CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-173

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #22-173/000

Sponsor:	Eli Lilly and Company
Drug:	Olanzapine Pamoate Depot
Proposed Indication:	Schizophrenia
Material Submitted:	Resubmission to CR Letter
Correspondence Date:	March 11, 2009
Date Received:	March 12, 2009
Related NDA:	NDA 20592 (olanzapine oral tablet)

I. Background

The original NDA was submitted on April 27, 2007 for the indications of acute and maintenance treatment of schizophrenia, and was granted a not approvable status on 25 February 2008. The primary deficiency in this application is the lack of sufficient information on the risk of a severe adverse event, the post-injection delirium/sedation syndrome (PDSS), characterized with severe central nerve system (CNS) depression and temporally associated with olanzapine pamoate depot (OP Depot) injection, which has been observed in approximately 1% of patients who have participated in the development program for OP Depot.

On 7 May 2008, Lilly met with FDA to discuss aspects of a proposed amendment to the application that would address the primary deficiency, PDSS, including enhanced label language and risk-minimization activities. FDA suggested a medication registry in addition to the sponsor's proposed risk management plan.

On 13 June 2008, Lilly submitted a completed response package to the Not Approvable (NA) letter dated on 25 Feb. 2008. The submission includes an amended risk management plan, including additional information regarding the medication registry and draft training materials.

On 15 December 2008, FDA issued a Complete Response (CR) Letter and requested the sponsor submitting a revised Risk Evaluation and Mitigation Strategy (REMS) and a revised Medication Guide to address the deficiencies identified by the division of Risk

Management (DRISK), the Office of Surveillance and Epidemiology (OSE).

On 11 March 2009, the sponsor submitted this resubmission in response to the CR letter dated on December 15, 2008. This resubmission includes a draft labeling including USPI and Medication Guide; revised REMS and REMS supporting document; and other minor clarifying information requested by FDA.

DRISK will continue to follow up REMS and Medication Guide. Please refer to their review for pertinent information. In this review, the writer will focus on labeling review only.

II. Labeling Review

Dosage and Administration

The sponsor proposed following table intended to guide prescribers how to switch from oral olanzapine to OP Depot. The sponsor proposed a high starting dose regimen for the first 8 weeks of treatment (middle column of the table). This regimen has never been systemically tested in clinical trials, and was proposed by the sponsor based on the results of relative risk analyses (risk to relapse) on data obtained from study HGKA. HGKA is a 24-week, randomized, double-blind, maintenance study comparing the efficacy and safety of OP Depot (150 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks) with oral olanzapine (10, 15, and 20 mg/day) and low dose OP Depot (45 mg/4 weeks) in clinically stabilized outpatients with schizophrenia. Relative risk analysis result showed incrementally less risk of exacerbation when switching patients to higher OP Depot doses. Based on the results, Lilly proposed a high starting dose regimen—starting patients with higher doses for the first 8 weeks. The original analysis data were submitted to FDA on 27 December 2007 as an amendment. The clinical review with regards to this issue was included in my NDA review for the resubmission to the NA letter dated on 8 December 2008.

Target Oral ZYPREXA Dose	Dosing of ZYPREXA RELPREVV During the First 8 Weeks	Maintenance Dose After 8 Weeks of ZYPREXA RELPREVV Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

In this resubmission, the sponsor submitted some simulation data to support the high starting dose regimen. Andre Jackson, PhD, from the Office of Clinical Pharmacology (OCP) is the primary reviewer for these data. He concurs that the simulation data support the high starting dose regimen.

Even though Lilly proposed higher starting dose regimen has not been tested systemically in the clinical trials, all proposed starting doses had been tested in the controlled clinical trials and had been well tolerated by patients. The simulation data showed that with higher loading dose in the first 8 weeks the blood olanzapine concentrations reached to steady status faster. From a clinical point of view, the proposed starting doses appear to be safe to be used in clinical practice.

(b) (4)

(b) (4)

(b) (4)

Adverse Reactions

I recommend removing the subsection (b) (4) (b) (4) under section *6.1 Clinical Trial Experience* because the data in this subsection do not provide useful information for the prescribers.

The rest labeling changes proposed by the sponsor are acceptable from a clinical point of view.

III. Recommendation on Regulatory Action

Based on the data available at this time point and after considering the risks and benefits of having this product available to treat a severe mental illness, schizophrenia, I recommend that this NDA be granted approvable status.

Final approval is contingent on satisfactory response to the agency's requests on REMS and Medication Guide, and mutual agreement on labeling.

Jing Zhang, M.D., Ph.D.
22 July 2009

cc: NDA 22-173
HFD-130 (Div. File)
HFD-130/M Mathis
/T Laughren
/G Zornberg
/J Zhang
/K Kiedrow

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/s/

Jing Zhang
7/22/2009 01:07:03 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 13, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Complete Response action for olanzapine pamoate depot formulation (OP Depot) for the treatment of schizophrenia

TO: File NDA 22-173
[Note: This overview should be filed with the 6-13-08 complete response to FDA's 2-25-08 NA letter for this NDA.]

1.0 BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including maintenance claims for both. This NDA provides evidence that is intended to support claims for OP Depot for the treatment of both acutely exacerbated schizophrenia and also the maintenance treatment of schizophrenia.

We met with Lilly a number of times between 1999 and 2007 during the development of this depot product. We had agreed with the sponsor that a single short-term trial (HGJZ) would be sufficient for filing this application. The development program included a total of 8 clinical studies in schizophrenia, including 2 controlled efficacy and safety studies and 6 open-label studies.

There are currently only 3 depot antipsychotics available for use in the US, including 2 typical antipsychotics (fluphenazine decanoate and haloperidol decanoate) and 1 atypical antipsychotic (Risperdal Consta). The depot formulation for an antipsychotic drug is felt to be an important treatment option, since so many schizophrenic patients are noncompliant with oral medications and this is often difficult to ascertain.

Following review of the 4-30-07 original application for this NDA, we concluded that the sponsor had shown that this formulation is effective in the acute and maintenance treatment of schizophrenia and had a safety profile generally similar to other formulations. There was, however, a new adverse event for this formulation that was of considerable concern, i.e., infrequent instances of profound sedation and delirium shortly following injections. At the time we brought this application to the PDAC in February, 2008, it was our understanding that all

such events occurred within 3 hours of injection, and most, in fact, within the first hour. However, after that meeting, we became aware of a case that occurred beyond 3 hours, perhaps as late as 5 hours. This new case raised doubt about both the feasibility of monitoring for the emergence of such events as well as the mechanism. Consequently, we issued a Not Approvable letter for this application on 2-25-08, asking the sponsor to better characterize the nature of this event and its time course. We also cited several CMC and OCP concerns. We met with the sponsor on 5-7-08 to discuss approaches to addressing this concern about these infrequent adverse events. We proposed a strict registry as an approach to relatively quickly developing a database to better characterize the incidence and distribution of time to onset of this event under more typical conditions of use in the community. Lilly agreed to this requirement and resubmitted the application on 6-13-08.

2.0 CHEMISTRY

The CMC issues for this application conveyed in the 2-25-08 NA letter have all been resolved. The CMC group, therefore, is recommending an approval action, pending agreement on (1) the established name recommended by the LNC, i.e., "(olanzapine) for extended release injectable suspension," and (2) the dissolution specifications recommended by OCP. This would permit an expiry of 36 months.

3.0 BIOPHARMACEUTICS

The only remaining OCP issue is the dissolution specifications, and we will include these recommendations in the CR letter.

4.0 CLINICAL ISSUES AND LABELING

4.1 REMS

Following our discussions with the sponsor about the sedation/delirium events occurring post-injection, they proposed an alternative name, i.e., Post-Injection Delirium/Sedation Syndrome (PDSS), and we have accepted this name. Although the sponsor had accepted our recommendation for a mandatory registry as the sole source of OP Depot, their 6-13-08 response provided only limited details on how this registry would actually be implemented. We have obtained consultation from DRISK in OSE on the sponsor's proposed program, and they have recommended a full Risk Evaluation and Mitigation Strategy (REMS) to address this event. This would include "Elements to Assure Safe Use," an "Implementation System," and a "Timetable for Assessments." This proposal goes well beyond what the sponsor had proposed regarding the educational and monitoring aspects of this program. In addition, we have decided that a Medication Guide is needed to convey this concern about the PDSS events to patients and their families, and the Medication Guides would also need to address the metabolic concerns with this drug.

4.2 Labeling

We have carefully considered the sponsor's proposed labeling, and have made numerous changes. This revised label will be included with our CR letter.

5.0 CONCLUSIONS AND RECOMMENDATIONS

Although I believe that Lilly has submitted sufficient data to support the conclusion that OP Depot is effective in the treatment of schizophrenia, and they have proposed a registry that, in principle, should provide for the reasonably safe use of this product, they have not submitted sufficient detail regarding the implementation and monitoring of this program. In addition, we feel a Medication Guide is needed to fully inform patients and their families about the risks of using this product. Consequently, we will issue a Complete Response letter requesting these additional measures. We will attach our counter-proposal for labeling.

cc:
Orig NDA 22-173
HFD-130/TLaughren/MMathis/GZornberg/JZhang/KKiedrow

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/s/

Thomas Laughren
12/13/2008 01:53:41 PM
MEDICAL OFFICER

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

DATE: December 9, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Medical Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Complete Response action for TRADENAME (olanzapine pamoate) Depot for treatment of schizophrenia (short-term efficacy and maintenance treatment).

TO: File NDA 22-173 (Olanzapine Pamoate) Depot
Response (13 June 2008) to NA action (25 February 2008)

REVIEWERS: Dr. Gita Akhavan-Toyserkani, Division of Risk Management; Dr. Jing Zhang, Clinical; Dr. David Claffey, ONDQA; Biopharmaceutics, Dr. Andre Jackson.

1.0 BACKGROUND

ZYPREXA olanzapine pamoate (OP depot) is an extended release injectable suspension antipsychotic drug formulation developed for use in the treatment of schizophrenic patients with poor adherence to treatment. Eli Lilly has 3 approved olanzapine products: 1) Zyprexa tablets [NDA 20-592, 3- SEP 1996]; 2) Zyprexa Zydis Orally Disintegrating tablets [NDA21-086, 06-APR-2000]; and 3) Zyprexa IM [NDA 21-253, 29-MAR 2004]. Olanzapine pamoate monohydrate (OP) depot is a monohydrate, low aqueous soluble crystalline salt. This NDA seeks a claim for the use of OP Depot in the short-term and maintenance treatment of patients diagnosed with schizophrenia who are able to tolerate oral olanzapine and tend to be poorly adherent with treatment. DNP met initially with the applicant on 26 AUG 1999 to discuss the required program to support registration of OP Depot and on 22 JUL 2003 as well as 09 SEP 2005 to discuss a number of CMC and clinical pharmacology issues. Eli Lilly and Company submitted one short-term efficacy and one maintenance trial in patients diagnosed with schizophrenia.

The cardinal safety issue that has delayed approval is the still poorly characterized risk of Postinjection Delirium/Sedation Syndrome (PDSS). PDSS encompasses adverse drug

reactions that resemble the CNS depression and associated symptoms of olanzapine overdose. In the original application, 20 of 24 patients were hospitalized. Five of the patients were diagnosed as having acute alterations of their levels of consciousness in hospital. These 25 episodes of severe CNS depression and associated symptoms occurred in 24 patients (one patient experienced 2 serious PDSS events). In one patient, after 2 hours, bilateral miosis was observed coupled with the absence of photo-motor reflexes, the presence of automatic movements and a positive Babinski sign. Of 24 patients, two patients with CNS depression within 3 hours postinjection were intubated. None of the patients had elevations of sedating drugs such as benzodiazepines, alcohol, barbiturates, opioids, or illicit drug levels on toxicological evaluation that would confound the clinical picture. At the PDAC (6 February 2008), it was shown that at least 7 of 24 patients were not using concomitant medications around the time of the event that could reasonably be considered causal to PDSS. There were no deaths and the episodes of CNS depression resolved in all 25 events.

It is noteworthy that after the sponsor became aware of the occurrence of PDSS events in the clinical research, the healthcare providers were systematically trained in the administration of OP depot. Nonetheless, no change in pattern of PDSS risk occurred after the administration training program required by the sponsor took place. Lilly reported that following recovery from these acute episodes and the patients chose to continue to be treated with elevated olanzapine serum levels for the duration of the intended time for systemic exposure. It is notable that no other antipsychotic drug, including the long-acting formulations have been associated with a relatively common incidence of CNS depression progressing into coma in some patients and not observed in placebo treated patients.

On 27 December 2007, Lilly submitted to the NDA additional analyses of clinical trial data to justify modification of the starting regimens to further reduce the risk of psychotic exacerbations in the effort to optimize treatment. These modifications have been depicted in a revised Table 1 in the **DOSAGE AND ADMINISTRATION** section of the sponsor's proposed labeling.

The Psychopharmacologic Drug Advisory Committee (PDAC) held 6 February 2008 recommended authorization of OP Depot as a potentially important treatment option in patients diagnosed with schizophrenia with poor adherence to treatment. The PDAC found generally that the positive efficacy findings in view of the established efficacy of Zyprexa coupled with the resolution of all PDSS episodes of excessive sedation and the absence of deaths related to PDSS favored approval. Following the PDAC, however, Lilly submitted additional data to suggest that there was inadequate information regarding the unpredictable pattern of time to PDSS event. A nonapprovable action letter was issued on 25 February 2008 due to inadequate information to support approval regarding the occurrence of serious PDSS event in patients administered OP Depot.

Lilly met with FDA on 7 May 2008 to discuss proposed amendments to the application to mitigate and reduce the risk of PDSS, which would allow a path forward.

2.0 CHEMISTRY

Dr. David Claffey has provided in an email dated 23 October 2008 the revision of the initial recommendation of the Labeling and Nomenclature Committee that the established name drug product be changed from "olanzapine long-acting injection" to "olanzapine for injectable suspension".

As Lilly requested the term “extended release” in the tradename, the division recommends that the drug product be labeled as “TRADENAME (olanzapine) for Extended Release Injectable Suspension”. Moreover, if Lilly adopts the sponsor adopts the dissolution specifications recommended below by the Clinical Pharmacology reviewer, Dr. Jackson, an expiry period can be assigned by Dr. Claffey.

At present, I am not aware of ONDQA issues that would preclude a Complete Response action for this NDA.

3.0 BIOPHARMACEUTICS

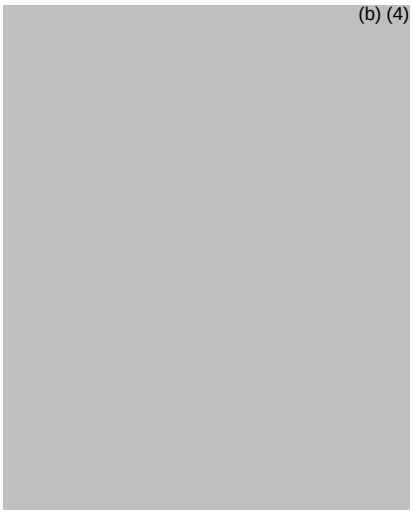
The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewer, Dr. Andre Jackson, has requested that the sponsor adopt the following the dissolution specifications as of this date, to be resolved before an expiry period can be assigned by CMC.

