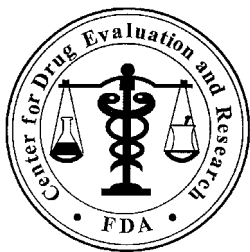


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-173**

**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**

Date: September 11, 2009

To: Thomas P. Laughren, M.D., Director  
Division of Psychiatry Products (DPP)

Thru: Claudia Karwoski, Pharm.D., Director  
Division of Risk Management (DRISK)

From: Zyprexa Relprevv<sup>®</sup> REMS Review Team  
Scientific Lead: Gita A. Toyserkani, Pharm.D., MBA, Senior Drug  
Risk Management Analyst, DRISK

Team Members:  
Kendra Biddick, Consumer Safety Officer, OC  
Marcia Britt, Ph.D., Regulatory Health Specialist, DRISK  
Mary Dempsey, Risk Management Program Coordinator, DRISK  
Jodi Duckhorn, MA, Patient Labeling and Patient Education Team  
Leader, DRISK  
Latonia M. Ford, RN, BSN, MBA, Patient Product Information  
Reviewer, DRISK  
Brian Gordon, MA, Social Science Reviewer, DRISK  
LaShawn Griffiths, MSHS-PH, BSN, RN, Patient Product  
Information Acting Team Leader, DRISK  
Mary Willy, Ph.D., Senior Drug Risk Management Analyst Team  
Leader, DRISK

Subject: Review of Zyprexa Relprevv<sup>®</sup> Risk Evaluation and Mitigation  
Strategy (REMS)

Drug Name(s): Zyprexa Relprevv<sup>®</sup> (olanzapine) extended-release injectable  
suspension

Application Type/Number: NDA 22-173

Applicant/sponsor: Eli & Lilly Co. (Lilly)

OSE RCM #: 2009-513

# CONTENTS

1	INTRODUCTION .....	2
2	BACKGROUND .....	2
3	METHODS AND MATERIALS.....	3
4	RESULTS OF REMS REVIEW.....	4
4.1	Goals .....	4
4.2	REMS Elements.....	4
4.2.1	Medication Guide.....	4
4.2.2	Communication Plan.....	5
4.2.3	Elements To Assure Safe Use .....	5
4.2.4	Implementation Plan .....	6
4.2.5	Timetable for Submission of Assessments .....	6
4.2.6	Information Needed for Assessments .....	7
5	CONCLUSION.....	8
	APPENDICES .....	9

## 1 INTRODUCTION

This memorandum is in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa Relprevv® (olanzapine) extended-release injectable suspension.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Given the risk of negative outcomes in patient who experience Zyprexa Relprevv® induced post-injection delirium/sedation syndrome (PDSS), OSE and DPP determined that a REMS is necessary for Zyprexa Relprevv® to ensure that the benefits of the drug outweigh the risks. The risk of negative outcomes may be mitigated by ensuring that Zyprexa Relprevv® is prescribed, dispensed, and administered by healthcare professionals who understand the conditions for safe use and agree to adhere to them, including, administering Zyprexa Relprevv® in a certified healthcare facility with access to emergency response services and observing patients in the healthcare facility for at least 3 hours for PDSS events. The requirements of the REMS were conveyed to the applicant in a Complete Response letter, dated December 15, 2008.

The elements of the REMS will consist of a Medication Guide, a communication plan, elements to assure safe use, an implementation plan, and a timetable for the submission of assessments of the REMS. DRISK's review of the Medication Guide was completed on July 20, 2009.<sup>1</sup> This memorandum documents our review of the other elements of the applicant's proposed REMS for Zyprexa Relprevv®.

## 2 BACKGROUND

Zyprexa Relprevv® is a long-acting atypical antipsychotic proposed for deep gluteal intramuscular injection (IM) for the treatment of schizophrenia in adults. During the Zyprexa Relprevv® clinical trials, some patients experienced PDSS events, a syndrome characterized primarily by signs and symptoms related to delirium and/or excessive sedation. The PDSS events raised a serious safety concern because of severity of sedation, unpredictable characteristics, delayed onset (a few hours after injection) in some cases, and relatively high risk of occurrence (0.07% of injections and 1.5% of patients).

On June 13, 2008, Lilly submitted a proposed risk management plan (RMP) for Zyprexa Relprevv®. The proposed RMP consisted of labeling, education and training, routine pharmacovigilance, and targeted surveillance. Additionally, Lilly proposed a mandatory registry to collect postmarketing experience data on the risk of PDSS. Based on the review of the RMP, DRISK and DPP determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of PDSS events and recommended that the REMS consist of a Medication Guide, elements to assure safe use, an implementation plan, and a timetable for submission of assessments of the REMS.

---

<sup>1</sup> Latonia Ford. DRISK Review of Zyprexa Relprevv Medication Guide, dated July 20, 2009.



DRISK advised DPP that the elements to assure safe use should include at minimum the following<sup>2</sup>:

- Enrollment of all patients, physicians, and healthcare facilities as well as training and certification of healthcare professionals that will be prescribing or administering Zyprexa Relprevv®.
- Administering Zyprexa Relprevv® only in certified healthcare facilities that can observe patients for several hours and provide the medical intervention necessary in case of an event. Appropriate monitoring at the time of the injection and several hours post-injection to ensure the safe use of Zyprexa Relprevv®. Due to the varying degree of sedation observed in the clinical trials ranging from dizziness to coma, the healthcare facilities must be equipped and have certified staff to provide for resuscitation and intubation if needed. These criteria should be required in order for the healthcare facility to obtain certification.
- Documentation of safe-use conditions including appropriate monitoring and evaluation of patients prior to discharge from healthcare facilities.

A complete response (CR) letter was sent to the applicant on December 15, 2008, that outlined the REMS requirements.<sup>3</sup> On March 12, 2009, Lilly resubmitted the NDA for Zyprexa Relprevv® in response to the CR letter which included a proposed REMS, REMS Supporting Document, and education and registration materials.

### **3 METHODS AND MATERIALS**

The Zyprexa Relprevv® REMS proposal was reviewed for responsiveness to Agency comments communicated to the applicant and for conformance with the Food and Drug Administration Amendments Act of 2007.

The following materials were reviewed from the applicant's electronic NDA 22-173 submissions, Agency reviews, and comments communicated to the applicant. The materials are listed by the date of the document.

- DRISK Review of Olanzapine Pamoate Depot Risk Management Plan. RCM # 2008-1285, dated December 15, 2008.
- Complete Response Action Letter (NDA 22-173), dated December 15, 2008.
- Complete Response resubmission (NDA 22-173), dated March 12, 2009.
- DRISK Zyprexa Relprevv® Interim comments (NDA 22-173), dated June 2, 2009.
- Information Request Letter (NDA 22-173), dated June 2, 2009.
- REMS Regulatory Response and REMS resubmission (NDA 22-173), dated July 15, 2008.
- Latonia Ford. DRISK Review of Zyprexa Relprevv® Medication Guide, dated July 20, 2009.
- DRISK Zyprexa Relprevv® Interim comments (NDA 22-173), dated August 13, 2009.
- REMS Regulatory Response and REMS resubmission (NDA 22-173), dated August 17, 2008.

---

<sup>2</sup> DRISK: Review of Olanzapine Pamoate Depot Risk Management Plan. RCM # 2008-1285, dated December 15, 2008.

<sup>3</sup> NDA 22-173: Olanzapine Pamoate Depot Complete Response Letter, dated December 15, 2008.

- DRISK Zyprexa Relprevv® Interim comments (NDA 22-173), dated August 31, 2009.
- REMS Regulatory Response and REMS resubmission (NDA 22-173), dated September 2, 2009.

## 4 RESULTS OF REMS REVIEW

The following REMS proposal submitted on September 2, 2009, reflect revisions based upon interim comments sent to Lilly.

In the original submission, Lilly referred to the REMS program as the Zyprexa Relprevv® Registry. We were concerned that the term “registry” would not appropriately convey the purpose of the REMS program to healthcare professional and patients and may be construed as an observational required postmarketing study. We informed the applicant that a REMS is not a “registry” and their REMS proposal described as a “registry” is insufficient in defining the program. Lilly agreed to remove all references to the registry and proposed branding the REMS program. The proposed REMS program name is Zyprexa Relprevv® Patient Care Program™, which the Agency deems acceptable.

### 4.1 GOALS

#### *Original Proposal*

The Applicant’s original goal of the Zyprexa Relprevv® REMS was to mitigate the risk of negative outcome to patients who experience post-injection delirium/sedation syndrome (PDSS) events and to further evaluate the risk of PDSS associated with administration of Zyprexa Relprevv.

#### *Revised Proposal*

The revised goals are:

To mitigate the risk of negative outcomes associated with Zyprexa Relprevv® post-injection delirium/sedation syndrome (PDSS) by:

1. Ensuring Zyprexa Relprevv® is administered only in certified healthcare facilities with ready access to emergency response services;
2. Informing prescribers, pharmacists, and patients about the risks and the need for continuous observation of patients for at least 3 hours in certified healthcare facilities; and
3. Establishing long-term safety and safe use of Zyprexa Relprevv® through periodic monitoring for the risk of PDSS events among all patients who receive Zyprexa Relprevv®.

### 4.2 REMS ELEMENTS

The REMS includes a Medication Guide, a communication plan, elements to assure safe use, an implementation plan, and a timetable for submission of assessments. Each element is described below and a formatted REMS proposal is presented in Appendix D. We understand additional formatting revisions may be necessary as this REMS goes through the final clearance process.

