New Molecular Entity (NME) Post-Marketing Safety Evaluation Pilot Program Progress Report

1. Introduction

The purpose of this report is to describe the progress to date on the FDA Center for Drug Evaluation and Research (CDER) pilot program to assess the value of regular and systematic evaluation of the safety of new molecular entities (NMEs). NMEs are products that include an active substance that has never before been approved for marketing in any form in the United States. This project is led by the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) within CDER.

This effort is in addition to CDER's current postmarketing evaluations. Staff in OSE and OND review the postmarketing safety of marketed drug and therapeutic biologic products continuously as part of their core functions. Activities include review of the reports of serious and unexpected adverse drug experiences that must be submitted to FDA by manufacturers within 15 days, the periodic safety reports that are submitted to the FDA by drug companies, and reports of serious problems sent to FDA directly by healthcare professionals and consumers. FDA also considers information from the medical literature, data from clinical trials, information from other members of a drug's pharmacologic class, and information from other sources.

The purpose of the pilot program, which began in January, 2007, is to determine the value of an additional effort: the periodic systematic and collaborative review of the safety of marketed drugs. To examine the value of these reviews, a sample of NMEs with different durations of marketing and different extents of use were chosen for evaluation. The results of the pilot program are intended to help FDA determine the value of such regular reviews for all, or a specified subset of, NMEs. The pilot program is also expected to provide valuable information about the required resources and appropriate methods for conducting such a systematic evaluation.

The selection of NMEs for evaluation in the pilot program was based on three criteria:

(a) Length of time on market – NMEs that had been marketed for varying lengths of time were selected to evaluate when after approval there would be sufficient information to conduct a useful safety evaluation.

(b) Number of post-marketing reports in the Adverse Event Reporting System (AERS)[1]– NMEs with varying numbers of reported adverse events in AERS were selected to obtain information as to whether there should be a "threshold" number of reports in AERS before conducting an evaluation.

[1] The Adverse Event Reporting System (AERS) is a computerized database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. For more information see http://www.fda.gov/cder/aers/default.htm.

(c) Indication – NMEs with a variety of indications (e.g., psychiatric, neurologic, cardiac) were selected to assess the usefulness of the evaluation across many different drugs.

The NME evaluation consists of a comprehensive review of safety data, including a review of adverse event reports in FDA's Adverse Event Reporting System (AERS) database, a data mining analysis of AERS data, a review of sponsor-submitted periodic safety reports, a literature review, a medication error analysis, an analysis of product use, and a review of post-marketing clinical trial and epidemiologic study findings.

As of the date of this report, OSE and OND have completed evaluations for two NMEs. The findings for these two NMEs, Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules, and Ranexa (ranolazine) Extended-Release (ER) Tablets, are presented in this report. Completion of the project is expected by the end of 2008.

In September 2007, after the pilot program was well under way, the Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted. Section 915 created a new section 505(r)(2)(D) of the Federal Food, Drug, and Cosmetic Act that directed FDA to prepare

> *by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number. . .*

FDA is working to implement this and other provisions of FDAAA and the results of this NME pilot program will be used to inform our work in implementing this provision.

2. Procedure for NME Post-Marketing Safety Evaluation Pilot Program

OND and OSE personnel worked both independently and collaboratively to develop a standardized approach for the preliminary review of postmarketing data for the NMEs selected for the pilot program. Approximately 50 reviewers from these offices, as well as the Office of Clinical Pharmacology (OCP) and the Safety Policy and Communications Staff (SPCS), provided input into the development of this standardized approach.

Each NME was evaluated using the agreed-upon approach, and preliminary findings were discussed by primary reviewers and senior staff from OND, OSE, OCP, and SPCS at separate meetings on each product. After discussion of these early findings, the group developed a consensus regarding the safety signals that merited further investigation and agreed on the type of follow-up required (e.g., OSE safety review, request to sponsor for further information) and the projected timeline for completion.

The follow-up evaluations have been completed for duloxetine and ranolazine. A team of senior staff concluded that the labeling for duloxetine needed several changes, but that

ranolazine labeling did not need revision. The safety-related findings from these two evaluations are summarized below.

3. Summary of Findings

Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules

Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules, by Eli Lilly and Company, is a serotonin and norepinephrine reuptake inhibitor (SNRI) for oral administration initially approved in August 2004 to treat major depressive disorder. Subsequently, FDA approved duloxetine for the treatment of diabetic peripheral neuropathic pain (September 2004) and generalized anxiety disorder (February 2007) in adult patients.