1% Sodium Lauryl Sulfate in USP buffer pH 6.8 medium using USP Apparatus 4 (or Ph.Eur.2.9.3 Flow-Through Apparatus) at 3 ml/min flow rate.

210 mg:
%released at 30 min
% released at 2 hrs
% released at 8 hrs

300 mg:
%released at 30 min
% released at 2 hrs
% released at 8 hrs

405 mg:
%released at 30 min
% released at 2 hrs
% released at 8 hrs



Within one year after the date of this letter, Lilly is required to resubmit or take one of the other actions available under 21 CFR 314.110. If Lilly does not take one of these actions, we will consider the sponsor’s lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A

partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

I am aware of no biopharmaceutics issues that would preclude a complete response action for this NDA.

4.0 CLINICAL REVIEW OF RISK MANAGEMENT

4.1.1 Risk Management Plan (RMP) Proposed by Lilly

Post-injection Delirium/Sedation Syndrome
The term Post-injection Delirium/Sedation Syndrome PDSS was coined by Lilly to capture the cardinal identified clinical risk syndrome of serious CNS depression associated with a spectrum of associated symptoms consistent with olanzapine overdose. Lilly initially used the term "Inadvertent Intravascular Injection" to describe these events based on their hypothesis regarding the mechanism of action. As the mechanism of action remains poorly delineated, the PDSS clinical descriptor is more informative. The risk of PDSS appears to be unique to OP Depot and is well described by Dr. Zhang in her clinical review (8 December 2008).

Lilly submitted a RMP on 30 April 2008 as part of the original NDA submission. The central feature of the RMP turned on enhanced warnings in labeling, routine pharmacovigilance, and a post-marketing observational pharmacovigilance study (B034). On 13 June 2008, Lilly submitted a revised RMP with a mandatory registry for postmarketing data collection the study the occurrence and risk factors for PDSS as the central component of the complete response as a path forward for the application, as described in Dr. Zhang's review.

Lilly proposed to perform targeted surveillance, as well as routine pharmacovigilance activities in the 13 June 2008 RMP. The sponsor provided a Draft of their proposed Clinical Case Definition of Postinjection Delirium/Sedation Syndrome (RMP, Appendix 4, page 100).

1. At least 3 signs or symptoms from the list below with at least one of moderate severity combined with either a state that is unarousable, unconscious, stuporous, or comatose.

i. Sedation/somnolence
ii. Delirium/confusion/disorientation/other cognitive impairment
iii. Dysarthria/other speech impairment
iv. Ataxia/other motor impairment
v. EPS
vi. Agitation/ irritability/ anxiety/ restlessness
vii. Dizziness/weakness/general malaise
viii. Seizure

2. Condition develops within 24 hours of OP depot injection.

3. Cannot be explained by a significant dose increase of OP Depot or new exposure.
4. Underlying medical conditions have been ruled out.

While the sponsor had provided sufficient evidence to support the claim of short-term treatment of acute psychosis and longer-term maintenance treatment with olanzapine OP Depot as efficacious treatment of patients diagnosed with schizophrenia and proposed a required registry to improve the benefit compared to the risk of PDSS, the unpredictable and serious nature of the risk of PDSS was found on clinical review of the response to the NA action in consultation with the Division of Risk Management to require a REMS.

Changes in Weight, serum Lipids, and Serum Glucose Levels
The profile weight gain and risk of associated elevations of serum lipids and glucose in patients exposed to OP depot resembles that observed in patients administered oral olanzapine. In the clinical review of the original NDA, a dose response relationship was observed i patients who gained at least 7% of baseline weight, as well as those patients who experienced elevated serum levels of fasting triglycerides (TG) in the 8-week, placebo-controlled trial. Weight gain and elevated serum TG levels were most often observed in the 300 mg/2Wk group. These weight related issues were not addressed in this version of the RMP submitted by Lilly in response to the NA. A Medication Guide, however, is being developed for use with labeling for all Zyprexa (olanzapine) formulations, with the same language to be highlighted in the OP Depot Medication Guide.

Healthcare Awareness Program (HAP)
Lilly proposed a HAP to educate those who would be involved with supplying, or administering OP Depot and caring for patients using OP Depot and provide a high level summary of the program found in Dr. Zhang's review.

Draft PLR Labeling – Modifications Proposed by Sponsor (in the event of a future approval action)
Boxed Warning.
Description of PDSS and proposed mechanism.
Description of most common symptoms to monitor.
Reconstitution and proper injection technique.
Recommendation that OP Depot should be administered in a healthcare facility.
Recommendation that patients be observed by a healthcare professional for at least 3 hours postinjection.
Recommendation that patients be informed that for the rest of the day, they should not operate heavy machinery.

4.1.2 Conclusions Regarding the Proposed RMP

I agree with Dr. Zhang's conclusion in her review that the proposed outline of pharmacovigilance surveillance activities are acceptable, in the absence of a full protocol. Dr. Akhavan-Toyserkani has recommended also that the sponsor collect data on all

patients on weight changes over time from first dose of OP Depot (along with demographic such as height, age, race, an gender), as well as time of occurrence related to injection, type and timing of interventional therapy administered as well as course and outcome of the PDSS event.

With regard to Lilly's proposed PDSS case definition above, the sponsor highlighted those symptoms most consistent with excessive sedation, which is consistent with CNS depression related to overdose. In addition, Lilly added in EPS as a feature of PDSS. EPS has already been well characterized in labeling and did not appear to be a cardinal feature of PDSS.

4.2 Risk Evaluation and Mitigation Strategy (REMS)

4.2.1 REMS Requirements

In consultation with DRISK of OSE, it has been decided that a REMS is required for authorization in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for OP Depot (olanzapine), NDA 22-173, to ensure the benefits of the drug outweigh the risks of post-injection delirium and sedation syndrome (PDSS). . Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategies (REMS) if FDA has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). The REMS must include the following elements:

I. Medication Guide:

The Medication Guide should include information about the risk for PDSS and the need to seek immediate medical assistance should these events occur following discharge from a healthcare facility. The Medication Guide for OP Depot should also include the final language for the Medication Guide that is under review regarding changes in weight, serum lipids and glucose observed with olanzapine treatment in response to the approvable letter sent 1 August 2008 (NDA 20-592/s-039/040/041; 21-520/012; 21-086/021; 18-936/077).

II. Elements to Assure Safe Use:

1. A plan to ensure that OP Depot will only be prescribed by prescribers who are specially certified under 505-1(f)(3)(A) through the certification process described below.
2. A plan to ensure that OP Depot is only dispensed/administered in healthcare settings that are specially certified under 505-1(f)(3)(B) through the certification process described below.
3. A plan to ensure that the drug is dispensed to patients with documentation of the following safe use conditions under 505-1 (f) (3)(D).

III. Implementation system
The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that requires that the drug be dispensed to patients with documentation of safe-use conditions and an intervention plan to address any findings of non-compliance with the elements to assure safe use.

IV. Timetable for Assessments: We have determined that the REMS must include a timetable for assessments that shall be no less frequent than every 6 months for the first year and annually thereafter, after the REMS is approved. We recommend that Lilly specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval. The REMS, once approved, will create enforceable obligations. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved with dates of additional assessments if needed.

5.0 Safety Update

5.1 Ten month Safety Update

No new or unexpected findings were reported in the 10-month safety update. No additional cases of PDSS were reported with onset after 3 hours postinjection. Adverse drug reactions commonly reported with olanzapine use such weight gain, elevated triglycerides, and elevated prolactin levels were found with expected frequency and severity as reviewed by Dr. Zhang. Two deaths that occurred after database lock did not appear to be related to OP Depot exposure.

6.1 Labeling

Medication Guide Issues

In the effort to maximize the safety of this potentially valuable treatment option, when an approval action will be taken, FDA will require major modifications to Lilly's proposed Zyprexa OP Depot draft labeling for the schizophrenia indication that was submitted in PLR format along with the Medication Guide. Lilly will be providing a Medication Guide for OP Depot containing critical information regarding the clinical syndrome of PDSS and on the risks of hyperglycemia, hyperlipidemia, and clinically significant weight gain. In the Complete Response, the agency will request that Lilly create a satisfactory Medication Guide to be submitted for review.

Dosage and Administration

Labeling will not be negotiated during this cycle when the Complete Response action will be taken. In preparation for future negotiations, the sponsor provided additional data to support more detailed OP Depot starting dose recommendations in table 1 of the proposed draft labeling to help reduce risk of psychotic exacerbation upon initiation of therapy. The relative risk analyses indicate that patients were at greater risk of exacerbation during the first 2 months of treatment with OP Depot, particularly at the lowest dose levels. Patients who were switched to higher doses of OP Depot were found to be at reduced risk of exacerbation. Table 1 provides recommended starting and, after 2 months, maintenance doses to help optimize treatment.

In addition to modification of the possible starting dose regimens, Lilly also provided proposed language to use oral olanzapine supplementation when clinically necessary during initial treatment. As the combination of higher starting doses and oral supplementation would confer potential new safety risks, the Dosage and Administration starting regimens will need to be more carefully crafted by Lilly for labeling in response to the recommended Complete Response action.

7.0 CONCLUSIONS AND RECOMMENDATIONS

On the path forward to ensure that the benefits outweigh the risks, I recommend to the Division Director that a Complete Response letter be issued by the action date.

Before an approval action can be taken in Lilly's future response to the Complete Response, the anticipated draft OP Depot REMS with Medication Guide including language regarding risk of PDSS must be reviewed, as well as risks of weight gain and associated hyperlipidemia and elevated serum glucose levels with all Zyprexa formulations, which is under review. In keeping with requirements under FDAAA, Eli Lilly and Company must submit a satisfactory REMS and Medication Guide with labeling in order to mitigate the potential for serious PDSS events and their potential consequences associated with OP Depot use. The REMS must include the 4 required elements: a Medication Guide, elements to assure safe use, the implementation system, and a timetable for assessments.

The Medication Guide should provide information on the nature of PDSS along with monitoring postinjection for at least 3 hours and seeking medical assistance in the event of PDSS. All certification and educational materials must be submitted to FDA prior to approval. The patients, physicians and pharmacists must be enrolled in the REGISTRY program and receive training to prescribe, dispense or administer OP Depot. Repeat training and/or certification may be necessary. The patients will be required to be enrolled in the registry and sign a patient-physician agreement upon initiation of treatment. Patients will be required to be monitored for at least 3 hours periodically by a healthcare professional in a controlled environment to ensure that the benefits outweigh the risks. Drafts of adverse event, and other data collection, forms as well as other REMS related materials must be submitted to FDA prior to approval. The implementation system must include a plan to monitor distribution and prescribing data

to ensure that OP Depot is only prescribed, dispensed and administered by the certified entities. In terms of Communication Plan, all educational materials for the REMS should be submitted for review prior to approval.

FDA has determined that the REMS must include a timetable for assessments that shall be no less frequent than every 6 months for the first year and annually thereafter, after the REMS is approved. We recommend that Lilly specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval. The REMS, once approved, will create enforceable obligations. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved with dates of additional assessments if needed.

The full observational pharmacovigilance study B-034 protocol to evaluate risk factors for PDSS must be submitted for review. I concur with the recommendations of Dr. Akhavan-Toyserkani as described in detail in her review for the collection baseline weight and height (and other demographic data) with follow up weight assessment, and PDSS event related data collection with a proposed AE data collection form in the proposed pharmacovigilance study detailed in the DRISK consultation. I agree, too, with Dr. Zhang's recommendation to ensure that data is collected in the observational study to enhance understanding of the well established association between olanzapine use and weight gain.

With respect to the sponsor's proposed starting and maintenance treatment regimens in the revised Table 1 of Lilly's proposed labeling (27 December 2007), the dose levels are acceptable as they have been shown to be safe and effective in the OP Depot clinical trials. Lilly must provide more data, however, to support the new proposal of an oral maintenance program, particularly in view of the new proposal of elevated starting dose regimens. For the **Dosage and Administration** sections of future labeling, I agree with Dr. Zhang that Lilly needs to provide more information to support and clarify the initial dosing and the oral supplementation program, as well as the switch to maintenance treatment. At present, we recommend that either the higher starting dose or the oral supplementation be used, one at a time to optimize the safety of the starting regimens.

Based on the requirements regarding the REMS and the Medication Guide outlined in the Complete Response letter in accordance with FDAAA to ensure that the benefits of OP Depot outweigh the risks, I recommend to the Division Director that the Complete Response letter be issued by the 16 December 2008 action date.

cc:
Orig NDA 22-173
HFD-130
HFD-130/GZornberg/JZhang/MMathis/TLaughren /KKiedrow/SHardeman

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Filed on 9 December 2008 becuase DFS was not available 8 December when uploading was attempted.

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/s/

Gwen Zornberg
12/9/2008 09:10:52 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 22-173
Submission Number	000
Submission Code	N (Resubmission)
Letter Date	June 13, 2008
Stamp Date	June 14, 2008
PDUFA Goal Date	December 16, 2008
Reviewer Name	Jing Zhang, MD, PhD
Review Completion Date	December 5, 2008
Established Name	Olanzapine Pamoate Depot
(Proposed) Trade Name	Pending
Therapeutic Class	Atypical Antipsychotic
Applicant	Eli Lilly
Priority Designation	S
Formulation	Intramuscular Injection
Dosing Regimen	210 mg/3 ml, 300 mg/3 ml, and 405 mg/3 ml
Indication	Schizophrenia
Intended Population	Adults

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1. Background

This NDA was initially submitted on April 27, 2007 by Lilly for the indications of acute and maintenance treatment of schizophrenia, and was granted a not approvable status on 25 February 2008. The primary deficiency in this application is the lack of sufficient information on the risk of a severe adverse event characterized with severe central nerve system (CNS) depression and temporally associated with olanzapine pamoate depot (OP Depot) injection, which has been observed in approximately 1% of patients who have participated in the development program for OP Depot.

"Inadvertent Intravascular (IAIV) injection Events" had been used by the applicant in the original NDA submission to describe these severe adverse events with clinical presentations similar to oral olanzapine overdose. During the course of FDA reviewing, terms such as "excessive sedation" and "severe CNS depression" had been used to name these events. In this submission, the sponsor proposed a term "post-injection delirium/sedation syndrome (PDSS)". The division agreed that PDSS seems a better term to describe this event. From this point forward, PDSS is used throughout this document.

On 7 May 2008, Lilly met with FDA to discuss aspects of a proposed amendment to the application that would address the primary deficiency, PDSS, including enhanced label language (black box warning, 3 hours post injection on-site observation, accompaniment of all patients to their destination and avoidance of driving or operation of heavy machinery for the remainder of the day) and risk-minimization activities (dear HCP letter, physician and nurse training, and other educational programs). FDA suggested a medication registry in addition to the sponsor's proposed risk management plan. The registry will provide an opportunity to quickly develop a database to better estimate the incidence of this event and the distribution of time to onset of this event under conditions of more typical use in the community.