#### 4.2.1 MEDICATION GUIDE

Lilly has proposed to supply a Medication Guides that will be dispensed with each prescription for Zyprexa Relprevv in accordance with 21 CFR 208.24. The Zyprexa Relprevv® Medication

Guide will be included inside each Zyprexa Relprevv® convenience kit, which is a single unit of use. Lilly will also include instructions in the Zyprexa Relprevv® REMS healthcare professional training that requires the prescriber to review the Medication Guide with the patient or patient's guardian prior to starting the patient on Zyprexa Relprevv® therapy and to provide the Medication Guide prior to each injection. The Medication Guide will also be available on the Zyprexa Relprevv® Patient Care Program website.

The Medication Guide was submitted to the FDA with the CR resubmission on March 12, 2009 and has been reviewed; high level comments on the Medication Guide were provided in the June 2, 2009 information request letter (Appendix A) and additional comments were conveyed to the Applicant by email correspondence on September 3, 2009.

#### **4.2.2 COMMUNICATION PLAN**

The CR letter of 2008 did not specify a communication plan as an element of the REMS and the original REMS proposal did not include a communication plan. However, in the original REMS submission, Lilly included a Dear HealthCare Professional (DHCP) Letter as an optional tool. Since the proposed DHCP letter describes the REMS program, we requested that it be included in the REMS under a communication plan. We provided recommendations on the DHCP letter to the Applicant in our June 2, 2009 interim comments, which were incorporated in the REMS resubmission of July 15, 2009.

Lilly has proposed to issue a DHCP letter in accordance with the United States (US) Federal Food, Drug, and Cosmetic Act (FDCA) 505-1(e)(3), to targeted psychiatrists as well as pharmacists within 60 days of product approval to support the implementation of the Zyprexa Relprevv® Patient Care Program™ and the conditions of safe use. In the final submission, the applicant clarified that the DHCP letter will be issued by mass mailing one time after product launch.

#### **4.2.3 ELEMENTS TO ASSURE SAFE USE**

Key features of the Zyprexa Relprevv® Patient Care Program are:

- 1. Healthcare providers who prescribe Zyprexa Relprevv® are specially certified under 505-1(f)(3)(A).**
  - a. Lilly will ensure that prescribers enrolled in the Zyprexa Relprevv® Patient Care Program™ are specially certified. Lilly will ensure that, to become certified, prescribers attest to their understanding of the Zyprexa Relprevv® Patient Care Program™ requirements, the risks associated with Zyprexa Relprevv®, and that prescribers adhere to the conditions of safe-use as defined in the REMS document (Appendix D). Prescribers will be retrained and recertified every 3 years from time of enrollment.
- 2. Zyprexa Relprevv® will only be dispensed by pharmacies, practitioners, or health care settings under FDCA 505-1(f)(3)(C) who are specially certified under FDCA 505-1(f)(3)(B).**
  - a. Lilly will ensure that to be certified to dispense Zyprexa Relprevv®, each pharmacy, practitioner, and health care setting (pharmacy service providers) adhere to the conditions of safe-use as defined in the REMS document. Pharmacy service providers will be recertified every 3 years from time of enrollment.
  - b. Lilly will ensure that to be certified to administer Zyprexa Relprevv®, each practitioner or health care setting will adhere to the conditions of safe-use as defined in the REMS

document. Practitioners and healthcare facilities will be recertified every 3 years from time of enrollment.

**3. Zyprexa Relprevv® will be dispensed to patients with evidence or other documentation of safe-use conditions under FDCA 505-1(f)(3)(D).**

- a. Lilly will ensure that each patient treated with Zyprexa Relprevv® is enrolled in the Zyprexa Relprevv® Patient Care Program™ and assigned a unique identifying number before Zyprexa Relprevv® is dispensed to him or her. Lilly will ensure that, to become enrolled, each patient or patient's guardian must sign the Patient Registration Form.
- b. For each injection of Zyprexa Relprevv®, the practitioner or healthcare facility staff must observe the patient for at least 3 hours post-injection and record and submit the required information for each patient by completing either the Single or Multiple Patient Injection Form and returning this form to the Zyprexa Relprevv® Patient Care Program™ coordinating center within 7 days. The rationale for the observation period of at least 3 hours was based upon the reported PDSS events in the NDA clinical trials.
- c. Lilly will ensure that the required information is collected by the practitioner or healthcare setting staff for any report of PDSS in patients administered Zyprexa Relprevv® and submitted to the Zyprexa Relprevv® Patient Care Program™ coordinating center within 24 hours.

**4.2.4 IMPLEMENTATION PLAN**

The Implementation System will include the following. Lilly will:

- 1) Maintain a validated and secured (21 CFR Part 11 compliant) database of all certified prescribers, pharmacies, healthcare facilities, and patients, as well as a database of the completed data forms. The database links each reported PDSS event to the enrolled patient and the associated prescriber and healthcare facility.
- 2) A plan to ensure that the Single/Multiple Injection Forms and the PDSS Forms are received by the Zyprexa Relprevv® Patient Care Program™ coordinating center within the specified timeframes.
- 3) Review distribution data and prescription data to assess compliance with the requirement that Zyprexa Relprevv® is only prescribed, dispensed, and administered by the enrolled entities.
- 4) Assess pharmacies compliance with the requirement to dispense Zyprexa Relprevv® to prescribers and healthcare facilities only after confirming eligibility with the Zyprexa Relprevv® Patient Care Program™ coordinating center.
- 5) Based on evaluation of the implementation of elements to assure safe use provided for under Section 4.2.3 above, and in the manner described in the REMS supporting document, take reasonable steps to improve implementation of these elements to meet the goals of the REMS.

**4.2.5 TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

The proposed timetable for submission of assessments (6 months and 1 year after the approval date of the NDA for Zyprexa Relprevv®, and annually thereafter) is acceptable. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60

days before the submission date for that assessment time interval. The assessment is to be received by the FDA on the due date.

#### **4.2.6 INFORMATION NEEDED FOR ASSESSMENTS**

The following information needed for assessment of the REMS was provided to DPP to be included in the approval letter. Since the Medication Guide is packaged with the product as a unit-of-use packaging, the assessment of the distribution and dispensing of the Medication Guide is not necessary to be included in the REMS assessments. The REMS assessment plan should include but is not limited to the following information:

- a. Healthcare providers and patients' (or caregiver) understanding of risks and conditions of safe use of Zyprexa Relprevv® through surveys.
- b. A description of specific measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.
- c. An assessment of enrollment and discontinuation statistics for prescribers, pharmacies, healthcare facilities, and patients:
  1. The number of patients enrolled in the Zyprexa Relprevv® Patient Care Program™ (during the reporting period and cumulative).
  2. The number of person-years for enrolled patients.
  3. The number of patients who received Zyprexa Relprevv® that were not enrolled (during the reporting period and cumulative).
  4. The number of patients who stopped Zyprexa Relprevv® (during the reporting period and cumulative).
  5. The number of prescribers enrolled in Zyprexa Relprevv® Patient Care Program™ (during the reporting period and cumulative).
  6. The number of pharmacies enrolled in the Zyprexa Relprevv® Patient Care Program™.
  7. The number of pharmacies who prescribed/dispensed Zyprexa Relprevv® that were not enrolled (during the reporting period and cumulative).
- d. Assessment of compliance with the requirement that Zyprexa Relprevv® is only shipped to registered pharmacy service providers. This summary will include an assessment of the amount of drug shipped to each site compared to actual prescriptions dispensed and monitoring of variations in ordering patterns.
- e. Assessment of pharmacy compliance to include, number and summary of instances where pharmacies dispensed Zyprexa Relprevv® directly to the patient and corrective actions taken.
- f. An assessment of compliance with the requirement that all patients are associated with a registered healthcare facility prior to enrollment.
- g. Assessment of Healthcare facility compliance including:
  1. Compliance with submission of completed Injection and PDSS Forms.
  2. Evaluation of compliance with conditions of safe use through review of injection form and PDSS form responses.
    - Was the patient observed for at least 3 hours post-injection?
    - Was the patient accompanied from the facility?
    - Once a PDSS event was suspected, was the patient's monitoring initiated in a facility capable of resuscitation?

Responses will be analyzed to determine the compliance level with these required safe use conditions.

- h. Number of cases of PDSS reported during the reporting period and cumulatively.

- i. A narrative summary and analysis of all cases of PDSS (reported during the reporting period) based upon data provided by prescribers and healthcare facility staff reported on the PDSS form or information reported spontaneously to Lilly.
- j. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed will be included with each REMS assessment report.

The applicant included in the original REMS submission, surveys to evaluate healthcare professionals and patients' understanding about the safe use of Zyprexa Relprevv®. DRISK reviewed the proposed survey methodology and instruments and provided comments in the June 2, 2009 interim review comments (Appendix A). Lilly has accepted the recommended changes to the surveys and updated the information in their REMS resubmission of July 15, 2009

## **5 CONCLUSION**

The Zyprexa Relprevv® (received on September 2, 2009) contains agreed upon REMS components which include a Medication Guide, a communication plan, elements to assure safe use, an implementation plan, and a timetable for submission of assessments. We find the proposed revised REMS for Zyprexa Relprevv® to be acceptable at this time. The REMS program (Zyprexa Relprevv® Patient Care Program™) is designed to, the extent possible, mitigate and further evaluate the risk of negative outcomes in patients who experience Zyprexa Relprevv® induced PDSS.