Between August 2004 and December 2006, more than 3 million patients in the United States received a prescription for duloxetine.[2] Approximately 50% of use was in patients ages 41-60 years. Pediatric patients (ages 0-16 years) accounted for less than 1% of total dispensed prescriptions.[3]

As a result of the NME pilot program evaluation for duloxetine from January 2007-March 2007, a number of adverse events requiring further evaluation and more detailed review were identified. These events included reports of bleeding, blindness, drug interactions, falls, loss of consciousness, hyponatremia, urinary hesitancy/retention, and liver toxicity. Medication errors were also observed. The cases of blindness were subsequently determined to be related to underlying disease or other causes, rather than to drug use. The potential for loss of consciousness already appeared to be appropriately reflected in current labeling.

As a result of the review of the remaining adverse events identified in this NME evaluation —bleeding, hyponatremia, falls, urinary retention/hesitancy, and the observed medication errors, it was concluded that labeling or packaging should be modified. Additional information on bleeding, urinary retention/hesitancy, and the observed medication errors is available in reviews. Based on these recommendations, the following changes have been made to the duloxetine labeling or to the product container label:

(a) Bleeding: Information on the risk of bleeding has been added to the Warnings/Precautions and Patient Information sections and language has been added on concomitant use of duloxetine with warfarin and other drugs that affect hemostasis. The revised labeling states that concurrent use of an NSAID, aspirin, warfarin, or any other drug that affects hemostasis may potentiate the risk of bleeding. In addition, it states that patients receiving

[2] Verispan, LLC: Total Patient Tracker, Aug04-Dec06, extracted Feb07.
[3] Verispan, LLC: Vector One®: National, Aug04-Dec06, extracted Feb07, Mar07.

warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued.

(b) Hyponatremia and falls: Although hyponatremia (low serum sodium levels) had already been described in the duloxetine labeling at the time of the NME evaluation, FDA concluded that labeling would be more informative if it better described the symptoms of hyponatremia. Changes have been made to the hyponatremia section of labeling, as well as to the overdosage section of labeling. Labeling was updated to describe clinical manifestations of hyponatremia, including headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls, as well as hallucination, syncope, seizure, coma, respiratory arrest, and death in more severe and/or acute cases.

(c) Urinary Hesitancy/Retention: The existing product labeling had described the possibility of urinary hesitation with duloxetine. The labeling has been updated (cautionary information in the Warnings/Precautions Section) to inform healthcare providers of the potential for serious outcomes (catheterization and/or hospitalization).

(d) Medication Errors: Cases of medication errors were reviewed and classified as: wrong strength, administration errors associated with opening the capsules, and wrong drug. For each of these error types, reviewers identified contributing factors associated with the container label, carton, and insert labeling. Changes have been made to the product container labels and labeling in an effort to prevent future medication errors, including warning against opening the capsules, which can affect the enteric coating.

The potential risk of liver toxicity associated with duloxetine use had been previously identified in clinical trials and prior analyses of postmarketing information, and is reflected in current labeling. However, analysis of additional reports of liver injury is ongoing and labeling will be modified as needed.

FDA is currently reviewing cases of drug interactions associated with duloxetine use.

Ranexa (ranolazine) Extended-Release Tablets

Ranolazine, by CV Therapeutics, Inc., is an antianginal drug originally approved in January 2006. The mechanism of action of ranolazine is unknown.

From January 2006 through March 2007, approximately 39,000 patients received a prescription for Ranexa. Most use was in people over 70 years of age (47%), with about 26% and 20% of use in patients aged 61-70 years and 51-60 years, respectively.[4]

[4] Verispan LLC: Total Patient Tracker, extracted Apr07.

As part of the NME pilot program evaluation for ranolazine from March 2007-May 2007, cases of death and torsade de pointes were reviewed. Few deaths were reported, and details surrounding them were not provided in most cases. No pattern in the deaths suggested a causal role of ranolazine. Cases of torsade de pointes were determined to have been related to underlying disease or other causes, rather than to ranolazine. The NME pilot program evaluation of ranolazine thus did not result in changes to the label or other FDA regulatory action.

4. Conclusions

With the first two pilot program evaluations completed, it is possible to draw some conclusions about the pilot program process and the two drugs evaluated thus far. The process involved effective collaboration between OND and OSE, and required considerable resources from both Offices. For duloxetine, a drug with substantial duration and extent of use, it was possible to discern several areas in which existing labeling would benefit from modification. For ranolazine, a drug that has seen only limited use during its brief marketing period, no labeling revisions were indicated. It was the conclusion of the evaluation team that the comprehensive reviews necessary to carefully examine a drug in the pilot program are most informative after the drug has been on the market longer, or has had more use, than ranolazine. The optimal timing within the lifecycle of a drug for these evaluations will merit consideration for future NMEs examined by the pilot program. It should be appreciated that not discovering major new adverse effects or major labeling deficiencies does not represent a "failure" of the evaluation process, but rather suggests that the existing process of monitoring of adverse events by FDA and drug sponsors, and the resulting labeling revisions, are effective. For the two drugs reviewed, a thorough review of available data did not uncover any serious problems.