On 13 June 2008, Lilly submitted this completed response to the Not Approvable (NA) letter. This submission includes an amended risk management plan, including additional information regarding the medication registry and draft training materials; updated US labeling, including Lilly's response to comments received from DMETS; safety update; and Lilly's response to the deficiencies cited in the NA letter by the FDA Offices of Clinical Pharmacology and New Drug Quality Assessment.

This review focuses on clinical issues—labeling revisions, the RMP, 10-month safety update, and starting dose issues. Pre-clinical issues are reviewed by correspondent divisions. The review of risk management plan (RMP) and risk evaluation and mitigation strategy (REMS) is performed in consultation with the Office of Surveillance and Epidemiology (OSE). Gita Akhavan-Toyserkani, Pharm.D., MBA, from the division of risk management (DRISK), OSE, is the scientific lead of OSE olanzapine depot REMS review team. Please refer to their review for more information regarding the REMS review.

In addition, Lilly submitted an amendment to original NDA 22173 on Dec. 20, 2007 and proposed a labeling revision recommending higher starting doses when switching patients from oral olanzapine to OP Depot treatment. This submission was not reviewed in the first review cycle because NDA 22173 was granted a not approvable status. Because the division is re-considering this product's approval status after Lilly committed to enhance labeling language, conduct risk minimization activities and implement a medication registry at the time of approval, this submission is reviewed along with the completed response package. The review of this submission is located in section 4. Additional Labeling Issues.

2. Risk Management Plan Review

The sponsor submitted an original RMP as part of the original NDA submission on April 30, 2007, which consisted of labeling, routine pharmacovigilance, and a postmarketing observational study (Study B034). 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.

In the post NDA action meeting on May 7, 2008, the Division agreed 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 restricted 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.

The sponsor proposed a revised RMP in the complete response package submitted on June 13, 2008. This RMP limited to those identified and potential risks specific to the OP Depot formulation. Lilly has also proposed a mandatory registry to collect postmarketing data on the risk of PDSS event. Additionally, Lilly has proposed to perform an observational study that will be conducted outside the US to determine the incidence of PDSS event in clinical practice (Study B034).

2.1 Identified and Potential Risks Specific to This Formulation

The overall safety profile of OP Depot is similar to that of oral olanzapine with the exception of PDSS events and injection-site-related adverse events based on the safety data from the original NDA submission and from safety updates. Additionally, medication error (confusion between rapid-acting IM ((RAIM)) olanzapine formulation and OP Depot formulation) is identified by the sponsor as an important potential risk.

2.1.1 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 more than 40,000 OP Depot injections given to 2054 patients in clinical trials through 31 May 2008, PDSS events have

occurred in approximately 0.07% of injections or 1.4% of patients. Because PDSS events are specific to OP Depot IM injection, no background incidence or prevalence exists.

The symptoms reported with PDSS events are consistent with adverse events (AEs) reported with oral olanzapine overdose. The majority PDSS events occurred within the first hour post-injection, and occurred rarely between 1 and 3 hours and very rarely after 3 hours post-injection. The events typically started with milder symptoms that progressed in severity. Twenty-two of the 28 patients (79%) was hospitalized or seen in the emergency room. All PDSS events resolved within 72 hours, and majority of patients who experienced an event (19/27, 70%) continued to receive further injections of OP Depot.

Pharmacokinetic data collected for 10 events reveal that olanzapine plasma concentrations during these events substantially exceed the typical olanzapine plasma concentration values observed after oral or OP Depot doses.

Higher dose, greater age, and lower body mass index (BMI) have been identified as weak risk factors for a PDSS event. However, the sponsor stated that identification of 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 the identified risk factors are present.

2.1.2 Medication Error

With approval of OP Depot, olanzapine will have two IM 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 rapid-acting formulation of olanzapine rather than the long-acting OP Depot formulation may be administered, and vice versa.

2.2 Proposed Risk Management Plan

2.2.1 Pharmacovigilance Plan

Lilly proposed to perform routine analysis of all serious and non-serious 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. The Lilly Safety System (LSS) database contains serious and non-serious events reported spontaneously from post-marketing experience (including literature and regulatory reports) and serious clinical trial events. Lilly has created a list of targeted surveillance terms for specific AEs identified for targeted follow-up. Two separate sets of terms are proposed by the sponsor: one for olanzapine, regardless of the formulation (Table 1), and another one specifically created for PDSS events (Table 2). The list of AE surveillance terms is reviewed routinely and is updated as needed to reflect current safety issues identified through overall ongoing surveillance.

Table 1 Targeted Surveillance Terms for Olanzapine

Adverse pregnancy outcomes, including gestational diabetes	Overdose of olanzapine alone (and where either the patient died, or survival after olanzapine overdose >200 mg or olanzapine plasma concentration >200 ng/ml
Bradycardia with serious outcome	Pancreatitis
Convulsions (seizures for which initial report does not specify presence or absence of other risk factors)	QT interval prolongation
Eosinophilia with serious outcome	Respiratory depression/Hypoventilation/Apnea
Hematological effects	Sinus pause
Hepatic effects	Sudden death
Hyperglycaemia/Diabetes mellitus/Ketoacidosis	Thromboembolic events
Hypertriglyceridemia/Hyperlipidemia	Withdrawal symptoms (including infants)
Hypotension	

Table 2 Proposed Targeted Surveillance Terms for OP Depot

Aggression	Dysarthria
Agitation	Extrapyramidal disorder
Altered state of consciousness	Fatigue
Anticholinergic syndrome	Hypersomnia
Anxiety	Hypersomnia related to another mental condition
Apathy	Hypertension
Asthenia	Incoherent
Ataxia	Lethargy
Bradyphrenia	Listless
Cholinergic syndrome	Malaise
Coma	Psychomotor retardation
Confusion	Sedation
Confusional state	Sense of oppression
Consciousness fluctuating	Sleep disorder due to general medical condition (hypersomnia type)
Decreased activity	Sluggishness
Decreased interest	Somnolence
Delirium	Sopor
Depressed level of consciousness	Stupor
Disorientation	Toxic encephalopathy
Disturbance in attention	Unresponsive to stimuli
Dizziness	

Lilly will develop a targeted questionnaire that will be used to obtain follow-up information for all suspected PDSS AEs.

Medication errors will be monitored through routine pharmacovigilance surveillance.

Reviewer's comments

Overall the sponsor's proposed pharmacovigilance plan and targeted surveillance activities are acceptable. However, in Table 1 Targeted Surveillance Terms for Olanzapine, no terms related to significant weight gain associated with olanzapine treatment were proposed. Weight gain and associated metabolic syndrome are serious safety issues related to all olanzapine products.

Significant weight gain should be monitored and weight gain related information should be collected in their pharmacovigilance database. Terms, such as significant weight gain (≥ 7% of body weight), should be included in Table 1.

Seizure has been observed in at least two PDSS cases. However, seizure or seizure related terms are not included in the list of proposed target surveillance terms. It is recommended that terms seizure and seizure related terms should be included in the Table 2.

A draft targeted questionnaire for suspected PDSS events should be submitted to the agency prior to OP Depot approval and a protocol of the observational study (Study B034) should be submitted to the agency within 3 years after the approval.

2.2.2 Risk Minimization Plan

The sponsor proposed RMP consists of two major components: enhancing labeling language and risk-minimization activities.

2.2.2.1 Labeling

The sponsor proposed the following revisions to address the risks related to PDSS events:

- Description of this risk proposed as a boxed warning
- 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 informing patients that, for the remainder of the day of the injection, patients should not drive or operate heavy machinery 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

Reviewer's Comments

The sponsor's proposed aforementioned labeling revisions are acceptable. In addition, following additions are recommended:

1. *Pharmacies, physicians and patients have to be registered to the registry program to dispense, prescribe or received OP Depot.*
2. *The healthcare facilities where the OP Depot will be administered have to have emergency service access to ensure every PDSS case will be managed appropriately.*
3. *Patients have to be accompanied to their destiny after 3 hour on-site observation.*
4. *A medication guide regarding risks of PDSS and metabolic syndrome associated with OP Depot treatment will be distributed to every patient who will receive OP Depot treatment.*

The line to line labeling review is attached to the Complete Response (CR) letter. Please refer to CR letter for detailed recommended labeling revisions.

2.2.2.2 Risk-Minimization Activities

Healthcare Awareness Program

Lilly proposed a healthcare awareness program intended to educate physicians, administrators of treatment (nurses, case managers, social workers), pharmacists, pharmacy technicians, patients, and Lilly staff (neuroscience medical component, sales, marketing, and call centers) supporting OP Depot. The awareness program includes education activities targeted for each of the aforementioned audience groups, specific labeling and packaging, and program evaluation, measurement, and follow-up.

Table 3 summarizes the overall proposed OP Depot Healthcare Awareness Program for the identified risks associated with PDSS events.

Table 3 Summary of the OP Depot Healthcare Awareness Program

Educational Element	Description (education material)	Status
Drug product and packaging	The following labeling components will be included in each convenience kit: • Appropriate cautions/warnings and observation recommendations in product labeling • A PPI that includes description of the potential for and presentation of PDSS events • Color instructions to reconstitute and administer Zyprexa RELPREV	• Product labeling will be finalized with the FDA prior to launch. • The PPI will be finalized with the FDA prior to launch. • A color instruction sheet will be finalized with the FDA prior to launch.
Sponsor-targeted internal activities	• Sales force and neuroscience medical component (eg, medical liaisons, medical directors) education to convey warnings and information about potential PDSS events • Provide training to Lilly call center to prepare staff for answering questions and providing information with regard to PDSS events	• Sales force and medical component will be trained prior to launch, with periodic training updates. • Call center staff will be trained prior to launch, with periodic training updates; 1-800-LillyRX is the call number.
Sponsor-targeted external activities	• Convene external advisors (eg, Lilly US Schizophrenia Advisory Board, Lilly US Treatment Team Advisory Board) to explain how to best disseminate education materials to physicians, pharmacists, and patients	• Advisors will be consulted on best dissemination method (medium: DVDs, slide sets, lectures, letters, and/or web sites; delivery: direct mailings, internet, and/or in person) prior to launch. • Education program will be available prior to launch.
Pharmacist- and pharmacy technician-targeted activities	• Dear Healthcare Professional Letter describing potential for and presentation of PDSS events • OP Depot distribution restricted to only those pharmacies that agree to participate in the REGISTRY	• Letters will be distributed at time of launch. • REGISTRY will be started at product launch.

Educational Element	Description (education material)	Status
Physician-targeted activities	• Provide educational material, including explanation of importance of proper administration technique; need for observation time; following product labeling; fully informing patients about event risk and presentation; and training of internal support staff. • Disseminate Dear Healthcare Professional Letter describing potential for and presentation of PDSS events. • Educate and enroll prescribers in the REGISTRY.	• Education materials will be disseminated to targeted prescribers and registry-enrolled participants at time of launch. • Letters will be distributed to targeted psychiatrists who treat adult patients at time of launch • Education materials will be disseminated at time of launch. • Prescribers will be enrolled prior to prescribing OP Depot post-approval.
Administrators of treatment-targeted activities (nurses, case managers, social workers, as appropriate)	• In-person training for reconstitution and proper administration technique) • Provide training on patient tools that will be available for distribution to patients. • Provide education materials, including details on reconstitution and injection technique, as well as how to recognize events; fully inform patients about event risk. • Provide education about the REGISTRY.	• Mock kits will be used during training sessions. Reconstitution and administration training will be conducted at time of launch • Tools will be available at time of launch. • Education material will be distributed at time of launch. • Registry education will be provided prior to launch.
Patient activities	• Provide HCPs with educational tools for dissemination including a patient take-away card, wristband, patient brochure, and patient DVD).	• Educational tools will be disseminated at time of launch.

In addition, Lilly also proposed to launch an OP Depot Registry (REGISTRY) program in the US for at least 18 months. Details will be discussed in following section Proposed Draft of the Registry Design Elements.

Lilly has not proposed any long term plan to evaluate the healthcare awareness activities. Evaluation of the trainings and educational programs will be completed post launch.

Proposed Draft of the REGISTRY Design Elements

Lilly agreed that, if approved, OP Depot will be launched in the United States with an initial strict patient registry to collect post-marketing experience data around the risk of PDSS. Participation in the REGISTRY will be mandatory for all prescribers of OP Depot and all patients treated with OP Depot until such time as FDA and Lilly agree that adequate data have been accumulated to represent typical post-marketing experience.

Summary of the REGISTRY Design

This REGISTRY is designed to estimate the incidence and to characterize the time to onset and outcomes of PDSS events among all patients treated with OP Depot in a post-marketing, clinical practice setting in the US. This REGISTRY will be conducted for at least the first 18-months after product launch in the US.

General Requirement

Only prescribers enrolled with the REGISTRY and who agree to comply with the program, including data collection and reporting requirements, will be able to prescribe OP Depot. Only patients who enrolled in the REGISTRY and who agree to comply with the program will be able to receive OP Depot. Only pharmacies enrolled with the REGISTRY and who agree to comply with the program will be able to dispense OP Depot.

The prescribers have to agree to comply with the REGISTRY program, including all data collection requirements, to complete mandatory training regarding OP Depot, and to provide counseling to all patients on the benefits and risks of OP Depot treatment.

Patients must agree to have his/her data entered into the REGISTRY and agree to contact their prescriber if symptoms of PDSS develop.

Pharmacies that enroll in the REGISTRY have to agree to comply with the REGISTRY program, including that appropriate pharmacy staff will be trained about the REGISTRY program and about the known risks, potential benefits, and appropriate use of OP Depot. These pharmacies only accept and dispense prescriptions from prescribers in the REGISTRY program for patients enrolled in the REGISTRY.

Data Collection

For each injection, the following information will be recorded and submitted to the REGISTRY: OP Depot injection date, time, and dose, verification that the patient left the facility absent signs and symptoms of olanzapine overdose, and any report of a PDSS event since the previous OP Depot injection.

More detailed data will be collected for PDSS events, such as signs and symptoms of the PDSS event, date/time of PDSS event onset and resolution, type and timing of interventional treatment or therapy administered, whether an emergency room visit or hospitalization occurred, outcome of PDSS event, and event follow-up using standard pharmacovigilance follow-up methods.

Monitoring and Evaluation

Lilly will monitor the OP Depot REGISTRY and report the results at minimum every 6 months to FDA. Overall results of the REGISTRY will be submitted to FDA at 18 months after approval of OP Depot and the need for continuing the REGISTRY will be assessed.

Statistical Methods

Crude incidence of PDSS events and 95% confidence intervals will be calculated based on the total number of patients enrolled in the registry and the total number of injections captured. Descriptive statistics will be used to describe the patient population and to characterize the clinical presentation of PDSS events, including time to onset.