## **APPENDICES**

**APPENDIX A: REMS Interim Review Comments for DPP**

<b>Drug Name:</b>	<b>BLA/NDA:</b>	<b>Date:</b>	<b>Comment Version # 1</b>
Zyprexa Relprevv (olanzapine long-acting intramuscular injection)	22-173	06/02/2009	
<b>DRISK Scientific Lead:</b> Gita Akhavan-Toyserkani, Pharm.D., MBA, Senior Drug Risk Management Analyst	<b>Reviewers:</b> <u>DRISK</u> Marcia Britt, PhD., Health Education Reviewer Jodi Duckhorn, MA, Patient Labeling and Education Team Leader Brian Gordon, MA, Social Science Reviewer Sharon Mills, BSN, RN, CCRP, Patient Product Information Reviewer Mary Willy, Ph.D., Senior Drug Risk Management Analyst Acing TL <u>OC</u> Kendra Biddick, Consumer Safety Officer <u>DDMAC</u> Susannah Hubert, Regulatory Review Officer Amy Toscano, Regulatory Review Officer		
<b>RCM #:</b> 2009-513			

**Introduction:**

On March 11, 2009, Lilly resubmitted the NDA for Zyprexa Relprevv in response the Complete Response letter that was issued December 15, 2008. The submission includes a proposed REMS, REMS Supporting Document and education and registration materials. The comments below are OSE/OC/DDMAC's preliminary review of the proposed REMS for Zyprexa Relprevv (olanzapine long-acting injection). We anticipate additional comments on all of the submitted materials as we continue our review. Please request for the Applicant to respond to these comments and questions within 2 weeks upon receipt.

**Materials Reviewed:**

- Proposed REMS and REMS Supporting Document dated March 11, 2009
- Proposed REMS educational and registration materials dated March 11, 2009
  - Healthcare Professional Training
  - Reconstitution and Administration Training
  - Zyprexa Relprevv Registry Information Packet
  - Zyprexa Relprevv Registry Welcome Letter
  - Zyprexa Relprevv Registry Instructions Brochure
  - Zyprexa Relprevv Registry Registration Forms
  - Zyprexa Relprevv Registry Data Collection Forms (Injection Forms and PDSS Forms)
  - PDSS Case Studies DVD (Script)



- Zyprexa Relprevv Registry Website
- Zyprexa Relprevv Registry Design Document

**Comments and questions for the sponsor:**

**1. REMS Goals and Objectives:**

A REMS is intended to ensure that the benefits outweigh the risks of the drug. Revise the goals of the REMS as follows:

- a. To mitigate negative outcomes associated with Zyprexa Relprevv induced post-injection delirium/sedation syndrome (PDSS).
- b. To establish long-term safety and safe use of Zyprexa Relprevv through periodic monitoring of all patients who receive Zyprexa Relprevv for the risk of PDSS events.

**2. Medication Guide:**

The Medication Guide has not been reviewed for content but for overall readability and format. We refer you to high level comments on the proposed Medication Guide. Submit the revised proposed Medication Guide for review and describe how you will ensure that a Medication Guide will be dispensed with each prescription of Zyprexa Relprevv as required by 21 CFR 208.24 in the REMS document.

**3. Communication Plan:**

You have submitted the Dear Health Care Professional (DHCP) as an optional tool and not part of the REMS materials. Since the proposed DHCP letter describes the REMS program we request that it be included in the REMS under a Communication Plan. Submit the DHCP letter as part of the REMS with the following revisions:

- a. Use verbatim language from the boxed warning in the prescribing information.
- b. Include as a safe use condition that healthcare facilities should make sure that the patient has transportation provided by someone other than themselves to their destination prior to administering the injection.
- c. Delete the statement:

(b) (4)  
(b) (4)

**4. Elements to Assure Safe Use (ETASU):** Address the following concerns regarding the ETASU in the proposed REMS.

- A. Reference is made in the REMS Document and REMS Supporting Document to the “Registry” which will “systematically follow and actively solicit information regarding the occurrence of signs and symptoms of PDSS.”

We remind you that a REMS will require a number of elements to assure safe use, not only 505-1(f)(3)(F). Revise the submission and remove references to the Registry and refer to the program as a REMS rather than a registry.

- B. Both the REMS and the supporting document state that the specialty distributors and pharmacy service providers will confirm enrollments before distributing the product. The flowchart (Figure 5.1 of the supporting document) indicates this confirmation will be via the Registry Database. The actual procedures for accessing the database are not provided in either document. Please provide the details.

- C. Describe the drug-handling processes and methods that will be used to ensure:
  - i. Zyprexa Relprevv goes directly from a pharmacy to a physician or the health care facility where the patient will receive the drug, without going through the patient's hands.
  - ii. no patient will receive an injection of Zyprexa Relprevv unless he or she will be accompanied when leaving the injection facility
- D. You have defined the Pharmacy Service Provider (PSP) as any hospital, pharmacy, physician, or properly licensed healthcare facility (or "entity" as described in Appendix 3 Registry Design Document) that can order and dispense Zyprexa Relprevv. Specify the role of the pharmacy service providers and how they will ensure that the drug is only administered in certified healthcare facilities.
- E. Describe the mechanism for distributing patient identification numbers to prescribers or healthcare facilities.
- F. How and by whom will healthcare facility eligibility be confirmed?
- G. The pharmacy and healthcare facility attestation forms do not explicitly state what the different entities are agreeing to or what the specific program requirements are. Revise the forms to specify what the requirements are.
- H. Provide detailed information about the dissemination of educational material to HCPs and patients.
  - i. Provide a dissemination plan for the training information to prescribers and healthcare facilities. It is unclear how the prescriber and healthcare facilities will receive the Zyprexa Relprevv Training Material Kit.
  - ii. Include as an instruction that training and enrollment are required to prescribe and dispense Zyprexa Relprevv to patients.
- 5. **Prescriber Attestation:** Revise the first prescriber attestation in section 4.2.1 and the corresponding prescriber enrollment form to: "I have completed the mandatory Zyprexa Relprevv training and understand the risks and benefits associated with its use."
- 6. **Patient Attestation:** Revise the patient attestation in section 4.2.4 and the corresponding patient enrollment form as follows:
  - A. Revise the eighth attestation to: *"I agree to seek medical care right away if I have a reaction such as excessive sleepiness, dizziness, confusion, difficulty talking, difficulty walking, muscle stiffness or shaking, weakness, irritability, aggression, anxiety, increase in blood pressure or convulsions."*
  - B. Revise the tenth attestation to: *"I may be asked to complete occasional surveys about my understanding of the risks and benefits of treatment with Zyprexa Relprevv."*
  - C. Add the following attestations:
    - i. the patient received a copy of the Medication Guide;
    - ii. your doctor has explained the risks and benefits of using Zyprexa;

- iii. you or your caregiver has discussed any questions or concerns about your treatment with Zyprexa Relprevv.

**7. Implementation System:** Address the following concerns regarding the implementation system in the proposed REMS.

- A. Provide details on the processes and procedures for verifying and collecting information on the administration of Zyprexa Relprevv.
- B. How will the healthcare facilities be monitored to ensure that they are administering Zyprexa Relprevv in accordance with the program requirements?
- C. Will there be reminder systems or alerts in place to ensure that the facilities responsible for administering Zyprexa Relprevv are in compliance with the program requirements (i.e. injection forms submitted within 7 days, PDSS forms submitted within 24 hours)?
- D. Describe plans to monitor the coordinating center and certified pharmacies and correct any deficiencies, including at a minimum
  - i. Training
  - ii. Adequacy and implementation of written procedures related to Zyprexa Relprevv registration, distribution, and dispensing
  - iii. Deviations definition, tracking, and resolution
  - iv. Fulfillment of reporting requirements

**8. Comments on specific materials:**

- A. We were not able to locate the Zyprexa Relprevv Registry Welcome Letter that was mentioned in the REMS supporting document. If this letter is part of the REMS materials, please submit for review.
- B. The following materials were submitted as part of the REMS but were considered to be promotional in nature.

(b) (4)

Remove these materials from the REMS. Materials intended for promotion should be submitted to DDMAC for review prior to distribution.

- C. Healthcare Training Program: The training program for healthcare providers submitted as part of the REMS is not acceptable. The slides are promotional in nature and include information about the clinical studies. Revise the training slides as follows:
  - i. Provide instructions about the risks associated with the use of this drug per the PI, registration, prescribing and dispensing the medication, dosing and administration, how to recognize PDSS in patients and the need for risk minimization.
  - ii. Remove the slides that refer to clinical trials unless they provide important information about the appropriate use of Zyprexa Relprevv.
- D. Reconstitution and Administration Recorded Presentation Script: Revise this material as follows:

- i. Provide the instruction that all HCPs that administer this product must view this video before giving the injection.
- ii. Provide the instruction that the HCP should make sure that patients receiving injections have adequate transportation to their destination following the injection and 3 hour waiting period. Provide a definition of adequate transportation as transportation being provided by someone other than the patient.
- iii. Add the following statement to the *instructions to patients*. Advise patients *and their caregiver* to be vigilant for symptoms of a post-injection delirium/sedation syndrome event for the remainder of the day and to obtain assistance if needed.
- iv. In Chapter 4: Step Two, HCPs are instructed to refer to the table in the full color reconstitution and administration instructions for proper volumes of diluent to add for each vial strength. Revise this instruction. The full color reconstitution and administration instructions should be referring the HCP to the full color poster.
- v. In Chapter 6: Step Four, HCPs are instructed to refer to the table in the instructions for the correct injection volume. This instruction is not clear. Provide a location for these instructions and the table.

E. Registry Instruction Brochure: Currently #2 in the Prescriber Information section (Three Steps to Patient Enrollment) states that (b) (4) (u) (4) Revise the instruction to state that a copy of the registration form should be provided to each patient or their guardian.

F. In the Pharmacy Service Provider Information three steps to enrollment, include in the review section that *Pharmacy staff should review the training and education material within this document before dispensing the medication.*

G. Zyprexa Relprevv Registry Website Screenshots:

- i. Provide the instruction that prescribers and all healthcare professionals should refer to the full prescribing information for full details about the risks associated with the use of Zyprexa Relprevv.
- ii. For first time users, provide instructions for obtaining the username and password.
- iii. It is not clear if the healthcare administer will be able to download the poster for future reference.
- iv. It is unclear what training is specific to staff that monitors patients. Will they be required to complete the healthcare professional training?
- v. Provide the content for the pharmacy service provider.

