 1 (Sequence 0000)
Applicant/sponsor:	Forest Laboratories, Inc.
OSE RCM #:	2012-2420

1 INTRODUCTION

This review documents DRISK's evaluation to assess the need for a Risk Evaluation and Mitigation Strategy (REMS) for Fetzima® (levomilnacipran) oral tablets. The New Drug Application (NDA 204-168) was submitted by Forest Laboratories, Inc. on September 25, 2012 and is currently under review in the Division of Psychiatry Products (DPP) for the treatment of Major Depressive Disorder (MDD).

1.1 BACKGROUND

Fetzima is a selective serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) reuptake inhibitor (SNRI). It is an active enantiomer of milnacipran. Milnacipran is currently approved for treatment of fibromyalgia in the United States (Savella® approved 2009). In some European and Asian countries, milnacipran is approved for treatment of MDD.

A sustained-release (SR) formulation of levomilnacipran, which allows for once-daily dosing, was used for the development program and is to be the marketed dosage form. The Sponsor asserts that the efficacy and safety data demonstrate that Fetzima improves symptoms and functionality in MDD patients and is generally well tolerated in the intended population.

Depression affects approximately 18 million adults in the United States at a given time. The prevalence in the U.S. alone is 8.3% and likely on the rise. The Sponsor's rationale for additional therapies for MDD includes the significant burden that the disease puts on patients, their families and society. Overall economic burden may be reduced by providing appropriate treatment. The current major treatment options for MDD in the United States include Monoamine Oxidase Inhibitors (MAOIs), Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), SNRIs, and atypical antidepressants. Fetzima is similar to other SNRIs (duloxetine, venlafaxine, and desvenlafaxine); however, it preferentially inhibits the reuptake of NE over 5-HT in vitro by approximately two-fold.

If approved, Fetzima SR capsules will be marketed in 20 mg, 40 mg, 80 mg, and 120 mg strengths. The proposed dosing regimen is for patients to be initiated at 20 mg for two days then increased to 40 mg daily. The dose can be increased in increments of 40 mg at intervals of two days if needed. The maximum recommended dose is 120 mg.

The SNRIs share a mechanism of action with the SSRIs and as a result have a similar safety profile. This includes an increased risk of suicidality, serotonin syndrome, increased blood pressure and heart rate and abnormal bleeding. There is a contraindication in this class of medication for patients that are on MAOIs due to the risk of serotonin syndrome.

The submission did not contain a REMS proposal.

1.2 REGULATORY HISTORY

- The Sponsor had a Type B End-of-Phase-2 meeting with the Agency on May 18, 2009. At this meeting the Phase III clinical program was discussed including the planned primary endpoint. The Sponsor discussed their plans to monitor for

sexual side effects seen in antidepressants, as well monitor for blood pressure and heart rate effects.

- In a Type C meeting in March 2010, the Sponsor and the Agency discussed the Sponsor's plans to evaluate improvement (b) (4) in their clinical program.
- The Type B Pre-NDA Meeting held on May 4, 2012 focused on the content and format of the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS). The need for a REMS was not discussed.
- In August 2012 the company was notified that if they submitted the application on or after October 1, 2012, their application would be under "The Program" of PDUFA V. In this case, they were strongly encouraged to discuss the need for a REMS before submission.
- Forest Laboratories, Inc. NDA for Fetzima was received on September 25, 2012 for indication of treatment for MDD. The action goal date is July 25, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The materials that informed this review were:

- Forest Laboratories, Inc. Clinical Overview for Fetzima (levomilnacipran), received September 25, 2012
- Forest Laboratories, Inc. Summary of Clinical Safety for Fetzima (levomilnacipran), received September 25, 2012
- Forest Laboratories, Inc. Summary of Clinical Efficacy for Fetzima (levomilnacipran), received September 25, 2012
- Forest Laboratories, Inc. Draft Labeling for Fetzima (levomilnacipran), received September 25, 2012 and December 18, 2012

3 RESULTS OF REVIEW OF PROPOSED FETZIMA RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The Fetzima clinical program included a total of five short-term, placebo-controlled studies in adult patients with MDD. These included three pivotal short-term (8 weeks) double-blind, placebo-controlled studies, one supportive short-term (10 weeks) double-blind, placebo-controlled study, and one short-term (8 weeks) double-blind placebo-controlled study. These studies provided the main safety database, Group1. In addition, one study investigating relapse prevention was also conducted. There was also a 48-week open-label safety extension study.