Reviewer's Comments

The RMP is reviewed in consultation with DRISK, OSE. After reviewing, the DRISK determined that a REMS is necessary at the time of approval to ensure that benefits of the drug outweigh the risk of PDSS events. The DRISK requested the REMS must include following 4 elements: a medication guide, elements to assure safe use, implementation system, and timetable for assessments. I agree with DRISK's review.

Medication Guide

The DRISK has determined that OP Depot poses a serious and significant public health concern requiring the distribution of a medication guide. Patients should be made aware of the risks of PDSS events and metabolic syndrome associated with OP Depot treatment, which could affect patients' decisions to use, or continue to use. A draft Medication Guide must be submitted to FDA for review prior to approval. If this product is approved for marketing, the sponsor is responsible for ensuring that the Medication Guide is distributed to every patient who receives OP Depot treatment.

The Medication Guide should include information regarding the risks of PDSS and metabolic syndrome associated with OP Depot treatment, and how to seek for medical assistance in case PDSS events occur following discharge from a healthcare facility.

Elements to Assure Safe Use

Besides enrollment in the REGISTRY program and receiving particular training for all prescribers, pharmacies and healthcare facilities that will prescribe, dispense or administer OP Depot, the DRISK also request all prescribers, pharmacies, healthcare facilities must be certified to prescribe, dispense or administer OP Depot. In the REMS CR letter, the DRISK provided detailed guidance regarding how to train and how to certify prescribers, pharmacies and healthcare facilities. Repeating training and re-certification may be necessary. Please refer to the REMS CR letter and the DRISK's review for more detailed guidance.

Patients have to be enrolled in the REGISTRY program, and a physician-patient agreement that documents safe use conditions have to be signed. Patients have to be consulted about the risks of PDSS events and metabolic syndrome associated with OP Depot treatment. A Medication Guide has to be given and a physician-patient agreement has to be signed. During the 3 hours post-injection monitoring, patients have to stay in a controlled environment and are observed periodically by healthcare professionals for sedation or other early signs and symptoms of PDSS event.

Implementation System

The DRISK requested that the implementation system must include:

- *A database of all certified prescribers and healthcare facilities as well as a database of the completed data forms.*
- *A plan to monitor distribution and prescribing data to ensure that OP Depot is only prescribed, dispensed, or administered by the certified entities. A follow up plan, such as periodic audits of certified healthcare facilities, is required.*

Timetable for Assessments

The DRISK recommended timetable for assessments is no less frequent than 6 months for the first year and annually thereafter after the REMS is approved.

3. Safety Update

The sponsor submitted a 10 month safety update in the complete response package. This 10-month safety update extends submitted information by combining previous data with safety data that has accrued since the data cut-off date for the NDA (30 June 2006). Accrued data are from 2 ongoing, open-label OP Depot studies (F1D-MC-HGKB [HGKB] and F1D-MC-HGLQ [HGLQ]). The data cut-off date for locked safety information from these studies was 30 September 2007.

Safety data from two databases were reviewed in this review: Summary of Clinical Safety (SCS) database and 10-Month Safety Update (SU300) database.

The SCS database is the same database that was previously submitted in the original NDA. It includes safety data from 5 open-label studies and 2 double-blind comparator studies that were conducted in patients with schizophrenia or schizoaffective disorder. This database contains validated and locked clinical data through 30 June 2006 for Study HGKB. In this database, all OP Depot treatment arms were pooled for analyses.

SU300 Database is a cumulative database consisting of all safety data that were included in the SCS Database integrated with new and additional safety data from the ongoing OP Depot studies HGLQ and HGKB through 30 September 2007.

Safety Summary of the 10-Month Safety Update

Safety data that have accrued since the NDA was submitted are consistent with the safety data and conclusions that were presented in the NDA. Based on new and additional OP Depot exposures, no new significant safety issues have been identified. The following are the key findings from this 10-month safety review:

- Since the NDA was submitted, safety information for 279 new OP Depot patients and additional safety information for 710 continuing OP Depot patients have accrued. Patient exposure years have increased by 87.5% from 1038.49 to 1947.61, and the number of patients who received at least 1 OP Depot injection has increased by 15.5% (276/1778). Cumulative exposure represents a maximum length of approximately 3.3 years.

- Two additional deaths have occurred in patients receiving OP Depot treatment since the datalock of Lilly's last 4-month safety update (data cut-off date on 31 January 2007). One death was due to pneumonia, and 1 was due to cardiomyopathy. A brief summary of these two cases can be found in the Appendix.

- The percent of patients who have experienced a serious adverse event (SAE) increased slightly (8.9% in SCS to 10.9% in SU300), which might be caused by an increase in exposure time.

- Overall, discontinuations due to AEs have remained low (6.4% in SU300 compared with 5.1% in SCS).

- No pattern in treatment emergent adverse events (TEAEs) was seen that would suggest a new OP Depot safety concern.

- Clinical laboratory findings were as expected; incidence rates for abnormal values were low, representing small increases or decreases in analyte values, none of which were considered clinically meaningful.

- Results of the analyses of vital signs and weight, ECGs, and extrapyramidal symptoms (EPS) scales were consistent with results reported in the original NDA.

- Twelve new PDSS events were confirmed between 01 January 2007 and 29 February 2008. The updated risk of a PDSS event is 0.07%, or about 1 event per 1413 injections. Signs and symptoms reported with PDSS events are consistent with those reported with an oral olanzapine overdose; all patients have recovered, and the majority have continued to receive further injections of OP Depot.

- Analysis of the 3-hour observation data revealed no notable changes in post-injection vital signs. Relatively few AEs were observed during the post-injection period. The assessment of mental status prior to a patient's release from the site was an effective method for identifying potential PDSS events.

- Results from updates to the cardiovascular, metabolic parameters and weight gain, hepatic, and injection-site–related AE special safety topics revealed no new safety concerns that would affect OP Depot labeling.

4. Additional Labeling Issues

On Dec. 27, 2007 Lilly submitted an amendment to original NDA 22173 and proposed labeling revisions regarding higher starting doses in initial OP Depot treatment. Lilly noticed in their clinical studies schizophrenia exacerbation rates were highest in the first two months after patients were switched from oral olanzapine to OP Depot treatment and decreased in subsequent months. Lilly conducted analyses on time to exacerbation in Study HGKA as well as analyses of relative risk of switching to various OP Depot doses from different oral olanzapine doses. Study HGKA is a 24-week, randomized, double-blind, maintenance study comparing the efficacy and safety of OP Depot (150 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks) with oral olanzapine (10, 15, and 20 mg/day) and low dose OP Depot (45 mg/4 weeks) in clinically stabilized outpatients with schizophrenia. They found incrementally less risk of exacerbation when

switching patients to higher OP Depot doses. Based on the results, Lilly proposed higher starting doses of OP Depot treatment in this amendment.

Table 4 presents hazard ratios for exacerbation comparing each OP Depot dose group to oral olanzapine over the 24-week period of study. Patients who were stabilized on 10 mg/day oral olanzapine incurred little or no additional risk if switched to a dose of 405mg/4 weeks OP Depot (hazard ratio [HR]=1.03); patients stabilized on 15 mg/day oral olanzapine incurred little or no risk if switched to a dose of 405mg/4 weeks or 300 mg/2 weeks OP Depot (HRs=1.44 and 0.68, respectively); and patients incurred little or no risk if switched from 20 mg/day oral olanzapine to a dose of 300 mg/2weeks OP Depot (HR=1.13). However, patients treated with the 150 mg/2 weeks OP Depot dose, which was the lowest therapeutic dose tested in this study, incurred twice as much risk or more relative to remaining on the preceding oral dose. Thus, while the 150 mg/2 weeks OP Depot dose was shown to be an effective dose in maintenance treatment over 24 weeks, this dose may have some limitations, especially as a starting dose.

Table 4 Relative Risk of Exacerbation Compared to Oral Olanzapine at 24 weeks (All Treatment Groups Shown by Preceding Oral Olanzapine Dose, Study HGKA)

		Vs. OLZ		
Oral dose	Therapy	HR	95% CI	p-Value
10mg	OPD45	2.78	(1.13 , 6.84)	.027
	OPD150	2.08	(0.77 , 5.59)	.147
	OPD405	1.03	(0.40 , 2.67)	.954
	OPD300	0.25	(0.03 , 2.01)	.194
15mg	OPD45	5.59	(1.68 , 18.59)	.005
	OPD150	1.96	(0.44 , 8.74)	.380
	OPD405	1.44	(0.36 , 5.76)	.606
	OPD300	0.68	(0.08 , 6.08)	.727
20mg	OPD45	8.00	(3.53 , 18.14)	<.001
	OPD150	2.73	(1.05 , 7.11)	.039
	OPD405	1.70	(0.72 , 4.01)	.227
	OPD300	1.13	(0.34 , 3.75)	.843

Table 5 presents hazard ratios for exacerbation comparing each OP Depot dose group to oral olanzapine at 2 months, stratified by oral olanzapine dose prior to randomization. It would appear that from a dose of 10 mg/day oral olanzapine, switching to 405 mg/4 weeks or 300 mg/2 weeks OP Depot was adequate. And, from a dose of 20 mg/day, it appears that switching to a dose of 300 mg/2 weeks was also adequate. Although the results of the 15-mg oral olanzapine switch are difficult to interpret because of an insufficient number of oral patients relapsing, the sponsor expected that in a larger sample, the results would directionally mimic those from the original 6-month stratified analyses and would thus suggest an appropriate starting dose of 405 mg/4 weeks or 300 mg/2 weeks OP Depot.

Table 5 Relative Risk of Exacerbation Compared to Oral Olanzapine at 2 Months (All Treatment Groups Shown by Preceding Oral Olanzapine Dose, Study HGKA)

		Vs. OLZ		
Oral dose	Therapy	HR	95% CI	p-Value
10mg	OPD45	1.69	(0.38 , 7.57)	.492
	OPD150	2.49	(0.62 , 9.98)	.198
	OPD405	1.08	(0.27 , 4.31)	.917
	OPD300	0.56	(0.06 , 4.98)	.600
15mg	OPD45	8.12	(0.84 , 78.16)	.070
	OPD150	2.59	(0.16 , 41.41)	.501
	OPD405	2.85	(0.26 , 31.46)	.393
	OPD300	3.09	(0.19 , 49.61)	.425
20mg	OPD45	8.00	(2.90 , 22.08)	<.001
	OPD150	3.22	(1.02 , 10.17)	.046
	OPD405	2.14	(0.75 , 6.06)	.154
	OPD300	1.35	(0.32 , 5.67)	.678

In summary, these analyses indicate that patients were at greater risk of exacerbation during the first 2 months of treatment with OP Depot and patients who were switched to higher doses of OP Depot were at less risk of exacerbation. Based on these results, Lilly recommended that clinicians should initiate OP Depot treatment at doses higher than the recommended maintenance doses that is calculated based on blood concentrations at steady status compared to oral olanzapine doses. Table 6 is the revised dose guidance table in the proposed labeling.

Table 6 Recommended Dose Scheme for OP Depot Relative to Oral Olanzapine

Target Oral Olanzapine Dose	Recommended Starting Dose of OP Depot	Maintenance Dose after 2 Months of OP Depot Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

Lilly recommends that the clinician should select the starting dose of OP Depot based on the target oral olanzapine dose. For instance, if the clinician would expect that the patient could be stabilized on a dose of 10 mg/day oral olanzapine, the recommended starting dose of OP Depot would be 210mg/2 weeks or 405mg/4 weeks. After 2 months, the clinician can consider dose adjustments based on the maintenance dose correspondence in Table 6, particularly if tolerability concerns arise. However, in proposed labeling, Lilly did not specify when patients should be switched from starting dose to maintenance dose.

In the latest labeling, Lilly also included following languages regarding oral olanzapine supplementation in the initial OP Depot treatment:

> *Oral antipsychotic supplementation is not required. If clinically necessary however, patients may receive oral antipsychotic supplementation. Supplementation using doses of up to 20 mg/day oral olanzapine with ZYPREXA Relprev was allowed in an open-label clinical trial but has not been systematically studied.*

Reviewer's Comments

It is agreed that the risk of exacerbation of schizophrenia symptoms is greater at the beginning of OP Depot treatment. Starting regimens such as starting with higher doses or providing oral supplementation to long-acting antipsychotic injections had been approved by the agency to increase the initial drug blood concentration to prevent exacerbation of symptoms. Even though Lilly proposed higher starting dose regimen (starting with higher doses followed by maintenance doses) has not been tested systemically in the clinical trials, all proposed starting doses had been tested in the controlled clinical trials and had been well tolerated by patients. From the clinical point of view, the proposed starting doses appear to be safe to use. However, in the proposed labeling the sponsor did not provide instruction regarding how long patients should be on starting doses or how many injections patients should be given before switching them to maintenance doses.

Regarding proposed oral antipsychotic supplementation regimen, the sponsor needs to provide data from the open-label clinical trial to support this approach. In the proposed labeling, similar to that aforementioned, the sponsor did not provide any instruction regarding how long the oral supplementation should be given before switching patients to maintenance doses.

The sponsor needs to provide more precise guidance in the labeling regarding how to start OP Depot treatment or how to switch patients from oral olanzapine to OP Depot.

Because the proposed labeling languages are vague and lack of clear instruction regarding how to start the OP Depot treatment, it potentially may raise a serious safety concern if prescribers use both starting regimens (higher starting dose and oral supplementation) at same time and use both of them for a substantially long period. If in future the sponsor provides enough evidence demonstrated that both starting regimens are safe and effective to proceed, it is recommended that only one of these two starting regimens can be used at one time, either higher starting dose or oral supplementation, but not both.

5. Recommendation on Regulatory Action

Based on the data available at this time point and after considering the risks and benefits of having this product available to treat a severe mental illness, schizophrenia, I recommend that this NDA be granted approvable status.

6. Comments to Applicant

To ensure appropriate use of this product, especially to prevent or limit the risk of PDSS event after approval, we have following comments to applicant:

- In the pharmacovigilance plan, significant weight gain should be monitored and weight gain related information should be collected in their routine pharmacovigilance database.

Seizure or seizure related terms should be included in the list of OP Depot targeted surveillance terms.

- As part of the pharmacovigilance plan, a draft targeted questionnaires for suspected PDSS events should be submitted to the agency for review prior to OP Depot approval.

- A full protocol of the postmarketing observational study (Study B034) should be submitted to the agency within 3 years after the approval.

- All education and certification materials for the Healthcare Awareness Program and the REGISTRY should be submitted to FDA prior to OP Depot approval.

- REMS is required at the time of approval to ensure that benefits of the drug outweigh the risk of PDSS events. The sponsor needs to submit a REMS as requested by FDA prior to approval. The REMS must include following 4 elements: a medication guide, elements to assure safe use, implementation system, and timetable for assessments. Please refer to OSE's REMS review for detailed guidance.

- A Medication Guide is required at the time of approval. The Medication Guide should include information of the risks of PDSS events and metabolic syndrome associated with OP Depot treatment, and how to seek medical assistance in case PDSS events occur following discharge from a healthcare facility. A draft medication guide should be submitted to FDA for review prior to approval. If this product is approved for marketing, the sponsor is responsible for ensuring that the Medication Guide is distributed to every patient who receives OP Depot treatment.