## 9. Participant Registration Forms

A. Prescriber Registration Forms

- i. Provide an instruction at the top of the page that training must be completed before they can enroll in the program.
- ii. The REMS does not mention the use of a Data Entry Delegate. Please provide an explanation of their responsibility in the REMS.
- iii. Revise the prescriber attestation per comments made above.

B. Pharmacy Registration Forms

- i. Provide an instruction at the top of the page that training must be completed before they can enroll in the program.
- ii. Revise the pharmacy attestation to specify the program requirements as applicable. For example, verifying patient eligibility/enrollment, prescriber enrollment, and healthcare facility enrollment.

C. Patient Registration Form

- i. Revise the patient attestation statements as described above.
- ii. Remove the (b) (4) This section is redundant. A full explanation of the registry is found in a later section on the form.
- iii. The form includes a signature line for the individual conducting the consent discussion. Is this considered a consent or registration form? Please make this clear on the form and in the REMS document.
- iv. Provide a signature for the prescriber or healthcare provider completing the form. We recommend changing (b) (4) (b) (4) to “prescriber signature.”
- v. Add a checkbox for the prescriber to document on the patient enrollment form that patient has been shown to be tolerant of oral olanzapine.

D. Healthcare Facility Registration Form

- i. Provide an instruction at the top of the page that training must be completed before they can enroll in the program.
- ii. Revise (b) (4) to “institutional representative name” and include his/her position title.

**10. Data Collection Forms**

A. Injection Form

- i. Revise the form to verify the following information prior to administration of the drug:
  - Does the patient have someone accompanying them to their destination after leaving the clinic?

**11. REMS Supporting Document:**

- A. Section 6.2 of the REMS Supporting Document states that noncompliant prescribers, prescriber/dispensers, healthcare facilities, or pharmacy service providers may be de-enrolled. Describe the criteria and procedures that will be used to determine when to de-enroll a participant and the circumstances under which the participant may be re-enrolled.
- B. Section 6.2, fourth bullet states “*An assessment of compliance with the requirement that all patients are associated with a registered healthcare facility prior to enrollment.*” The patient enrollment form does not include information to link a patient to a particular healthcare facility. Clarify how this is achieved.

**12. Surveys:** Address the following concerns regarding the surveys in the proposed REMS.

- A. Clarify which method of sampling will be used for each of the surveys? Random sampling or sampling by site?
- B. The method you have proposed to define adequate comprehension of the education materials will not reveal if specific educational messages are being conveyed to the respondents. The evaluation is to assess the effectiveness of conveying specific educational messages about Zyprexa Relprevv to the healthcare professionals and patients; the evaluation is not a test of an individual respondent but rather an individual risk or concept that is conveyed (or tested) in a particular question. A more appropriate way to assess the effectiveness of conveying the specific educational messages would be to look at individual questions and determine if X% of respondents answered that question correctly.
  - i. Evaluate the effectiveness of the educational materials based on X% of respondents answering each individual question correctly.
  - ii. Specify what percentage of total respondents have to get an individual question correct to consider the educational message successfully conveyed.
- C. Revise the healthcare professional survey as follows:
  - i. For questions #1, #2, #4 and #5 add an answer choice of “I don’t know”; add “select all that apply” to questions #4 and #5
  - ii. Re-word question #4 to read “Zyprexa Relprevv can be administered at which of the following sites: Select all that apply.” Add two more possible responses to this question. “in the patient’s home” and “in my office” (my referring to the doctor or respondent)
  - iii. Change the answer choices for question #3 to True/False/I don’t know
  - iv. Add a question about the symptoms of PDSS. For example:
    - Which of the following are symptoms of PDSS? Select all that apply.
      - Dizziness
      - Confusion
      - Difficulty talking
      - Difficulty walking
      - Aggression
      - Convulsions
      - Excessive sleepiness
      - Stomachache
      - Headache
      - I don’t know
- D. Revise the patient survey as follows:
  - i. Clarify if caregivers will be allowed to complete the survey if the patient is unable.
  - ii. Clarify how the healthcare professional will notify selected patients. Will it be by telephone, mail or when the patient comes into the office?
  - iii. Add text explaining what the Medication Guide is or an image of it to help with recall for these questions below
  - iv. Add questions to the survey that ask if a patient read and understood the Medication Guide. For example:
    - Did you read the Medication Guide?
      - a. All

- b. Most
  - c. Some
  - d. None
  - e. I did not get a Medication Guide
- Did you understand what you read in the Medication Guide?
  - a. All
  - b. Most
  - c. Some
  - d. None
  - e. I did not get a Medication Guide
- Did your healthcare provider offer to explain to you the information in the Medication Guide?
  - a. Yes
  - b. No
  - c. I did not receive the Medication Guide
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
  - a) All
  - b) Most
  - c) Some
  - d) None
- Did or do you have any question about the Medication Guide? Yes or No (If Yes, list your question below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
- v.** For questions #1, #2, #3, #4, #5, #6 and #7 add an answer choice of “I don’t know”
- vi.** Add “select all that apply “ to questions 2 and 4
- vii.** In question #5 add an answer choice of “Rest and see if it goes away”; add “select all that apply”; separate the response “call my doctor” and “get medical assistance” because it makes the correct answers less obvious
- viii.** Re-word question #6. For example:
  - For the rest of the day after the injection, I should (select all that apply):
    - a. Watch out for symptoms of PDSS
    - b. Call my doctor after I get home
    - c. Not drive my car
    - d. Take a shower
    - e. Exercise
    - f. None of the above
    - g. I don’t know
- ix.** Add a question about the symptoms of PDSS. For example:

- Which of the following are symptoms of PDSS? Select all that apply.
  - a. Dizziness
  - b. Confusion
  - c. Difficulty talking
  - d. Difficulty walking
  - e. Aggression
  - f. Convulsions
  - g. Excessive sleepiness
  - h. Stomachache
  - i. Headache
  - j. I don't know

**13. Optional Patient Tools:** Patient ID Card, Patient Wristband, and Patient Brochure were submitted but are not considered as part of the REMS. Remove these materials from the REMS. Materials intended for promotion should be submitted to DDMAC for review prior to distribution.

**Additional Comments:**

- 14.** Format Request: The numerical system for the appendices was identical for the REMS document and REMS Supporting Document and thus made it very difficult to follow. For example, Appendix 1 in the REMS was the Healthcare Provider Training while the Appendix 1 in the Supporting Document was the Dear Healthcare Professional Letter. Revise the REMS and REMS Supporting Document using both a numeric and alpha numeric systems instead to differentiate the appendices.
- 15.** Please submit the revised Proposed REMS with appended materials and the REMS Supporting Document with a track changes and clean version of all revised materials and documents. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.



### High level comments on Zyprexa Relprevv Medication Guide:

- The readability scores for the MG that the applicant submitted on March 11, 2009 are not within the acceptable range. The proposed MG has a Flesch reading grade level of 10.3 and a Flesch reading ease score of 48.0%. To enhance patient comprehension, patient-directed materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. Simplify the language in the MG accordingly.
- The terms “doctor” and “healthcare provider” are used in the MG. We recommend using either “doctor” or “healthcare provider” consistently throughout the MG, except in the required verbatim statement at the end of the section “What are the possible side effects of Zyprexa Relprevv?” where the term “doctor” is required.
- The following proposed section titles should be revised as follows:
  - “What should I tell my doctor?” should be renamed “What should I tell my doctor before taking Zyprexa Relprevv?”
  - (b) (4) should be deleted. This information goes at the end of the section “What should I tell my doctor before taking Zyprexa Relprevv. The applicant should refer to the MG approved for Zyprexa on March 19, 2009, which includes the following language:

**Tell your doctor about all the medicines that you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYPREXA and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take ZYPREXA with your other medicines. Do not start or stop any medicine while taking ZYPREXA without talking to your doctor first.

- (b) (4) should be renamed “What are the possible side effects of Zyprexa Relprevv?”
- Add the section “What should I avoid while taking Zyprexa Relprevv?” Information about avoiding alcohol and the need for caution when driving or operating machinery should be added. Refer to the Zyprexa MG.
- Revise the Zyprexa Relprevv MG to make it consistent with the MG for Zyprexa and Zyprexa Zydis, to the extent possible, given the differences in formulation, setting of use, the risk of Post-injection Delirium/Sedation Syndrome (PDSS) and the fact that patients go home after receiving these injections.
- Submit the revised proposed MG for our review.

**APPENDIX B: REMS Interim Review Comments for DPP**

<b>Drug Name:</b>	<b>BLA/NDA:</b>	<b>Date:</b>	<b>Comment Version # 2</b>
Zyprexa Relprevv (olanzapine long-acting intramuscular injection)	22-173	08/13/2009	
<b>DRISK Scientific Lead:</b> Gita Akhavan-Toyserkani, Pharm.D., MBA, Senior Drug Risk Management Analyst	<b>Reviewers:</b> <u>DRISK</u> Marcia Britt, PhD., Health Education Reviewer Jodi Duckhorn, MA, Patient Labeling and Education Team Leader Brian Gordon, MA, Social Science Reviewer		
<b>RCM #:</b> 2009-513	Mary Willy, Ph.D., Senior Drug Risk Management Analyst Acing TL		

We are in the process of reviewing the revised Zyprexa Relprevv REMS resubmission and have the following comments for the Sponsor. Please request that they respond to these comments promptly to prevent any delays in this application. We will be sending the review division additional comments upon completion of the review.