The efficacy of Fetzima was established in the three pivotal studies and one supportive study. In each of the four studies, statistically significant improvement was seen for the

Fetzima treated group relative to placebo in the primary (change from baseline to endpoint in the Montgomery-Åsberg Depression Rating Scale [MADRS] total score).

A total of 2655 patients were exposed to Fetzima for a total of 899.5 patient-years. A total of 324 patients were exposed for at least 48 weeks. Additionally, 637 subjects in clinical pharmacology and biopharmaceutical studies received Fetzima.

3.2 SAFETY CONCERNS

The antidepressant class of medication—SSRIs share one mechanism of action with Fetzima (reuptake inhibition of serotonin). These drugs contain labeling with a boxed warning for risk of suicidal thinking or behavior. This would be a particular concern with Fetzima since it directly affects the serotonin pathways. In Group 1, most adverse events (AEs) associated with suicidality were similar in both of the treatment groups. However, suicidal ideation was higher in the Fetzima treated patients than placebo (0.4% versus 0.1%). The Sponsor has proposed a boxed warning for suicidality, consistent with the current milnacipran label.

No deaths occurred in the Fetzima clinical development program during study treatment. Two deaths occurred outside of the treatment period which do not appear related to the study. In the short term controlled treatment periods, the Serious Adverse Event (SAE) rate for Fetzima treated patients was lower than that of placebo treated patients (0.7% vs. 1.3%). There were five SAEs per 100 patient years of Fetzima exposure compared with approximately nine SAEs per 100 patient years in the placebo group. No single SAE occurred more than once in the Fetzima treated patients. There was one SAE of a suicide attempt in a Fetzima treated patient.

The Sponsor reports that of the AEs considered by their investigators to be both severe and to be drug-related, the only one observed in at least 1% of patients was headache (1.1% for levomilnacipran vs. 0.4% for placebo). The most common reported AE in Fetzima treated patients was nausea. According to the Sponsor, of the AEs that occurred more commonly in Fetzima treated , most did not demonstrate a dose-dependent relationship with the exception of urinary hesitation and erectile dysfunction. There was no serotonin syndrome or neuroleptic malignant syndrome seen in the clinical program.

The AE profile was expected and consistent with that described in the currently approved and marketed milnacipran label with the following exception. Labeling for milnacipran discusses [redacted] (b) (4) under *Warnings and Precautions* (WP) which has not been a remarkable safety issue for Fetzima. This WP is being investigated but, according to the review division, was not a significant safety signal for either milnacipran or Fetzima in premarket clinical trials. [redacted] (b) (4) . The review division is internally discussing the need for labeling regarding this issue. However, there is no concern with [redacted] (b) (4) at this time that would warrant a REMS. Labeling for Fetzima will be consistent with milnacipran and approved SSRIs, except as noted above.

Overall, there were no unexpected serious AEs observed or unusual rates of serious AEs associated with Fetzima that would require a REMS.

4 DISCUSSION

Fetzima is an SNRI currently under review for the indication treating MDD. The review division has indicated there are no concerning AEs or unique safety signals that would warrant a REMS. The Sponsor has proposed labeling that discusses the risks associated with this type of medication and they have also included a boxed label warning for suicidality. These measures are sufficient to address this risk and are consistent with that seen in SSRI labeling. The sponsor has also provided a proposed Medication Guide discussing the risks, including suidicality, on a patient friendly level.

5 CONCLUSION/RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling and a Medication Guide are not warranted for Fetzima at this time. The safety issues identified with Fetzima are consistent with currently approved SSRIs and can be communicated in the label.

Should DPP raise additional concerns with risks discussed in this review, or identify additional risks associated with Fetzima warranting more extensive risk mitigation or a formal REMS, please send a consult to DRISK.

This memo serves as the primary DRISK review for Fetzima under NDA 204-168. Please notify DRISK if you have any questions.

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

/s/

KIMBERLY LEHRFELD
07/24/2013
Final REMS Review: Recommendation is that a REMS is not required.

CLAUDIA B MANZO
07/24/2013
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