- Besides enrolling in the REGISTRY program and receiving particular training, all prescribers, pharmacies and healthcare facilities must be certified to prescribe, dispense or administer OP Depot. Repeating training and re-certification may be necessary.

- Drafts of specific data collection forms, adverse event forms and other REMS related materials must be submitted to FDA for review prior to approval.

- Patients have to be enrolled in the REGISTRY, and sign up a physician-patient agreement. During the 3 hours post-injection monitoring, patients have to stay in a controlled environment and have to be observed periodically by healthcare professionals for sedation or other signs and symptoms of PDSS event.

- Several labeling revisions have been recommended. The line to line labeling review is attached to the Complete Response (CR) letter. Please refer to CR letter for detailed labeling revision recommendation.

- Regarding the sponsor's proposed starting treatment regimens (higher starting dose and oral supplementation), the sponsor needs to provide more data to support the oral supplementation regimen. In the labeling, the sponsor needs to provide more precise guidance to prescribers regarding how to dose patient at the beginning of the OP Depot

treatment or how to switch patients from oral olanzapine to OP Depot treatment. It is recommended that only one regimen, either higher starting dose or oral supplementation, should be used at a specific period.

7. Appendix

Narratives of Deaths

Two deaths in OP Depot-treated patients occurred after datalock (30 September 2007) and they were first reported in this 10 month safety update. Following is briefly summaries:

- Patient HGKB-163-7155, a 69-year-old Caucasian male with a medical history of sinus bradycardia, right branch block, and first degree atrioventricular block, received his last injection of 405 mg/4 weeks OP Depot on 03 December 2007. On (b) (6) (b) (6) after beginning OP Depot, the patient experienced fever and dyspnea and was hospitalized on the same day. Pneumonia was diagnosed. The patient received ampicillin sodium plus sulbactam sodium, beginning on (b) (6). The patient worsened and died that same day. The reported cause of death was pneumonia, and no autopsy was performed.

- Patient HGKB-224-7593, a 47-year-old Caucasian male, with a body mass index (BMI) of 34.4, received his last injection of 405 mg of OP Depot on (b) (6) (b) (6). Six days later, on (b) (6), the patient was found dead in the morning by his mother. An autopsy was performed on (b) (6) and established the cause of death as hypertrophic myocardiopathy (cardiomyopathy). Time on study drug and medical history was not reported at the time of the event and has been requested. The only concomitant medication taken at the time of death was trihexyphenidyl.

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/s/

Jing Zhang
12/8/2008 05:43:13 PM
MEDICAL OFFICER

Gwen Zornberg
12/8/2008 08:23:01 PM
MEDICAL OFFICER
I agree with Dr. Zhang that a REMS and labeling with a Medication Guide are required at the time of approval. For this submission, a Complete Response letter is expected to be issued to the sponsor by the 16 December 2008 action date.

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 24, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for not-approvable action for olanzapine pamoate depot formulation (OP Depot) for the treatment of schizophrenia

TO: File NDA 22-173
[Note: This overview should be filed with the 4-30-07 original submission of this NDA.]

1.0 BACKGROUND

Zyprexa (olanzapine) is an atypical antipsychotic (5HT2 and D2 receptor antagonist) that is approved for both schizophrenia and bipolar disorder in adults, including maintenance claims for both. This NDA provides evidence that is intended to support claims for OP Depot for the treatment of both acutely exacerbated schizophrenia and also the maintenance treatment of schizophrenia.

We met with Lilly a number of times between 1999 and 2007 during the development of this depot product. We had agreed with the sponsor that a single short-term trial (HGJZ) would be sufficient for filing this application. The development program included a total of 8 clinical studies in schizophrenia, including 2 controlled efficacy and safety studies and 6 open-label studies.

There are currently only 3 depot antipsychotics available for use in the US, including 2 typical antipsychotics (fluphenazine decanoate and haloperidol decanoate) and 1 atypical antipsychotic (Risperdal Consta). The depot formulation for an antipsychotic drug is felt to be an important treatment option, since so many schizophrenic patients are noncompliant with oral medications and this is often difficult to ascertain.

2.0 CHEMISTRY

CMC issues for this application have been largely resolved, including agreement on labeling. However, several deficiencies remain, including specifications for viscosity. Therefore, the

chemistry group is recommending an approvable action. The deficiencies will be included in the action letter.

3.0 PHARMACOLOGY

All pharmacology/toxicology issues for this application have been resolved, including agreement on labeling.

4.0 BIOPHARMACEUTICS

Biopharmaceutics issues for this application have been largely resolved, including agreement on labeling. However, several deficiencies remain, in particular dissolution specifications. Therefore, the biopharmaceutics group is recommending an approvable action. The deficiencies will be included in the action letter.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review of OP Depot focused on 2 trials conducted by Lilly.

Study HGJZ was an 8-week study involving acutely ill patients with schizophrenia. This was a double-blind trial in which patients were randomized in a 1:1:1:1 ratio to 3 fixed doses of OP Depot (300 mg q 2 weeks; 405 mg q 4 weeks; 210 mg q 2 weeks) or placebo. No oral antipsychotic supplementation was permitted. The primary endpoint was change from baseline to endpoint in PANSS total score, and all 3 active drug groups were statistically significantly superior to placebo. There was a slight numerical, but not statistically significant, advantage for the highest dose group (300 mg q 2 weeks) compared to the other 2 dose groups.

Study HGKA was a 24-week maintenance study in stable schizophrenic patients who were initially switched from whatever antipsychotic drug they were stable on to oral olanzapine monotherapy. After a minimum of 4 weeks of continued stability on oral olanzapine, patients were randomized in a 2:1:1:1:2 ratio to OP Depot (405 mg q 4 weeks; 300 mg q 2 weeks; 150 mg q 2 weeks; 45 mg q 4 weeks) or oral olanzapine (10, 15, or 20 mg/day). One objective was to show noninferiority of OP Depot to oral olanzapine monotherapy and a second was to show superiority of the 3 higher dose OP Depot arms to the 45 mg q 2-week arm on time to worsening of positive symptoms. Our focus was on the superiority hypothesis. All 3 of the higher dose OP Depot arms were statistically significantly superior to the 45 mg q 2-week arm. As for study HGJZ, there was a slight numerical, but not statistically significant, advantage for the highest dose group (300 mg q 2 weeks) compared to the other 2 dose groups.

Our judgments about the efficacy of OP Depot are based in part on the knowledge that oral olanzapine has been shown in several trials to be effective in the treatment of acute

exacerbations of schizophrenia and in one trial to be effective as a maintenance treatment in schizophrenia, and in part of the results of these 2 studies. Given the positive outcomes for these 2 trials with OP Depot, I agree with Drs. Zhang, Zornberg, and Kordzakhia that the sponsor has demonstrated that OP Depot is effective both in the treatment of acute exacerbations of schizophrenia and as a maintenance treatment in schizophrenia.

5.2 Safety Data

The safety data for this NDA were derived from a total of n=1915 schizophrenic or schizoaffective patients exposed to OP Depot among 8 clinical trials (2 efficacy trials and 6 open-label trials). These patients received a total of n=27,210 injections. Overall, the safety profile for OP Depot was similar to that observed with oral olanzapine. The exceptions were injection site pain, and also the CNS depression events that were the subject of a PDAC meeting for this NDA.

The CNS depression events were characterized by profound sedation/somnolence, dizziness, confusion, ataxia, and altered speech/dysarthria. As of November, 2007, there were reports of 25 CNS depression events in 24 patients during OP Depot clinical trials. There have been 3 additional events since then. All patients have fully recovered. The sponsor has referred to these as inadvertent intravascular (IAIV) events because they believe this represents the mechanism. These instances of CNS depression have occurred shortly after an injection (1 to 3 hours, with 21/25 of these within 1 hour). However, the most recent case occurred in a patient who apparently had no indication of such an event after 3 hours of observation but was then found unconscious 2 hours later. He was subsequently determined to have had such an event that was similar to the others, except for the later onset. These events are believed to have resulted from rapid release of olanzapine into the systemic circulation, and this view is supported by limited plasma level data available (from 7 of these events) suggesting that patients having these events had unusually high plasma concentrations of olanzapine. The first 25 of these events have occurred in 24 out of 1915 patients exposed to OP Depot (i.e., roughly 1.2% of patients). The estimated risk per injection is 0.07%.

Description of Last Case: The last case is particularly informative because the onset of the event was so delayed. Lilly is still in the process of obtaining information on this case, including more details on the time of onset of the event and plasma level data. This was a 45 year-old male who was getting monthly injections of 405 mg. He was observed for 3 hours after his injection on 1-31-08, apparently with no indication of any CNS depression, and was discharged. Two hours later he was discovered unconscious on the hospital grounds, and upon further evaluation, was determined to have had a CNS depression event similar in character to the others observed, with the exception of a later time of onset. Time of onset was not possible to determine, but was greater than 3 hours and may have been up to 5 hours. There was no indication of alcohol or substance abuse. He was roused, and described as delirious and ataxic. He was admitted to the hospital and treated supportively for 5 days before he was sufficiently recovered to be discharged. At some point early in the episode patient was noted to have a generalized tonic-clonic convulsion.

There are several points to consider regarding these events:

-These are not instances of a little sleepiness, but rather, very profound CNS depression that resulted in hospitalization for the majority of the patients (20/24) who experienced this event.
-These events have mostly occurred within a very short period of time after the injection (21/25 occurred within the first hour), but 4 others were later (up to 3 hours), and the last case occurred between 3 and 5 hours. It is not clear we have adequately characterized the time interval for the risk of this event.
-These events appear to be entirely unpredictable, and could occur with any patient on any injection. They ranged from occurrence with the first injection up to the 40th. The average number of days from starting OP Depot to occurrence of the event was 278 days.
-Although the sponsor feels they understand the mechanism (i.e., IAIV), we are not convinced this is the case. If it were simply inadvertent injection into a blood vessel, one would think that training of staff to avoid this would largely eliminate it; that appears not to be the case.
-The sponsor conducted a logistic regression to try to identify risk factors that might be associated with these events. The factors that emerged from this model included dose, older age, and lower BMI. We have not confirmed this analysis, however, these findings all tend to suggest that volume of injection relative to body mass might contribute to increasing the risk, perhaps through some mechanical route. Experiments indicate that olanzapine pamoate is quite soluble when exposed to substantial amounts of blood.
-The events may be related to the rate of change of olanzapine concentration rather than simply the absolute level
-One might be concerned that, as you move from the relatively controlled setting of clinical trials to a real world environment, the risk of this event might actually increase; we cannot know that, of course, but it is a concern.
-Another concern is what might happen if a patient who receives an injection is injured at the injection site several days later; would that patient be at risk of having such an event?
-Finally, although inadvertent intravascular injection is a concern for any IM product, we have not seen events that are similar in character to these events for other depot antipsychotics. The sponsor refers to reports of retinal artery occlusion occurring with Risperdal Consta as a result of intravascular injection of this product. The difference is that this event can be avoided by attempting to aspirate before injection, while this appears not be the case with OP Depot.

Sponsor's Risk Management Plan (RMP) for OP Depot
-Bolded warning describing the event, proper injection technique, recommendation for 3 hour observation period, and recommended management of these events if they occur
-Information and advice for caregivers

Pharmacovigilance Plan
-Routine pharmacovigilance and targeted surveillance
-Observational study: this would be a prospective cohort study in approximately 5000 patients with the goals of estimating the crude incidence of these events over a 2-year period, identify potential risk factors, further characterize the event, compare the incidence of events in this more naturalistic setting to that observed in clinical trials

PDAC Discussion: We presented this application to the Psychopharmacologic Drugs Advisory Committee (PDAC) on 2-6-08. They voted unanimously (11-0) in favor OP Depot's efficacy for both the treatment of acutely exacerbated schizophrenia and for the maintenance treatment of

schizophrenia. They also voted unanimously (10-0; with 1 abstention) in favor of questions of whether or not there are circumstances under which OP Depot would be acceptably safe for the treatment of either acutely exacerbated schizophrenia and for the maintenance treatment of schizophrenia. The committee was concerned about the period of observation needed after each injection, and the consensus appeared to be that at least 3 hours would be needed. They also felt that this treatment should be limited to patients with a history of non-compliance to oral antipsychotic medications. However, there did not seem to be a sentiment in favor of second line status, i.e., they seemed comfortable allowing clinicians to decide for whom this treatment would be appropriate.

It is important to note that the committee was not made aware of the details of the most recent case, in particular, the fact that the onset of the CNS depression event in this patient may have been as late as 5 hours after the injection. In fact, in response to a question regarding how confident the sponsor was that these CNS depression events would only occur within a narrow window of 3 hours post-injection, they indicated a high degree of confidence, based on a theoretical argument that the diluent would be rapidly reabsorbed from the injection site, certainly within 3 hours, leaving a relatively solid mass of OP Depot that would not be able to easily enter the systemic circulation. I believe this was a determinative factor in the committee's willingness to conclude that OP Depot could be safely used with a relatively brief observation period for this event.

Comment Regarding the Safety of OP Depot: This new case is of critical importance in my thinking about how this drug product could be safely and feasibly used in the community. There is now renewed doubt that the period of risk for onset of these CNS depression events can be reasonably estimated. Simply extending the period of observation to 5 hours does not seem adequate, since this new case now also raises doubts about our understanding of the mechanism underlying such events. Extending the observation period beyond 5 hours raises questions about how such a product could be feasibly used in any outpatient setting.

Thus, it is my view that additional work is needed to better understand the risk and underlying mechanism for this event before this product can be approved. Conducting the sponsor's planned 5000 patient observational study would help to better characterize the nature of the event and its time course, including both onset and duration. However, I would also like the sponsor to consider additional work to try to better understand the mechanism underlying this event. I recognize that these events have not been observed in animal models the sponsor has utilized thus far, however, we can ask them to consider other animal models that might more closely mimic humans regarding this event.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, however, we will not issue our modified label to the sponsor at this time, since it is my view that a not-approvable action is most appropriate, given the lack of sufficient data to adequately characterize the risk of severe CNS depression and to determine how to safely and feasibly use this product in the community.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would add important new information to the existing database regarding the safety of OP Depot.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, olanzapine pamoate depot is not approved anywhere at this time for the treatment of schizophrenia.

8.0 DSI INSPECTIONS

Inspections were conducted at 3 US sites and data from these sites were deemed to be acceptable.

9.0 LABELING AND NOT-APPROVABLE LETTER

10.1 Labeling

As noted, we will not be including our modified version of labeling with the not-approvable letter.

10.2 Foreign Labeling

OP Depot is not approved anywhere at this time for the treatment of schizophrenia.

10.3 Not-Approvable Letter

The not-approvable letter details what we feel to be significant deficiencies for this application.