**Comments for the Sponsor:**

1. Please describe how you will monitor the dispensing of Zyprexa Relprevv by the Pharmacy Service Providers to ensure that the drug is not dispensed directly to a patient, considering especially the dispensing of Zyprexa Relprevv by pharmacies in retail setting. FDAAA requires that sponsors take reasonable steps to evaluate the implementation of elements (b), (c), and (d) by healthcare providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements.
2. Please describe how healthcare providers will be able to identify Pharmacy Service Providers that carry Zyprexa Relprevv to ensure that patients, especially those in rural or medically underserved areas will have access to the drug.

**APPENDIX C: REMS Interim Review Comments for DPP**

<b>Drug Name:</b>	<b>BLA/NDA:</b>	<b>Date:</b>	<b>Comment Version # 3</b>
Zyprexa Relprevv (olanzapine long-acting intramuscular injection)	22-173	08/31/2009	
<b>DRISK Scientific Lead:</b> Gita Akhavan-Toyserkani, Pharm.D., MBA, Senior Drug Risk Management Analyst	<b>Reviewers:</b> <u>DRISK</u> Marcia Britt, PhD., Health Education Reviewer Jodi Duckhorn, MA, Patient Labeling and Education Team Leader Brian Gordon, MA, Social Science Reviewer		
<b>RCM #:</b> 2009-513	Mary Willy, Ph.D., Senior Drug Risk Management Analyst Acing TL		

We have reviewed the revised Zyprexa Relprevv REMS submission dated July 15, 2009 and have incorporated our changes and comments in the appended REMS document and REMS materials. We acknowledge that the sponsor has submitted a new version on August 29, 2009 to update with the program name, however, since this was just submitted and the appendices were not provided in word format, the changes were incorporated in the July 15, 2009 REMS materials. Please request that the sponsor incorporate the changes and resubmit the entire submission and appendices in PDF and word format.

1. We have reviewed the following materials and have no additional comments:

- Dear Healthcare Professional Letter
- Healthcare Facility Registration Form
- Post-Injection Delirium/Sedation Syndrome (PDSS) Form
- Single Patient Injection Form
- Multiple Patient Injection Form
- Patient Registration Form—Patient Copy
- Patient Registration Form
- Instructions to Reconstitute and Administer ZYPREXA RELPREVV (poster)
- Clinical Case Definition of Post-Injection Delirium/Sedation Syndrome
- Registry web shots

**We have the following comments/questions for the Sponsor:**

2. The requirement for the prescribers to include the patient identification number (PIN) and healthcare facility unique identifier on the actual prescription is not included in the registration forms and may lead to confusion in complying with the program requirements. It is also unlikely that retail pharmacies maintain the PIN and healthcare facility unique identifier in the patient record within the pharmacy system to access when refilling a prescription.

Please explain the utility of providing this information on the prescription. Can the pharmacy service providers verify patient and healthcare facility eligibility on-line without having a

PIN or unique facility number, similarly to calling the coordinating center (i.e., using the patient's first and last name, date of birth, and prescriber's name)? If it is necessary, it should be included in the prescriber registration form.

3. Page 18 of the Training for Healthcare Professionals slides states that: A Patient education brochure, Getting Started with My Medicine, and a Medication Guide are available for ZYPREXA RELPREVV. Prescribers or other healthcare professionals should instruct patients, their families, and their caregivers to read these documents and should assist them in understanding the contents.

This statement suggests that the Medication Guide and Getting Started with My Medicine are similar in importance. The sponsor should state that the Medication Guide should be given to patients, their families or their caregivers prior to each injection. For additional information about ZYPREXA RELPREVV, patients can receive the educational brochure, Getting Started with My Medicine.

4. Submit the final Reconstitution and Administration Training Video to the Agency for review prior to circulation.
5. Please see the following attachments for additional changes and comments:
  - Zyprexa Relprevv REMS Document
  - Zyprexa Relprevv Patient Care Program Instructions Brochure
  - Buy and Bill Pharmacy Service Provider Registration Form
  - Pharmacy Registration Form
  - Prescriber Registration Form



REMS



AppREMS



AppREMS



AppREMS



AppREMS

nt 83109.doc (g Instruct Brocyl Bill Reg 24Augmacy Reg 24 rscriber Reg 24/

6. Please revise the supporting document to be consistent with the changes in the REMS document and to include the pertinent information provided in the regulatory response of July 15, 2009 and August 17, 2009.

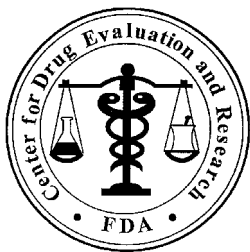
6 pages of RAMReview has been withheld in full immediately following this page as B4 CCI/TS

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

/s/  
-----

GITA A AKHAVAN TOYSERKANI  
09/11/2009  
Zyprexa Relprevv REMS Review

CLAUDIA B KARWOSKI  
09/11/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 15, 2008

To: Thomas P. Laughren, M.D., Director  
Division of Psychiatry Products (DPP)

Thru: Claudia Karwoski, Pharm.D., Acting Director  
Division of Risk Management (DRISK)

From: OSE Olanzapine Depot REMS Review Team  
Scientific Lead: Gita Akhavan-Toyserkani, Pharm.D., MBA, Senior Drug Risk Management Analyst, DRISK

Team Members:

Todd Bridges, R.Ph., Safety Evaluator Team Leader, DMEPA  
Marcia Britt, PhD., Regulatory Health Specialist, DRISK  
Daniel Brounstein, Regulatory Safety Project Manager, IO  
Mary Dempsey, Risk Management Program Coordinator, DRISK  
Ida-Lina Diak, Pharm.D. Safety Evaluator, DPV1  
Jodi Duckhorn, MA, Patient Labeling and Patient Education Team Leader, DRISK  
Brian Gordon, MA, Social Science Reviewer, DRISK  
Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator, DMEPA  
Tarek Hammad, MD, PhD, MSc, MS, Epidemiologist Team Leader, DEPI  
Solomon Iyasu, M.D., M.H.S., Director, Division of Epidemiology, DEPI  
Carol Pamer, R.Ph, MS, Epidemiologist, DEPI  
Mary Willy, Ph.D., Senior Drug Risk Management Analyst Acting Team Leader, DRISK

Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Olanzapine Pamoate (OP) Depot

Application Type/Number: 22-173

Applicant/sponsor: Eli & Lilly Co. (Lilly)

OSE RCM #: 2008-1285

# CONTENTS

EXECUTIVE SUMMARY .....	2
1 BACKGROUND .....	2
1.1 Introduction.....	2
1.2 Regulatory history.....	3
2 METHODS AND MATERIALS.....	4
2.1 Data and Information Sources.....	4
2.2 Analysis Techniques .....	4
3 RESULTS OF Review.....	4
3.1 Safety Concerns .....	4
3.2 Proposed Risk Management Plan.....	7
3.3 Proposed Pharmacovigilance Plan .....	7
3.4 Proposed Registry .....	7
3.5 Proposed Evaluation Plan .....	10
4 DISCUSSION.....	10
5 CONCLUSION and RECOMMENDATIONS .....	12

## EXECUTIVE SUMMARY

Olanzapine Pamoate Depot (OP Depot) is a long-acting atypical antipsychotic indicated for deep gluteal intramuscular injection for the treatment of schizophrenia in adults. During the clinical trials for OP Depot, some patients experienced adverse events (AEs) characterized primarily by signs and symptoms related to delirium and/or excessive sedation, termed as post-injection delirium/sedation syndrome (PDSS) events. The sponsor states that these events appear to be consistent with some of the most commonly reported AEs in patients with an oral olanzapine overdose and has suggested that the underlying mechanism is rapid absorption into the systemic circulation due to “vascular trauma” caused by the injection.

The excessive sedation events have raised a serious safety concern because of severity of sedation, unpredictable characteristics, delayed onset (a few hours after injection) in some cases, and relatively high risk of occurrence (0.07% of injections and 1.4% of patients). The original New Drug Application (NDA 22-173) received a Not Approvable letter on February 25, 2008 due to the lack of sufficient information on the risk of PDSS events. Lilly met with the FDA on May 7, 2008, to discuss the potential path forward for the application, including revisions to the risk management plan (RMP).

Lilly has submitted a revised RMP limited to those identified and potential risks *specific* to the OP Depot formulation, to include PDSS events and medication errors. The proposed RMP consists of labeling, education and training, routine pharmacovigilance, and targeted surveillance. The sponsor has also proposed a mandatory registry to collect postmarketing experience data on the risk of PDSS. Additionally, Lilly has proposed to perform an observational study that will be conducted outside the US to determine the incidence of PDSS in clinical practice.

We have reviewed the revised RMP and have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure the benefits of the drug outweigh the risk of PDSS events. The REMS should consist of a Medication Guide, elements to assure safe use, an implementation plan, a timetable for assessments, and assessments of the REMS. Specifically, we recommend a REMS that includes enrollment of all patients and healthcare facilities as well as training and certification of all healthcare professionals that will be prescribing or administering OP Depot. Certification should include a requirement that healthcare facilities that administer OP Depot observe patients for several hours and provide the medical intervention necessary in case of an event. Finally, the strategy should include systematic collection of information from all US patients receiving OP Depot on risk factors and other data of interest to further characterize the PDSS events.

DRISK has collaborated with DPP in drafting a complete response letter which outlines the REMS requirements.<sup>1</sup>

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review follows the August 5, 2008 request from the Division of Psychiatry Products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review Lilly’s proposed risk management plan (RMP) submitted on June 13, 2008.

---

<sup>1</sup> NDA 22-173: Olanzapine Pamoate Depot Complete Response Letter; cleared by OCC December 12, 2008.



Olanzapine Pamoate Depot (OP Depot), a thienobenzodiazepine derivative, is a long-acting atypical antipsychotic developed by Eli Lilly and Company (Lilly), with a proposed indication for the treatment of schizophrenia in adults. Olanzapine is a selective monoaminergic antagonist with high affinity binding to alpha-1, dopamine, histamine H-1, muscarinic, and serotonin type 2 (5-HT<sub>2</sub>) receptors. OP Depot is intended for deep intramuscular gluteal injection only. OP Depot is available as 150 mg, 210 mg, 300 mg, and 405 mg dosages to be administered every 2 weeks or every 4 weeks for the latter two strengths (the 300 mg strength can be administered every 2wks or 4wks). The sponsor recommends that tolerability with oral olanzapine be established in patients prior to initiating OP Depot treatment.

Oral olanzapine for the treatment of schizophrenia (marketed as Zyprexa<sup>®</sup>) received US approval 30 September 1996. Oral olanzapine is also indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder. Additionally, a rapid-acting intramuscular (RAIM) injection formulation of olanzapine (Zyprexa<sup>®</sup> IntraMuscular) indicated for agitation associated with schizophrenia and bipolar I mania, received approval in the US on 29 March 2004. The advantage of a long-acting OP Depot formulation would be to improve adherence and compliance by enabling bi-monthly or monthly administration.

During the clinical trials for OP Depot, some patients experienced AEs characterized primarily by signs and symptoms related to delirium and/or excessive sedation. The term post-injection delirium/sedation syndrome (PDSS) has been proposed by the sponsor to describe these events and is used throughout this document. The sponsor states that these events appear to be consistent with some of the most commonly reported AEs in patients with an oral olanzapine overdose.

The sponsor has proposed a revised RMP limited to those identified and potential risks *specific* to the OP Depot formulation. Lilly has also proposed a mandatory registry to collect postmarketing experience data on the risk of PDSS. Additionally, Lilly has proposed to perform an observational study that will be conducted outside the US to determine the incidence of PDSS in clinical practice.

## 1.2 REGULATORY HISTORY

Lilly received a Not Approvable letter from the FDA for the original NDA on 25 February 2008 for OP Depot for the treatment of schizophrenia.<sup>2</sup> As indicated in the letter, the primary deficiency in the Lilly application was the lack of sufficient information on the risk of PDSS events that had been observed in approximately 1% of patients who have participated in the development program for OP Depot. OP Depot is currently not marketed in the US or other countries. Risperidone is the only atypical antipsychotic medication with a depot formulation approved in the US and select EU Member states for the treatment of schizophrenia.

Pursuant to the NA Action, on February 6, 2008, the Psychopharmacologic Drugs Advisory Committee (PDAC) voted 10-0 (with 1 abstention) in favor of OP Depot on questions of whether or not there are circumstance under which OP Depot would be acceptably safe for the treatment of either acutely exacerbated schizophrenia or for the maintenance treatment of schizophrenia. However, these votes occurred at a time when the committee believed that for all cases of PDSS events, onset of the event occurred within a narrow window of up to 3 hours following injection. Post PDAC, a new case reported the onset of the CNS depression event as late as 5 hours after the injection. Thus, DPP concluded in the Not Approvable letter that the renewed doubt about the period of risk for onset of these events would require additional work to better understand the risk and underlying mechanism for this event before this product can be approved. Although, these

---

<sup>2</sup> NDA 22-173. Not Approvable Letter, Division of Psychiatry Products, FDA; dated February 25, 2008.

events have not been observed in animal models utilized thus far by the sponsor, the Division asked Lilly to consider other animal models that might more closely mimic humans regarding this event.

Following the Not Approvable action, Lilly met with the FDA on 07 May 2008 to discuss aspects of a proposed amendment to the application that would address this primary deficiency, including enhanced label language and risk minimization activities.<sup>3</sup> An RMP was included as part of the original NDA submission which consisted of labeling, routine pharmacovigilance, and a postmarketing observational study (Study B034).<sup>4</sup> Study B034 would be a non-interventional prospective cohort study designed to assess the incidence of PDSS over a period of two years in patients treated with OP Depot. Approximately 5,000 patients in 10 countries would be entered in this study.

DPP informed the sponsor that given Lilly's assertion that it is unlikely to be able to understand the mechanism of this event prior to approval, the Division requested that Lilly consider, as an alternative to Study B034, the initial marketing of this product under a strict registry. The registry could include similar features to Study B034, but would apply to all patients exposed to OP Depot. The Division considered this approach as a path forward for this application and agreed that further studies to try to understand the mechanism of this event represented a considerable challenge and would not be a precondition for resubmitting the application.

## **2 METHODS AND MATERIALS**

### **2.1 DATA AND INFORMATION SOURCES**

1. Proposed OP Depot RMP submitted April 30, 2007 by Eli Lilly & Co.
2. Proposed revised OP Depot RMP submitted June 13, 2008 by Eli Lilly & Co.
3. Proposed OP Depot labeling submitted June 13, 2008 by Eli Lilly & Co.
4. NDA 22-173. Not Approvable Letter, Division of Psychiatry Products, FDA; dated February 25, 2008.
5. NDA 22-173. Type A Meeting Minutes: Post NDA action meeting, FDA; dated May 7, 2008.
6. Psychopharmacologic Drugs Advisory Committee Meeting. Agency Background Package, FDA; dated February 6, 2008.

### **2.2 ANALYSIS TECHNIQUES**

The submission was reviewed for proposed risk mitigation strategies, as well as, conformance with the Food and Drug Administration Amendments Act of 2007.<sup>5</sup>

## **3 RESULTS OF REVIEW**

### **3.1 SAFETY CONCERNS**

---

<sup>3</sup> Type A Meeting Minutes: Post NDA action meeting, FDA; dated May 7, 2008.

<sup>4</sup> Proposed OP Depot RMP submitted April 30, 2007 by Eli Lilly & Co.

<sup>5</sup> Food and Drug Administration Amendments Act of 2007. [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_public\\_laws&docid=f:pub1085.110](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pub1085.110)

According to the sponsor, safety analysis from the original Summary of Clinical Safety (SCS) and the 10-Month Safety Update have demonstrated that the overall profile of OP Depot is generally similar to that of oral olanzapine, with the exception of PDSS events and injection-site-related AEs. Additionally, medication error was identified as an important potential risk. These identified and potential risks are described in more detail below.

#### Postinjection Delirium/Sedation Syndrome

As of 31 May 2008, a total of 29 PDSS events have been identified in 28 patients during OP Depot clinical trials (1 patient experienced 2 events). Based on an estimated 40,000 injections and 2054 patients in clinical trials being administered OP Depot injections, it was estimated that PDSS events were occurring in approximately 0.07% of injections or 1.4% of patients. Because PDSS events are specific to OP Depot injection, no background incidence or prevalence exists.

The sponsor and the medical reviewer opine that adverse event reports of PDSS events demonstrate a temporal association between the excessive sedation events and symptoms consistent with some of the AEs reported in patients experiencing oral olanzapine overdose, including profound sedation, seizure, dizziness, confusion, disorientation, slurred speech, altered gait, muscle spasms, possible convulsions, and weakness. However, orthostatic hypotension, arrhythmias, and cardiac arrest which have been observed in patients experiencing oral olanzapine overdose, were not reported in these cases.

The majority of initial signs and symptoms of the excessive sedation events occurred within 1 hour of injection. However, the time to onset of the excessive sedation events ranged from immediately post injection to up to 5 hours after the injection. Events started with milder symptoms that progressed in severity. The median time to onset of symptoms was 25 minutes. Pharmacokinetic data was collected for 10 of the 29 PDSS events. This data revealed that olanzapine plasma concentration during these events substantially exceeded the typical olanzapine plasma concentration values observed after oral or OP Depot doses.

Most events occurred after the patient had received several months of injections and ranged in occurrence from 1 event at the first injection to 1 event at the 40<sup>th</sup> injection. Only one patient experienced two events. Patients have fully recovered from the excessive sedation events within 3 to 72 hours and without permanent sequelae. Among these cases, 22 were hospitalized for monitoring or treatment during excessive sedation events. Level of sedation ranged from drowsiness to coma (2 cases: one was in coma for 13 hours and another patient had bilateral miosis, no photomotroic reflex and left side Babinski). Two patients were intubated for tonic clonic convulsions and severe agitation.

Lilly has suggested that PDSS events occur as a result of “vascular trauma”, allowing the drug to be more rapidly enter the systemic circulation, causing excessively high system olanzapine exposure. Lilly is basing this theory on the temporal relationship to the injection, substantially elevated olanzapine plasma concentrations during the event in which blood samples were obtained and an incidence rate similar to that of another IM-administered drug product (Penicillin G procaine) for which another adverse effect is presumed to be attributable to accidental intravascular injection. The main evidence upon which Lilly is basing this theory on is the equilibrium solubility of olanzapine pamoate monohydrate, which is higher in blood or plasma than in muscle tissues; thus, if direct contact between OP Depot and blood occurs, olanzapine pamoate monohydrate salt would likely dissolve too rapidly.

Lilly has identified possible risk factors associated with PDSS events to include higher dose, greater age, and low body mass index (BMI), based on logistic regression analysis. OP Depot is administered as a deep intramuscular injection in to the gluteal muscle. A 19-gauge needle is included in the kit and was most commonly used; however, obese patients may have required a

larger needle. The large bore (19-gauge) needle may play some role in causing local tissue or vascular injury. It is also important to note that the higher doses of OP Depot also correspond to an increased volume of IM injection because all doses of the drug product are prepared from a fixed suspension of 150 mg/mL. For example, the 405 mg dose corresponds to 2.7 mL; therefore, one way to mitigate the risk of higher doses may be divide the dose into two injections to reduce the volume size. However, Lilly recognizes that these are “weak” risk factors and therefore, these risk factors should not be used to guide clinical practice; precautions outlined in the label should be followed for all patients treated with OP Depot, whether or not any of these risk factors are present.