10.0 CONCLUSIONS AND RECOMMENDATIONS

Although I believe that Lilly has submitted sufficient data to support the conclusion that OP Depot is effective in the treatment of schizophrenia, I feel there is not sufficient information at this time to adequately characterize the risk of severe CNS depression with this product and to advise clinicians how to safely and feasibly use this product in the community. The problematic case of severe CNS depression arrived so late it is not reflected in the supervisory memo by Dr. Zornberg or the final addendum by Dr. Zhang. Consequently, their final documents recommend an approvable action for this application. However, we have discussed this case within the group, and there is agreement that this new case raises serious questions about the feasibility of this product. Thus, I will issue a not-approvable letter.

cc:
Orig NDA 22-173
ODE-I/RTemple
HFD-130/TLaughren/MMathis/GZornberg/JZhang/KKiedrow

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/s/

Thomas Laughren
2/24/2008 10:57:56 AM
MEDICAL OFFICER

ADDENDUM

Review and Evaluation of Clinical Data
NDA #22-173/000

Sponsor:	Eli Lilly and Company
Drug:	Olanzapine Pamoate Depot
Proposed Indication:	Schizophrenia
Material Submitted:	Original NDA submission
Correspondence Date:	April 27, 2007
Date Received:	April 30, 2007
Related NDA:	NDA 20592 (olanzapine oral tablet)

I. Background:

This NDA was submitted on April 27, 2007 and my original clinical review was completed on January 4, 2008. This NDA was presented to the Psychopharmacologic Drug Advisory Committee (PDAC) on Feb. 6, 2008, because of a serious adverse event, the excessive sedation event. At the time of completion of my review, several issues which we asked the PDAC for advice on were not definitively discussed in my previous review. This addendum intends to address these issues.

II. PDAC Meeting

The PDAC meeting was held on Feb. 6, 2008 regarding a unique serious adverse event, the excessive sedation event which occurred in 25 cases of 24 patients during olanzapine depot clinical trials. The questions to the committee for discussion included 1) What are the public health consequences of a depot antipsychotic that leads unpredictable to profound sedation in 1% or more of patients exposed to this product; and 2) If OP Depot were to be approved and marketed, what risk management procedures would be necessary, including labeling advice, to ensure the safe use of this products? The committee noted that there would be significant public health consequences (both positive and negative) of OP Depot. There was a predominant view among committee members that it would be worth trying to manage the risks of this new product in order to make it available to clinicians. There were concerns of a possibly greater risk of this excessive sedation event when this product would be used in a "real world" setting after approval. Regarding necessary risk management procedures, the consensus view seemed to be that a mandatory observation period was needed, however, there was not

clear agreement on exactly how long that period would need to be. The committee recommended that the label include the following: a mandatory observation period post injection and language limiting use to patients with documented non-adherence to oral antipsychotics. The committee further suggested that patients should be involved in the decision making process. The committee seemed opposed to relegating OP Depot to a second line status, instead, preferring to allow clinicians to make judgment calls regarding when to use it.

The questions to the committee requesting a vote included 1) Has OP Depot been shown to be effective for the treatment of acutely exacerbated schizophrenia patients? 2) Has OP Depot been shown to be effective for the maintenance treatment of schizophrenic patients? All eleven members voted "yes" to above two questions. 3) Are there circumstances under which OP Depot would be acceptably safe for the treatment of acutely exacerbated schizophrenic patients? and 4) Are there circumstances under which OP Depot would be acceptably safe for the maintenance treatment of schizophrenic patients? Ten of 11 members voted "yes" and 1 voted "abstain" for question 3 and 4.

III. Recommendation on Regulatory Action

Based on the data available at this time point and after considering the risks and benefits of having this product available to treat a severe mental illness, schizophrenia, I recommend that this NDA be granted approvable status.

To ensure appropriate use of this product, especially to prevent or limit the risk of the excessive sedation event after approval, substantial labeling changes were recommended (details can be found in the labeling revision section in this review). Final approval is contingent on mutual agreement on labeling changes and on the sponsor's Risk Management Plan (RMP) which was submitted on Feb. 7, 2008 by e-mail and is under review.

IV. Recommendation on Postmarketing Actions

In their RMP, the sponsor agreed to conduct a global observational study including 5000 patients during a period of 2 years to further study the excessive sedation events. No additional Phase 4 commitments or requests are recommended at this time.

The sponsor just recently submitted their RMP (by e-mail on 7 Feb. 2008) and the review has not been completed at the time of

completion of this addendum. The recommendations for risk management activity will depend upon the RMP review and will be addressed in separate addendum.

V. Re-Naming the Excessive Sedation Event

The SAE characterized with severe CNS depression and temporally associated with OP Depot injection was initially named by Lilly as Inadvertent Intravascular (IAIV) injection event. The division disagreed with the name because IAIV indicates the causality of the event which we believe is not fully established. Therefore, the division suggested a more descriptive name, the excessive sedation (ES) event, which is the name used in my original clinical review and in the PDAC meeting. However, the PDAC members thought both IAIV and ES were not an appropriate name for this event because the clinical presentation was a cluster of symptoms of CNS depression, not only the severe sedation and the causality of the event remained undetermined. After considering PDAC member's recommendation, the division recommends a name of severe central nervous system (CNS) depression. From this point forward, I will use the severe CNS depression instead of the ES event in this addendum and the labeling review.

VI. Labeling Revision

Major modifications to the sponsor's proposed labeling have been made, which include:

- A black box warning regarding the potential risk of the severe CNS depression events
- Use of OP Depot must be restricted to patients with a history of poor compliance to oral antipsychotics
- OP Depot is only administered in setting medically equipped to respond to severe CNS depression
- Tolerability to oral olanzapine must be established prior to initiating treatment
- After each injection, patients must be monitored by medical personnel capable of resuscitation (to include intubation) for 3 hours
- Patients should not drive or operate heavy machinery for 24 hours after every injection
- Patient Counseling Information will be adjusted accordingly in keeping with the other labeling changes

Jing Zhang, M.D., Ph.D.
February 13, 2008

cc: NDA 22-173
HFD-130 (Div. File)
HFD-130/M Mathis
/T Laughren
/G Zornberg
/J Zhang
/K Kiedrow

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/s/

Jing Zhang
2/19/2008 02:22:31 PM
MEDICAL OFFICER

Gwen Zornberg
2/19/2008 03:45:55 PM
MEDICAL OFFICER
I agree with Dr. Zhang's summary of findings from the PDAC (6 Feb 2008) and labeling revisions based on information available to FDA through 13 FEB 2008 conditional on no new Clinical, CMC, OCPB, and/or Pharm/Tox issues that would preclude an AE action.

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

DATE: February 12, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Acting Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for ZYPREXA (olanzapine pamoate) Depot for treatment of schizophrenia (short-term efficacy and maintenance treatment).

TO: File NDA 22-173 (olanzapine OP Depot long-acting injection)
Submitted 27 April 2007

REVIEWERS: Chemistry, Dr. David Claffey; Biopharmaceutics, Dr. Andre Jackson; Biostatistics, Dr. George Kordzakhia; and Clinical, Dr. Jing Zhang.

1.0 BACKGROUND

ZYPREXA olanzapine pamoate (OP depot) is a long acting injectable antipsychotic drug formulation developed for use in the treatment of schizophrenic patients with poor adherence to treatment. Eli Lilly has 3 approved olanzapine products: 1) Zyprexa tablets [NDA 20-592, 3- SEP 1996]; 2) Zyprexa Zydis Orally Disintegrating tablets [NDA21-086, 06-APR-2000]; and 3) Zyprexa IM [NDA 21-253, 29-MAR 2004]. OP depot is a monohydrate, low aqueous soluble crystalline salt. This NDA seeks a claim for the use of olanzapine pamoate monohydrate, OP Depot, in the short-term and maintenance treatment of patients diagnosed with schizophrenia able to tolerate oral olanzapine.

We met with the sponsors on 26 AUG 1999 to discuss the required program to support registration of OP Depot and on 22 JUL 2003 as well as 09 SEP 2005 to discuss a number of CMC issues, and they have conducted the long-acting formulation development program in accordance with our advice. Lilly has completed 1 short-term efficacy and one maintenance trial in patients diagnosed with schizophrenia This memo to file summarizes the findings at this point of a standard review.

2.0 CHEMISTRY

Dr. David Claffey has provided a status report on Lilly's submission of OP Depot in an email date 11 February 2008. The first CMC review was completed 31 January 2008. The chemistry reviewers are nearing the completion of their evaluation of Lilly's responses to the CMC letters dated 21 November 2007 and 4 January 2008. In an email dated 11 February 2008, Dr. Claffey stated that he thought that most of the issues that were raised have been adequately addressed by Lilly. It is expected that the remaining issues will be resolved also this week in communications with Lilly. The adequacy of the dissolution specification as of this date has not been determined as yet by OCPB. This issue needs to be resolved before an expiry period can be assigned by Chemistry.

The CDER Office of Compliance issued an overall acceptable recommendation regarding the manufacturing and testing sites for OP depot. Dr Raanan Bloom determined that this application qualifies for a categorical exclusion under 21 CFR 25.31 (b). The microbiology reviewer, Dr. Stephen Langille, has not yet completed his review.

At present, I do not expect any CMC issues that would preclude an approvable action for this NDA.

3.0 PHARMACOLOGY

The Pharmacology /Toxicology review has been completed by Dr. Sonia Tabacova who found the submitted body of nonclinical studies to be adequate. She recommended in her review dated 7 February 2008 that under 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility should be "…equivalent to 0.3 (males) and 0.8 (females) times the maximum recommended human dose of 300 gm every 2 weeks on a mg/m^2 basis."

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approvable action for this NDA.

4.0 BIOPHARMACEUTICS

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewer, Dr. Andre Jackson, has not determined the adequacy of the dissolution specification as of this date. This issue needs to be resolved before an expiry period can be assigned by CMC. Dr. Jackson has requested that Lilly clarify several points, such as whether it is the reconstituted suspension on which the dissolution testing is being conducted and the stable shelf life of the product per a stability indicating assay. Dr. Jackson has also requested that Lilly provide the content uniformity and assay results for relevant batches of this product.

I am aware of no biopharmaceutics issues that would preclude an approvable action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Study HGJZ (8-week, Placebo-Controlled Trial)
Our review of this application focused on 1 short-term (8-week), double-blind, randomized, parallel group, placebo-controlled trial (HGJZ) in patients diagnosed with DSM-IV or DSM-IV TR criteria for schizophrenia (n=404). Patients were discontinued from their previous antipsychotic drug and underwent a 2-7 day washout period prior to randomization. No oral antipsychotic supplementation was allowed throughout the trial. The patients were randomly assigned to receive olanzapine 210 mg/2 weeks, 405 mg/4 weeks, 300 gm/2 weeks, or placebo. {{The patients were able to continue as inpatients for the entire study or change to outpatient status after starting treatment inpatient. The primary efficacy endpoint analysis for the one short-term, placebo-controlled trial was mean change from Baseline to Week 8 endpoint (LOCF) in the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo (sham injections). The improvement in total PANSS scores from baseline to endpoint was significantly superior to placebo in each dose group. The effectiveness of olanzapine is further supported by the established effectiveness of oral formulation of olanzapine in the face of substantial clinical exposure.

George Kordzakhia, Ph.D. provided the primary findings from the application reproduced below (NDA 22173, Biometrics review dated 18 December 2007).

PANSS Total Score Change from Baseline to Endpoint, HGJZ Study Period II (ITT Population)

		Placebo	OPD 300mg/2WK	OPD 405 mg/4WK	OPD 210 mg/2WK
No patients	N=402	98	98	100	106
LS Mean Change from Baseline	Mean (SD)	-8.51 (23.03)	-26.32 (24.93)	-22.57 (22.15)	-22.49 (21.84)
Placebo-adjusted difference	LS mean (SE)	NA	-18.23 (2.82)	-14.43 (2.80)	-14.87 (2.76)
	95% CI	NA	(-23.78, -12.68)	(-19.93, -8.93)	(-20.29,-9.44)
	P-Value	NA	<0.0001	<0.0001	<0.0001

Source: Dr. Kordzakhia's results
Note: The reported p-values and 95% CI's are nominal and are not adjusted for multiplicity.

In the primary analysis of the PANSS Total score, patients in all olanzapine pamoate depot groups (i.e., 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were observed to show statistically significant improvement over patients in the placebo treatment group. The highest dose group, the 300 mg/2 weeks group, was associated with a numerically greater improvement than the 405 mg/4 weeks and the 210 mg/2 weeks groups as reflected in reduction on the PANSS total score.

Dr. Kordzakhia conducted sensitivity analyses on the primary endpoint. Change from baseline in PANSS Total score was analyzed also by a mixed effect repeated measures model. The model included treatment, investigator, visit, and interaction of treatment by visit as fixed effects, and baseline as a covariate. The unstructured variance-covariance matrix was used. The findings support the highly significant primary efficacy analysis results. No key secondary analyses had been identified *a priori* by the applicant.

Study HGKA (24-week comparison to the very low dose OP Depot 45/4week Group)
The efficacy of OP Depot was evaluated also in a multicenter, randomized, double-blind maintenance trial for time-to-relapse over 24 weeks in patients enrolled with stabilized schizophrenia (n=1065). Outpatients who met DSM-IV or DSM-IV-TR criteria for schizophrenia and who remained stable for 4 to 8 weeks on open-label treatment with oral olanzapine (mean baseline total PANSS score 56) were randomized to a 24 week continuation of their current oral olanzapine dose (10 mg, 15 mg, or 20 mg/day); or to OP depot 150 mg every 2 weeks, 405 mg every 4 weeks, 300 mg every 2 weeks, or 45 mg every 4 weeks, , which is equivalent approximately to oral olanzapine 1-2 mg per day. No oral antipsychotic supplementation was allowed throughout the trial. The primary efficacy measure was time to exacerbation of symptoms of schizophrenia defined in terms of increases in Brief Psychiatric Rating Scale (BPRS) positive symptoms or hospitalization. OP depot doses of 150 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks were each significantly superior to low dose OP depot 45 mg every 4 weeks.

For this study, exacerbation of symptoms of schizophrenia was defined as follows:

- An increase on any of the BPRS Positive items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score >4 and an absolute increase of $\geq$ 2 on that specific item since randomization at Visit 10, or
- An increase of any of the BPRS Positive items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score >4 and an absolute increase of $\geq$ 4 on the BPRS Positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization at Visit 10, or
- Hospitalization due to worsening of positive psychotic symptoms.