#### Injection-site-related AEs

Given the Sponsor’s theory that PDSS is related to improper injection, we looked at injection-site-related AEs. Injection-site-related AEs including injection-site pain, injection-site mass, and injection-site indurations were reported with OP Depot injections and accounted for 8.6% of the AEs. The majority of injection-site-related AEs were reported by the sponsor to be mild in severity (mostly injection site pain)

#### Medication Error

If OP Depot were to be approved, there would be two IM olanzapine formulations available for prescription: a rapid-acting formulation for the treatment of agitation associated with schizophrenia and bipolar disorder (RAIM) and a long-acting formulation for the treatment of schizophrenia (OP Depot). There is a potential risk that the OP Depot would be inadvertently administered instead of the rapid-acting RAIM formulation, and vice versa. In the proposed RMP, medication errors would be monitored through routine pharmacovigilance surveillance.

#### Potential for Overdose

In addition to the potential for symptoms of overdose due to a PDSS event described above, the sponsor has identified 3 potential risks resulting in olanzapine overdose during OP Depot treatment. The sponsor considers the likelihood of such overdoses to be minimal because OP Depot is administered by a healthcare professional (HCP).

- An overdose may occur if the patient obtains the drug directly from the pharmacy and administers it without an HCP, which could result in the drug being administered incorrectly, including the possibility of a PDSS event.
- An overdose could occur if an HCP administer OP Depot more frequently than recommended, for example, 405 mg every 2 weeks rather than every 4 weeks.
- Because of synergistic effects, a patient could experience an overdose-like experience by taking oral antipsychotic medication while receiving OP Depot.

#### Pharmacological Class Effects

Weight gain, hyperprolactinemia, glucose dysregulation (potentially hyperglycemia and diabetic mellitus), orthostatic hypotension, seizures, QTc prolongation, tardive dyskinesia, neuroleptic malignant syndrome, body temperature dysregulation, dysphagia, anticholinergic activity and increased cerebrovascular events and mortality in elderly patients with dementia-related psychosis have been reported as labeled risks associated with atypical antipsychotic treatment in adults patients with schizophrenia. The general safety profile of OP Depot and oral olanzapine appears to be similar.<sup>6</sup> Additionally, the DPP medical reviewer’s analysis of cardiovascular

---

<sup>6</sup> Psychopharmacologic Drugs Advisory Committee Meeting. Agency Background Package, FDA; dated February 6, 2008.

measures did not reveal any new safety findings during treatment with OP Depot that had not been previously reported during treatment with oral olanzapine.

### **3.2 PROPOSED RISK MANAGEMENT PLAN**

Lilly proposes to address the risks as described in the RMP submission for OP Depot through labeling and through education and training activities. The proposed labeling will include a boxed warning addressing the risk of PDSS events. Additionally, the labeling will include the following:

- Description of reconstitution and proper injection technique
- Recommendation that OP Depot should be administered in a healthcare facility (such as hospital, residential treatment center, or community healthcare center)
- Recommendation that patients should be observed at the healthcare facility by a healthcare professional for at least 3 hours post injection for signs and symptoms consistent with olanzapine overdose
- Recommendation for patient information that, patients should not drive or operate heavy machinery for the remainder of the day of the injection and should be advised to be vigilant for symptoms of post-injection adverse reactions and able to obtain assistance if needed
- Description of PDSS events and the proposed mechanism for the event
- Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in PDSS events

Lilly also proposes a health care awareness program targeted towards educating physicians, administrators of treatment (nurses, case managers, social worker), pharmacists, pharmacy technicians, patients, and Lilly staff supporting OP Depot. The awareness program will include, according to the sponsor, education activities targeted for each of the aforementioned audience groups, specific labeling and packaging, and program evaluation, measurement, and follow-up.

### **3.3 PROPOSED PHARMACOVIGILANCE PLAN**

Lilly proposes to perform routine pharmacovigilance of spontaneously reported cases for OP Depot. Lilly has also created a list of targeted surveillance terms for specific AEs identified that will be used to conduct follow-up. Lilly proposes to develop a follow-up questionnaire and follow-up activities specific for terms that will be used only for sedation- and delirium-related AEs that are reported as serious adverse events (SAEs) in association with OP Depot treatment. Lilly proposes to perform routine analysis of all serious and nonserious AEs through routine pharmacovigilance and targeted surveillance activities to further evaluate those risks in temporal association with OP Depot treatment in order to identify any possible risk factors or at-risk subpopulations.

### **3.4 PROPOSED REGISTRY**

Lilly proposed to launch a *Registry Design Elements Olanzapine Pamoate Depot* REGISTRY program (detailed on pages 82 through 93 of the revised RMP) in the US for at least the first 18 months after launch. All patients who receive treatment with OP Depot would be required to enroll in the REGISTRY. The proposed objective of the REGISTRY will be to estimate the

incidence of PDSS events in a postmarketing, clinical practice setting and to further characterize the PDSS events, including time to onset and outcome. Lilly plans to provide interim analysis of the data to the FDA at minimum every 6 months for the first 18 months of the REGISTRY, with the overall results submitted at 18 months after approval of the OP Depot.

The Division of Epidemiology (DEPI) reviewed the proposed registry and provided the following comments:

Study Objective:

The sponsor stated two study objectives for the proposed registry: to estimate the incidence of (PDSS) in a postmarketing, clinical practice setting and to further characterize the PDSS events, including time to onset and outcome, in a postmarketing clinical practice setting. All patients who would receive the drug would be required to participate in the registry. The registry would capture data from open-label, actual-use in a postmarketing clinical setting for at least (b) (4) from the time of approval. The intent of the registry was described to assure safe use of the product as well as to further understand PDSS.

*Reviewer's comments: Although the proposed study objectives would provide an estimate of the incidence among treated patients as well as a time period when these events would be expected, the study objectives (as well as the proposed data elements to be collected) do not include any assessment of patient-, facility-, or drug product-related risk factors for these events. Capture of those data elements would provide further insight as to which patients would be most at risk for PDSS during OP Depot treatment and how those risks could potentially be modified. This is particularly important since the use of the drug would likely be extended to medically more heterogeneous patient populations than the clinical trials and by clinicians who are less familiar with the product's characteristics in community-based practice settings. Page 17 – 20 of the June 2008 RMP submission provides a list of the types of patients not studied and exclusion criteria for the randomized clinical trials. Many of these criteria are potential risk factors for delirium, confusion, cognitive impairment, and other clinical features of PDSS.*

Study design:

A specific study design was not stated in the June 12, 2008 document.

*Reviewer's comments: As described, this prospective cohort of patients would consist of all patients who received the drug and developed or did not develop PDSS after the use of OPD. Capture of additional potential risk factors (e.g., baseline cognitive status, co-morbidities, etc) for all patients would allow for additional comparisons of two cohorts (those who experienced PDSS and those who did not) to potentially identify patients who may be most at risk for PDSS.*

Time period:

The sponsor has proposed (b) (4).

*Reviewer's comments: In the clinical trials, PDSS occurred relatively infrequently (i.e., 1.4% of clinical trial patients as of May 31, 2008). It is also possible that the market for use of this product will be small. Thus, a longer study period may be necessary to fully characterize these events at a statistically significant level.*

Data collection:

The sponsor proposed collection of data elements such as the following:

- Patient demographics at baseline
- Per injection: date, time, dose, verification that patient left facility absent signs of olanzapine overdose, any report of a PDSS event since last injection

- For PDSS events: signs and symptoms of the event, date and time of event onset and resolution, type and timing of interventional treatment or therapy administered, whether emergency room or hospitalization occurred, outcome of the PDSS event, event follow-up using standard pharmacoepidemiologic follow-up methods.

*Reviewer's comments: The data elements proposed for collection will meet the sponsor's stated objectives (i.e., estimate of crude incidence, time to onset of the PDSS, and description of the PDSS events) among the registry cohort. However, this minimal set of data elements will not provide additional insight as to the etiology of these events and possible patient groups who are most at risk of experiencing PDSS.*

*We propose collection of data elements such as those described in publications such as a recent Cochrane review (but not limited to) for all patients who receive OP Depot<sup>7</sup>. Additional clinical data elements should be recorded for all patients who experience PDSS at the time of each episode.*

*We also recommend that an extensive review of the medical literature and consultation with practicing and academic experts in the areas of psychiatry, geriatrics, pediatrics, dentistry, and/or anesthesiology be conducted to provide a comprehensive but clinically relevant set of covariates/risk factors which could reliably, consistently and objectively be measured in the registry-based clinical practice setting(s) in which OP Depot would be administered. A number of the mentioned medical specialties have developed consensus guidelines for assessment of patient risks and management of risks associated with the use of other sedating drugs in an ambulatory care setting.<sup>8,9,10</sup>*

#### Outcome measures:

The main outcome measure proposed by the sponsor is the crude incidence rate of PDSS events and 95% confidence intervals, based upon the total number of patients enrolled in the registry as well as the total number of injections captured. Descriptive statistics of the patient population and clinical characteristics of PDSS events would also be generated. This would include time to onset for PDSS. These results would be reported to FDA at a minimum every 6 months.

*Reviewer's comments: The crude incidence of PDSS with 95% confidence intervals, as well as descriptive statistics of the population and events, are appropriate measures for such events and closer patient follow-up from this registry will provide more information than that available from the clinical trials. Reporting of the results to FDA more frequently than every 6 months is advisable, given the potential seriousness of the PDSS events as occurred in the clinical trials.*

---

<sup>7</sup> Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalized patients (review). Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005563. DOI: 10.1002/14651858.CD005563.pub2.

<sup>8</sup> American Society of Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists: an updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 2002; 96:1004 – 1017.

<sup>9</sup> American Academy of Pediatrics and the American Academy of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Adopted 2006. AAPD website: [http://www.aapd.org/media/Policies\\_Guidelines/G\\_Sedation.pdf](http://www.aapd.org/media/Policies_Guidelines/G_Sedation.pdf). Accessed October 21, 2008.

<sup>10</sup> American Dental Association. Guidelines for use of sedation and general anesthesia by dentists. Adopted 2007. ADA website: [http://www.ada.org/prof/resources/positions/statements/anesthesia\\_guidelines.pdf](http://www.ada.org/prof/resources/positions/statements/anesthesia_guidelines.pdf). Accessed October 21, 2008.

#### Measurement of confounders and effect modifiers:

The currently outlined registry design provides for measurement of very few potential risk factors which may be present in the registry population. Principally these data elements are limited to the patient demographics at baseline.

*Reviewer's comments: As noted previously, recording of additional risk factor information for all patients may provide insight into the etiology of PDSS as well as which patients subgroups may be more at risk for this adverse event. This may include, but not limited to, a checklist for baseline medical and psychiatry history, medication use history (including non-prescription drugs and dietary supplements), and assessment of baseline psychiatric and cognitive status. No mention was made of measurement of serum olanzapine concentrations and the timing of those measurements.*

*Capture of additional data elements is detailed for an observational epidemiologic study (FID-MC-B034) which has been proposed to be conducted outside of the U.S. in the April 16, 2007 supplement on pages 73 – 118. However, this outline also did not recommend collection of more detailed medical, psychiatric, or cognitive status information at baseline which could be risk factors for prolonged sedation, delirium and other symptoms that occurred in the PDSS cases.*

#### Sample size:

No information was provided on sample size.

*Reviewer's comments: In the June 12, 2008 submission on page 21, Lilly estimated the use of OPD in the United States from 2009 to 2018 to be approximately 1.7 million patient injections and 140,000 patients exposed. PDSS occurred in approximately 1.4% of clinical trial patients as of May 31, 2008. An estimate of the number of patients treated during the proposed period of study would allow for power estimates and a possible threshold for statistically significant differences among patient subgroups.*

#### Statistical analysis:

No details were provided as to which statistical tests would be used.

*Reviewer's comments: Detailed information on and appropriate methods for calculation of incidence 95% confidence intervals and other outcome measure comparisons would allow for peer review of the methods and should be provided for all such studies.*

### **3.5 PROPOSED EVALUATION PLAN**

Lilly has not submitted a plan to evaluate the proposed RMP.

## **4 DISCUSSION**

The safety evaluation performed by the DPP medical reviewer has demonstrated that the safety profile of OP Depot is similar to that of oral olanzapine for most parameters that were measured, with the exception of injection-related adverse events and the excessive sedation events that Lilly has termed PDSS events. PDSS events are specific to OP Depot. The excessive sedation events have raised a serious safety concern because of the severity of sedation, combined with a relatively high incidence and unpredictability of event.

PDSS events have been reported in approximately 1.4% of patients during the clinical trials. The characteristic of PDSS events are not well understood and there is a great deal of variability. The severity of the events in the clinical trials ranged from dizziness to coma and convulsions requiring intubation. Due to the variability in the time to onset (ranging from immediately pos-



injection to 5 hours) and the number of injections (1 event at the first injection to 1 event at the 40<sup>th</sup> injection), it is impossible to predict an event. Additionally, the risk factors (higher dose, greater age, and low BMI ) that Lilly has identified are considered as “weak” risk factors and therefore, should not be used to guide clinical practice.

The mechanism underlying these events is unclear but has been suggested to be as a result of “vascular trauma” with olanzapine rapidly entering the systemic circulation leading to olanzapine overdose type effects. However, we note that olanzapine plasma levels were only measure in 34% of the patients experiencing PDSS events. Most of the injection-site-related AEs were considered to be mild in severity. Furthermore, during the clinical trials (July 2006), Lilly trained their study personnel and reinforced IM injection technique to reduce the incidence of “vascular trauma” resulting in potential PDSS events. Despite these efforts, the medical reviewer opines that the incidence of the excessive sedation events did not change and 10 additional cases were reported after the training.<sup>11</sup> The sponsor has proposed as part of the RMP labeling, training and brochures for healthcare professionals on proper reconstitution and administration of OP Depot. We remain concerned that despite the education that is to be provided to prescribers and other HCPs regarding proper reconstitution and administration of OP Depot, PDSS events are going to continue to occur.

Lilly assumes that OP Depot will be used most often in treating symptomatic schizophrenia patients who have difficulties adhering to oral treatment or who have failed “several oral options” but have shown positive response and favorable tolerability to oral olanzapine. Incidence of treatment resistance among schizophrenia patients is approximately 20%. (Kane et al.1988). In the clinical trials patients resistant to oral olanzapine were excluded. We recommend that language in the labeling be crafted as to help clinicians target OP Depot to a narrower patient population, including patients who have shown a good response to oral olanzapine or who have difficult adhering to oral therapy. This language should be reinforced in the key messages of the REMS.

Lilly has proposed an RMP that includes labeling, education and training, routine pharmacovigilance, and targeted surveillance. The sponsor has also proposed a mandatory registry that will be used to collect additional information about PDSS events. The data elements proposed for collection by Lilly will allow for estimation of the crude incidence for PDSS events, the mean time to onset of PDSS, and the general clinical course of PDSS. The minimal proposed set of data elements will not provide insight as to the etiology of PDSS and possible patient subgroups who are most at risk of experiencing PDSS. This is particularly important since the use of this drug would likely be extended to medically more heterogeneous patient populations than the clinical trials and by clinicians who are less familiar with the product’s characteristics in community-based practice settings.

Most importantly, the proposed registry does not include means to manage the risk of PDSS. Therefore, we believe that a special distribution program be developed instead to ensure informed prescribing, administration, and patient monitoring of all patients. We recommend risk mitigation strategies including enrollment of all patients and healthcare facilities as well as training and certification of all healthcare professionals that will be prescribing or administering OP Depot. Additionally, a plan to ensure that the drug is dispensed to patients with documentation of safe use conditions would allow for systematic collection of information from

---

<sup>11</sup> Psychopharmacologic Drugs Advisory Committee Meeting. Agency Background Package, FDA; dated February 6, 2008.

all US patients receiving OP Depot on risk factors and other data of interest to further characterize the PDSS events.

We agree with the sponsor, the key to mitigate the risk associated with PDSS events is to ensure that PDSS events are identified in a timely manner so affected patients can receive the appropriate medical intervention and that the events do not occur in a location that would place the patient or public at risk. Therefore, it is essential that OP Depot be only administered in healthcare facilities that can observe patients for several hours and provide the medical intervention necessary in case of an event. Appropriate monitoring at the time of the injection and several hours post-injection is necessary to ensure the safe use of OP Depot. Due to the varying degree of sedation observed in the clinical trials ranging from dizziness to coma, the healthcare facilities must be equipped and have certified staff to provide for resuscitation and intubation if needed.

## **5 CONCLUSION AND RECOMMENDATIONS**

We have reviewed the revised RMP and are concerned that despite the education that is to be provided as part of the RMP to prescribers and other HCPs regarding proper reconstitution and administration of OP Depot, PDSS events are going to continue to occur. Therefore, we have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary at the time of approval to ensure the benefits of the drug outweigh the risk of PDSS events. The REMS should consist of a Medication Guide, possibly a communication plan, elements to assure safe use, an implementation plan, a timetable for assessments, and assessments of the REMS.

The elements to assure safe use should include at minimum the following:

- Enrollment of all patients, physicians, and healthcare facilities as well as training and certification of healthcare professionals that will be prescribing or administering OP Depot.
- It is essential that OP Depot be only administered in healthcare facilities that can observe patients for several hours and provide the medical intervention necessary in case of an event. Appropriate monitoring at the time of the injection and several hours post-injection is necessary to ensure the safe use of OP Depot. Due to the varying degree of sedation observed in the clinical trials ranging from dizziness to coma, the healthcare facilities must be equipped and have certified staff to provide for resuscitation and intubation if needed. These criteria should be required in order for the healthcare facility to obtain certification.
- Documentation of safe-use conditions including appropriate monitoring and evaluation of patients prior to discharge from healthcare facilities.

If a determination is made that a separate registry above full enrollment of patients and data collection as part of the REMS is necessary to assess the safety of OP Depot or to collect additional data, it should be included as a PMR and the questions about the study objectives, study time period, plans for data collection and the statistical analysis, and the planned sample size would need further discussion. The DPP should work with DEPI in OSE to finalize the protocol for the registry. Finally, we recommend that language be crafted in the labeling to help clinicians target OP Depot to a narrower patient population (i.e., patients who have shown a good response to oral olanzapine or who are non-compliant with oral therapy). This language should be reinforced in the key messages of the REMS.

DRISK has collaborated with DPP in drafting a complete response letter which outlines the REMS requirements.<sup>12</sup> Please consult OSE Division of Risk Management once the sponsor submits a proposed REMS.

---

<sup>12</sup> NDA 22-173: Olanzapine Pamoate Depot Complete Response Letter; cleared by OCC December 12, 2008.

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

/s/

-----  
Gita Akhavan-Toyserkani  
12/15/2008 04:02:36 PM  
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski  
12/15/2008 04:05:44 PM  
DRUG SAFETY OFFICE REVIEWER