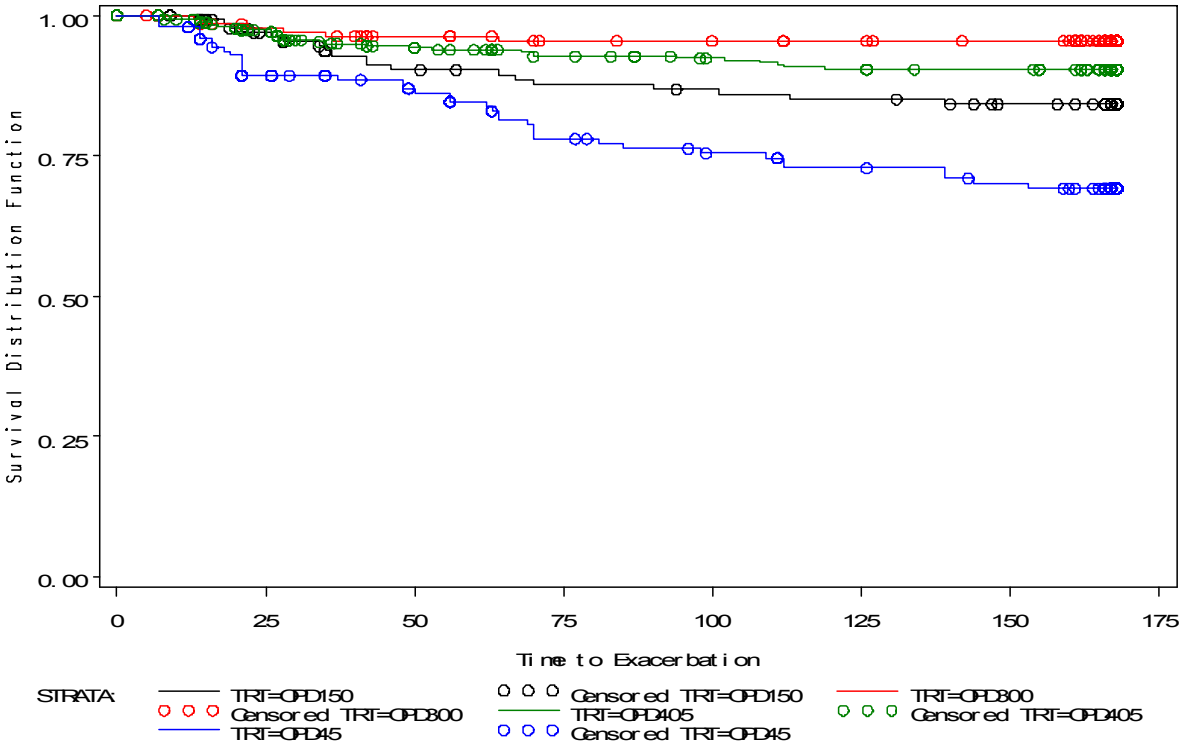
The primary superiority analysis was comparison of time to exacerbation of the higher dose groups: OP Depot 405 mg/4 weeks, OP Depot 300 mg/2 weeks, and OP Depot 150 mg/2 weeks versus the time to exacerbation in the low-dose OP Depot 45 mg/4 weeks group. The log-rank test was used to assess the pairwise comparisons of time to exacerbation (relapse) of clinically substantial psychotic symptoms.

Log-rank Test of Time to Exacerbation. OPD150, OPD300, OPD405 vs OPD45.

P-values from Log-Rank Test		
OPD300 mg /2WK v. OPD45mg/4WK	OPD405/4WK vs.OPD454WK	OPD150mg/2WK v. OPD454WK
<0.001	<0.001	0.006

Source: Figure HGKA.11.2. , HGKA Study Report (pg .200)
Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

Kaplan-Meier curves of Time to Exacerbation for the double-blind maintenance phase (curves from top to bottom: OPD300, OPD405. OPD150, OPD45).



Source: Dr. Kordzakhia's results

The 3 higher dose olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed a positive maintenance of efficacy effect compared with the low dose (45mg/ 4 weeks) for stabilized patients with schizophrenia in delaying time to relapse. As in the short-term trial, the greatest numerical improvement was observed in the 300 mg/2 weeks treatment group compared to all other treatment groups.

In summary, consistent with the findings in the oral olanzapine study populations, the primary efficacy analyses were statistically significant in both the short-term and the maintenance trials of schizophrenia in all OP Depot treatment groups.

Olanzapine Pamoate Depot Efficacy Data

Secondary Efficacy Variables

The sponsor did not identify any key secondary variables.

Clinical Predictors of Response

Gender, race, and age did not appear to materially influence treatment effect in any recognizable pattern.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has in my view, as well as in the views of Dr. Kordzakhia as detailed in his review, provided sufficient evidence to support the claim of short-term treatment of acute psychosis and longer-term maintenance of efficacy of olanzapine OP Depot as efficacious treatment of patients diagnosed with schizophrenia.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for this efficacy supplement were derived from a total of n=1915 subjects/patients exposed to olanzapine OP Depot across1 short-term clinical trial (N=404), one long-term trial (N=921) and 6 open-label studies comprising the Zyprexa OP Depot schizophrenia treatment program. The total exposure to olanzapine OP Depot was 1460.1 patient-years.

5.2.2 Common Adverse Drug Reaction Profile for Olanzapine OP Depot As Treatment of Schizophrenia

The profile of olanzapine OP Depot is similar to the profile of the oral formulation and thus continues to include the exacerbation of symptoms of schizophrenia as well as increased weight, insomnia, anxiety, sedation/somnolence, headache, nausea, vomiting increased appetite, and nasopharyngitis as some of the most commonly occurring types of adverse drug reactions (ADRs).

5.2.3 Adverse Reactions of Particular Interest

There were 3 deaths in the OP depot treated patients (namely, cardiomyopathy, leptospirosis, and chronic hypertension), which were considered by Lilly to be unrelated to study drug exposure.

Based on the findings of Dr. Zhang's review, over all the safety profile was similar to that observed with oral olanzapine. The metabolic adverse drug reactions including increased occurrences of weight gain and elevated triglyceride levels, though not serum glucose, compared to placebo in the 8-week placebo-controlled trial were similar to those frequencies observed with the oral formulation discussed in greater depth below.

There are 2 major exceptions to the oral olanzapine safety profile found with OP depot: 1) episodes of severe CNS depression, and 2) injection site reactions. The episodes of severe CNS depression were remarkable for their severity coupled with their unpredictable pattern and relatively common occurrence.

CNS depression Adverse Drug Reactions (ADRs): The drug reactions that we have characterized under the rubric of CNS depression encompasses adverse drug reactions that when observed, have certain characteristics in common. Twenty of 24 patients were hospitalized. Five of the patients were diagnosed as having acute alterations of their levels of consciousness in hospital. These 25 episodes of severe CNS depression occurred in 24 patients as one patient experienced 2 of these events, these CNS depression ADRs. In one patient, after 2 hours, bilateral miosis was observed coupled with the absence of photo-motor reflexes , the presence of automatic movements and a positive Babinski sign. Of the 24 patients, two patients with CNS depression observed within 3 hours of injection were intubated. None of the patients had elevations of sedating drugs such as benzodiazepines, alcohol, barbiturates, opioids, or illicit drug levels on toxicological evaluation that would confound the clincial scenario. In a slide presented at the PDAC, it was shown that at least 7 patients were not using concomitant medication around the time of the event that could reasonably be considered causal. There were no deaths and the episodes of CNS depression resolved in all 25 cases.

After the sponsor became aware of the frequency of these events, the healthcare providers were trained in the administration of OP depot. Nonetheless, no change in pattern occurred after the systematic training by the sponsor took place. After a high quality injection training program instituted by Lilly, the frequency has remained unchanged. To date, the pattern remains unpredictable.

The cause of the CNS depression events remains undetermined. There may be a number of contributing factors. Although two cases occurred at one site in Spain, the global occurrence of these events taking place over the entire drug development time span suggests that if the clinician administering the OP depot were a factor, that this would be only a small contribution.

The large 19-gauge needle required for administration that is provided in the OP depot kit may complicate the need to avoid intravascular injection as advised by Lilly. It remains to be seen whether the risk may change with length of needle. In labeling the sponsor provided language*: (For obese patients, 19-guage, 2-inch (50 mm) needles are recommended).* Moreover, the opacity of the suspended and unsuspended OP Depot product may hinder the healthcare provider's ability to detect aspirated blood in the 19-gauge needle.

Lilly reported that all patients recovered from these acute episodes and continued to be treated with elevated olanzapine serum levels for the duration of the intended time for systemic exposure (e.g., for the full 2 or 4 weeks, depending on the dose group).. There were no deaths observed. From our review of the post-marketing surveillance data, no other antipsychotic drug, including the long-acting formulations have bee associated with such a relatively high incidence of CNS depression progressing into coma. This ADR raises greater concern about the ability to prevent these episodes and reduce the frequency of occurrence. because in addition to being common with the risk of occurrence of approximately one patient in 100 who receives OP Depot, the pattern of occurrence is unpredictable and therefore more difficult to prevent than the usual ADR .

Injection site drug reactions: In labeling, the providers of the OP depot injection are cautioned to flush skin after contact with the medicine: *It is recommended that gloves are used when reconstituting as olanzapine pamoate may be irritating to the skin. Flush with water if contact is made with the skin.*

Metabolic profile: The metabolic profile is similar in patients exposed to OP depot compared with those exposed to oral olanzapine. No unexpected metabolic adverse drug reactions were reported. A dose response relationship was observed in the frequency of patients who gained at least 7% of baseline weight, which is considered potentially clinically significant, as well as those who experienced elevated serum levels of fasting triglycerides (TG) in the 8-week, placebo-controlled trial. Weight gain and elevated serum triglyceride levels were most often observed in the 300 mg/2Wk group.

Olanzapine Pamoate Depot - Weight Gain ≥ 7% Baseline Wt. at Endpoint*

Treatment	Number Patients	%	P-value vs. Placebo
Placebo	97	12.4	
210 mg q2Wk	106	23.6	0.05
405 mgq4Wk	100	27.0	0.01
300 mg q2Wk	99	35.4	< 0.001

*Results from Zyprexa OP Depot HGJZ CSR, p.

Olanzapine Pamoate Depot - Triglyceride levels Change from Normal to High (???Baseline to 8-Week Endpoint)

Treatment	Number Patients	%	P-value vs. Placebo
Placebo	88	3.4	
210 mg q2Wk	94	12.8	0.03
405 mg q4Wk	96	6.3	0.5
300 mg q2Wk	91	14.3	0.02

*Results from Zyprexa OP Depot HGJZ CSR, p.

5.2.4 Use in Elderly Patients

As olanzapine OP Depot safety profile regarding CNS depression remains to be better understood, the sponsor did not conduct any special population studies. Patients aged greater than 65 years were excluded from the short-term registration trials.
It is unclear how well medically ill patients would tolerate the potential for episodes of severe CNS depression that was observed in approximately one percent of adult patients as well adverse injection site reactions. In any event, the use of olanzapine in elders diagnosed with dementia-related psychosis is associated with an elevated risk of mortality.

5.2.5 Risk: Benefit Evaluation

In view of the known morbidity and mortality of such a serious disorder as schizophrenia, treatment of patients with poor adherence to antipsychotic drug treatment continues to pose a challenge. Certain patients will be unable to tolerate certain adverse drug reactions associated with the long acting antipsychotic drugs presently available on the market. Consequently, these pivotal trials demonstrate significant efficacy in an area of unmet clinical need. Because of the seriousness of the relatively common risk for CNS sedation associated with OP depot, certain restrictions will need to apply to limit use. The highest dose level, OP Depot 300 mg/2weeks, has been associated with the numerically greatest improvement of psychotic symptoms coupled with a greater risk of certain adverse drug reactions such weight gain, elevated triglycerides, and elevated prolactin levels.

5.2.6 Conclusions Regarding the Safety of Olanzapine Pamoate Depot As Treatment of Schizophrenia

5.3 Clinical Sections of Labeling

In the effort to maximize safety of this potentially valuable treatment option, the Division has made major modifications to the sponsors' proposed Zyprexa OP Depot labeling for the schizophrenia indication that was submitted in PLR format. We have added a warning regarding the potential risk for CNS depression in the black box of Zyprexa labeling regarding use in elders with dementia-related psychosis. These are the highlights of the points that we are recommending to Lilly.

Use of Zyprexa OP Depot must be restricted to patients with a history of poor compliance to antipsychotic drug treatment who are able to tolerate oral olanzapine. That is the primary benefit of depot treatment for schizophrenia. It reads in the black box:

"Patients are at risk of severe CNS depression (including coma) with each injection and must be monitored by medical personnel capable of resuscitation (to include intubation) for 3 hours after each injection."

In dosage and administration, labeling reads:

- Administer only in settings medically equipped to respond to severe CNS depression.
- Establish tolerability with oral olanzapine prior to initiating treatment.

Intended for deep intramuscular gluteal injection; do not administer intravenously or subcutaneously.

In **Warnings and Precautions,** added bracketed comments to the sponsor have language added to labeling below the NMS paragraph that reads:

[We are reviewing the additional information you submitted regarding olanzapine and hyperglycemia, hyperlipidemia, and clinically significant weight gain—see Approvable Letter. Therefore, there will be future modifications to these sections of labeling after we have reviewed your submissions.]

Patient Counseling Information will be adjusted accordingly in keeping with the other changes to enhance the safety of OP Depot administration.

6.0 WORLD LITERATURE

The sponsor provided certification that they reviewed the literature and found no relevant articles that would further adversely affect conclusions about the safety of olanzapine OP Depot in the treatment of patients diagnosed with schizophrenia.

7.0 FOREIGN REGULATORY ACTIONS

To the best of my knowledge, Zyprexa OP Depot has not been submitted previously for approval for any indication.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC)

The PDAC was held on 6 February 2008 to provide information regarding the common and unpredictable occurrence of CNS depression of a serious nature in which 20 of the 24 patients were hospitalized who experienced these events. At the PDAC, the sponsor reported that the diluent is absorbed within 3 hours, leaving the salt. This suggests that most of the rapid absorption of the drug during an episode may occur by approximately 3 hours, leaving the salt for the continuation of long-acting efficacy. On a slide presented briefly by the sponsor, it was evident that at least 7 patients apparently were not using concomitant medications.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 sites: Dr. Robert Litman in Rockville, MD; Dr. Adam Lowy, Washington, D.C.; and Dr. Matthew Brams, Houston, TX. Data from these sites were deemed by the Consumer Safety Officer, Diane Tesch, to be acceptable with no data integrity issues as documented in her review dated 14 December 2007.

10.0 PHASE 4 COMMITMENTS

The applicant has committed to conduct a large-scale study as part of an extensive ohase 4 commitment program.

11.0 LABELING AND APPROVABLE LETTER

We will include a modified version of labeling in PLR format submitted by Lilly with the approvable letter.

DMETS has not approved the use of RELPREV, nor ADHERA, to be the Tradename for ZYPREXA OP Depot marketing in the U.S.

12.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Eli Lilly and Company has submitted sufficient data, substantiated by a large oral olanzapine base of patient exposure, to support the conclusion that olanzapine OP Depot is effective treatment of schizophrenia. OP Depot offers clinically significant efficacy with the numerically greatest improvement on the PANSS and time-to-relapse in the 300 mg/2 weeks OP depot group.

The risk benefit analysis has been influenced strongly, however, by the severity of the unpredictable nature of CNS depression that occurs relatively commonly for such a serious adverse drug reaction. It should be taken into account that the episodes resolved in all patients and no death occurred. A Approximately one in a hundred patients who will receive the OP Dept injection has the risk of experiencing an episode of CNS depression (that may progress into coma) approximate in timing (within 3 hours) to intramuscular gluteal injection of olanzapine pamoate depot. At least 7 patients apparently were not using concomitant medications nor had elevated alcohol or illicit drug levels reported on toxicological evaluation. Based on the data supporting robust efficacy provided in the NDA application for a drug that could provide an important treatment option to very ill schizophrenic patients with confirmation of the findings by Biometrics, as well as the discussion of the risk/benefit analysis afforded by the Psychopharmacologic Drug Advisory Committee, I recommend that an approvable action be taken.

Before we can take an approval action, we need to review the updated OP Depot Risk Management Plan following the PDAC, to reach agreement with the applicant on OP depot labeling, and to incorporate in the OP Depot labeling the most recent recommendations by FDA on the description of metabolic adverse events associated with olanzapine exposure updated with the most recent data that has been submitted to FDA. Moreover, Lilly had agreed to conduct an observation study of 5,000 patients, which we may require as a post-marketing commitment.

I do not recommend that we require a Medication Guide for this population of chronically ill psychotic patients who do not adhere to treatment. It is not clear what realistic benefit

this would provide. The labeling should be clear to educate healthcare providers and those caring for patients of the risk around the three hours following injection particular to observe for changes in levels of consciousness that may require hospital treatment.

I support the waiver of a pediatric requirement in view of the risk of CNS impairment associated with the 1% risk of CNS depression in adults. It is unknown whether the risk may be higher in children and adolescents.

Thus, I recommend that we issue the approvable letter along with our proposed labeling, in anticipation of a complete response by Lilly.

cc:
Orig NDA 22-173
HFD-130
HFD-130/GZornberg/JZhang/MMathis/TLaughren /KKiedrow/SHardeman

DOC:Olanzapine OP Depot_TreatmentSZ_Zornberg_AE_Memo.doc

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/s/

Gwen Zornberg
2/12/2008 11:49:50 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 22-173
Submission Number	000
Submission Code	N
Letter Date	April 27, 2007
Stamp Date	April 30, 2007
PDUFA Goal Date	February 29, 2008
Reviewer Name	Jing Zhang, MD, PhD
Review Completion Date	January 4, 2008
Established Name	Olanzapine Pamoate Depot
(Proposed) Trade Name	Pending
Therapeutic Class	Atypical Antipsychotic
Applicant	Eli Lilly
Priority Designation	S
Formulation	Intramuscular Injection
Dosing Regimen	210 mg/3 ml, 300 mg/3 ml, and 405 mg/3 ml
Indication	Schizophrenia
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The information from this clinical review will be presented to the Psychopharmacologic Drug Advisory Committee (PDAC) on 6 February 2008 because of a serious safety concern regarding the excessive sedation events that occurred in 25 cases of 24 patients during olanzapine depot clinical trials. A total 1915 patients were administered olanzapine depot in these trials. At this time point, no regulatory action is recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A risk management activity plan is to be determined following the PDAC meeting. An addendum to this NDA review will be filed after the meeting.

1.2.2 Required Phase 4 Commitments

Phase 4 commitment requirement will be determined.

1.2.3 Other Phase 4 Requests

Other Phase 4 requests are to be determined.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The efficacy and safety of olanzapine pamoate depot (OP Depot) in the treatment of schizophrenia were evaluated by Lilly in a total of 8 studies (see Table 1):

- Controlled studies: One double-blind, placebo-controlled, fixed-dose study (HGJZ) and one double-blind, oral olanzapine-controlled, fixed-dose study (HGKA) were conducted to evaluate the efficacy and safety of OP Depot.
- Open-label studies: Six open-label studies were conducted at varying phases of clinical development for OP Depot.

Table 1 Overview of Studies in the Clinical Plan of Development for OP Depot

Study ID/ Study Status	Study Length	# Enroll/ Rand	Dose	Study Design and Objective
HGJZ/ Concluded	8 weeks	404 Rand	**OP Depot**: 210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks **Placebo**	Double-blind, placebo-controlled, fixed-dose PK, efficacy superiority, and safety study in patients with schizophrenia.
HGKA/ Concluded	24 weeks	1065 Rand	**OP Depot**: 45 mg/4 weeks (reference dose), 405 mg/4 weeks, 150 mg/2 weeks, 300 mg/2 weeks **Oral OLZ**: 10, 15, 20 mg/day	Double-blind, olanzapine-controlled, fixed-dose study of noninferiority of maintenance of efficacy, superiority of 3 therapeutic OP Depot doses compared to reference dose, safety, and PK in patients with schizophrenia.
HGKB/ Ongoing	Up to 4 years	931 Enroll (725 ongoing as of Jan 2007	**OP Depot**: Flexible doses ranging from 45 mg to 405 mg given at 2-, 3-, or 4-week intervals	Long-term, open-label safety, effectiveness, and PK (subset) study in patients with schizophrenia or schizoaffective disorder who previously completed an OP Depot clinical trial (HGJZ, HGKA, or LOBS).
LOBE/ Concluded	Up to 24 weeks	282 Enroll	**OP Depot**: single dose 50 to 450 mg **OP Depot**: multi-dose 100 to 405 mg/2 to 4 wks	Open-label, single- and multiple-dose study of safety and PK in symptom-stabilized patients with schizophrenia.
LOBO/ Concluded	8 weeks	9 Enroll	**OP Depot**: 4 injections of 300 mg/2 wks **Oral OLZ**: 5 to 20 mg (prior to enrollment)	Open-label study of safety, PK, and OP Depot metabolites in patients with schizophrenia or schizoaffective disorder.
LOBS/ Concluded	Approx 7 weeks	134 Rand	**OP Depot**: single-dose 405 mg **Oral OLZ**: 5, 10, 15, 20 mg daily **OLZ RAIM**: single-dose 5 mg	Oral lead-in phase followed by a fixed-sequence, parallel-design, open-label study of safety, PSD, and PQBP of OP Depot compared with oral OLZ or RAIM in stable patients with schizophrenia or schizoaffective disorder.
HGJW/ Concluded	24 weeks	14 Enroll	**OP Depot**: 300 mg/4 weeks	Open-label, one-arm, PET study of receptor occupancy, safety, and efficacy in patients with schizophrenia.
HGLQ/ Ongoing	Up to 2 years	524 Rand	**OP Depot**: 150 to 405 mg/4 weeks **Oral OLZ**: 5 to 20 mg/day	Randomized, open-label study of safety, effectiveness, and health outcomes in treatment with OP Depot or oral OLZ in patients with schizophrenia at risk for relapse.

In this submission, Lilly submitted completed Clinical Study Reports (CSR) from two controlled studies (HGJZ and HGKA) and the CSR & a report of pharmacokinetic analysis from an ongoing uncontrolled clinical study (HGKB). Integrated safety data obtained from all 8 OP Depot clinical trials were included in the Clinical Overview section.

The efficacy of OP Depot in the treatment of schizophrenia is demonstrated by efficacy data obtained from an 8-week, randomized, double-blind, placebo-controlled study (HGJZ) and a 24-week, double-blind, randomized, maintenance study (HGKA).

The safety evaluation of OP Depot in this review is primarily based on safety data obtained from two controlled studies (HGJZ and HGKA). The Overall Integrated Safety Database was used to detect pattern changes of common adverse events (AEs), unexpected or serious adverse events (SAEs), or deaths and AEs occurring with long-term exposure.

1.3.2 Efficacy

In the short-term (8 weeks) acute efficacy and safety study (HGJZ), the three OP depot treatment groups showed superior improvement over placebo in reducing the PANSS Total Score from baseline to end point starting at week 1 and continuing through the end of the study.

In the long-term (24 weeks) maintenance study (HGKA), the 3 higher dose OP Depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed positive maintenance of effect over 24 weeks for stabilized patients with schizophrenia.

1.3.3 Safety

The safety evaluation of OP Depot demonstrated that the safety profile 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 named as inadvertent intravascular (IAIV) injection events.

As of 30 November 2007, a total of 25 of these excessive sedation events have been reported in 24 patients. Since the causality of the events has not been established, we prefer to use the descriptive term—excessive sedation to connote the events. From this point forward in my review, the term of excessive sedation will be used to replace the term of IAIV injection events.

The excessive sedation events raised a serious safety concern because of the severity of sedation, combined with unpredictability and a relatively high incidence—0.07% of injection and 1.3% of patients (details can be found in section 7.1.12, Special Safety Studies).

1.3.4 Dosing Regimen and Administration

Both the short-term (HGJZ) and long-term (HGKA) controlled studies were fixed dose studies. In Study HGJZ, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2

weeks and placebo. In Study HGKA, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 150 mg/2 weeks, 45 mg/4 weeks and oral olanzapine (flexible doses 10 to 20 mg/d). All OP Depot injections were administered by gluteal intramuscular injection.

1.3.5 Drug-Drug Interactions

The existing olanzapine label addresses safety outcomes related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

1.3.6 Special Populations

The existing olanzapine label addresses safety outcomes related to pediatric population, geriatric population, nursing mothers and pregnant women. There have been no new data generated on these topics with respect to the OP Depot in this submission that have not already been addressed in current olanzapine labeling.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Oral olanzapine, an atypical antipsychotic, is a potent serotonin 5-$HT_{2A/2C}$, dopamine D_{1-4} antagonist with affinity for muscarinic receptors. Its mechanism of action is unknown; however, it has been proposed that olanzapine's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. Oral olanzapine (Zyprexa) was initially approved by FDA in 1996. Table 2 lists other formulations of olanzapine and their respective approval dates.

Table 2 FDA Approval Dates for Olanzapine Formulations

Approval Month and Year	Formulation Name	Indication
September 1996	Zyprexa (Oral olanzapine tablets)	Schizophrenia, acute manic or mixed episodes of bipolar I disorder
April 2000	Zyprexa Zydis (Oral olanzapine dispersible tablets)	Schizophrenia, acute manic or mixed episodes of bipolar I disorder
March 2004	Zyprexa IntraMuscular (Rapid-acting intramuscular [RAIM] injection formulation)	Agitation associated with schizophrenia and bipolar I mania

2.2 Currently Available Treatment for Indications

Numerous typical and atypical antipsychotics have been approved by FDA for the treatment of schizophrenia in the USA. Compared with the oral preparations, only a few long-acting antipsychotic injections are available in the USA: two typical antipsychotics—haloperidol decanoate and fluphenazine decanoate, and one atypical antipsychotic—Risperidal Consta.

2.3 Availability of Proposed Active Ingredient in the United States

Olanzapine is an approved drug in the United States.

2.4 Important Issues With Pharmacologically Related Products

The safety concerns regarding olanzapine related metabolic syndrome and increased risk of diabetes are under review by our safety team. At this point, no final conclusions regarding these issues have been reached.

2.5 Presubmission Regulatory Activity

26 August 1999	Lilly met with FDA to discuss the required preclinical, pharmacokinetic, and clinical program to support the registration of OP Depot.
14 September 1999	Lilly met with FDA to discuss the manufacturing plans to support the registration and commercial production of OP Deport.
08 November 2000	Lilly met with FDA to discuss the manufacturing plans to support the registration and commercial production of OP Deport.
31 July 2001	Lilly met with FDA to discuss completed preclinical studies and planned clinical studies for the OP Depot.
26 June 2002	FDA issued a written response to Lilly's briefing document dated 11 June 2002 regarding CM&C/Biopharmaceutics issues.
22 July 2003	Lilly met with FDA regarding CMC/Biopharmaceutics issues.
27 April 2004	Lilly met with FDA to discuss their in-vitro dissolution method development plan.
09 September 2005	Lilly met with FDA to discuss CMC/Biopharmaceutics issues.
17 July 2006	Lilly met with FDA (Pre-NDA Meeting) to obtain guidance from FDA on the overall content and format for the anticipated NDA for OP Depot.
27 April 2007	Lilly submitted the NDA for OP Depot.

2.6 Other Relevant Background Information

Olanzapine has not been withdrawn from the market worldwide for any reason.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

David Claffey, PhD. and Prafull Shiromani, PhD. are the CMC reviewers for this submission. Please refer to their reviews for detailed CMC review information.

3.2 Animal Pharmacology/Toxicology

There were no animal pharmacology/toxicology data provided in this submission and these studies were not deemed necessary.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy data to support this submission are from two controlled, parallel studies—HGJZ, an 8-week, double-blind, randomized, placebo-controlled study and HGKA, a 24-week, double-blind, randomized, olanzapine-controlled maintenance study of OP Depot in the treatment of schizophrenia.

The safety data to support this submission are primarily from the two controlled studies—HGJZ and HGKA. In addition, the integrated safety data from 8 OP Depot clinical trials (mainly from Study HGKB) were also reviewed.

4.2 Tables of Clinical Studies

Table 3 Table of Clinical Studies

Study ID/ Study Status	Study Length	# Enroll/ Rand	**Dose**	Study Design and Objective
HGJZ/ Concluded	8 weeks	404 Rand	**OP Depot**: 210 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks **Placebo**	Double-blind, placebo-controlled, fixed-dose PK, efficacy superiority, and safety study in patients with schizophrenia.
HGKA/ Concluded	24 weeks	1065 Rand	**OP Depot**: 45 mg/4 weeks (reference dose), 405 mg/4 weeks, 150 mg/2 weeks, 300 mg/2	Double-blind, olanzapine-controlled, fixed-dose study of noninferiority of maintenance of efficacy, superiority of 3 therapeutic OP Depot doses compared to reference dose, safety, and

Study ID/ Study Status	Study Length	# Enroll/ Rand	**Dose**	Study Design and Objective
			weeks **Oral OLZ**: 10, 15, 20 mg/day	PK in patients with schizophrenia.
HGKB/ Ongoing	Up to 4 years	931 Enroll (725 ongoing as of Jan 2007	**OP Depot**: Flexible doses ranging from 45 mg to 405 mg given at 2-, 3-, or 4-week intervals	Long-term, open-label safety, effectiveness, and PK (subset) study in patients with schizophrenia or schizoaffective disorder who previously completed an OP Depot clinical trial (HGJZ, HGKA, or LOBS).

4.3 Review Strategy

A list of the items examined during the course of the review is provided in Table 4. The efficacy results from Study HGJZ and HGKA were reviewed separately. The safety data from the controlled studies (HGJZ and HGKA) were reviewed individually and the integrated safety data from 8 OP Depot trials were combined for analyses.

Table 4 Items Utilized in the Review

Submission Date	Items Reviewed
30 April 2007	Clinical Study Report: HGJZ and HGKA Clinical Summary Clinical Overview Special Topic Report: IAIV Injection Events, Cardiovascular Effects, Metabolic Parameters and Weight Gain, Hepatic Measures Case Report Forms and Narratives
28 August 2007	4 Month Safety Update

4.4 Data Quality and Integrity

Inspectors from the Division of Scientific Investigation (DSI) have inspected 3 clinical sites. Since all studies are multi-center studies and no results from any site drove the efficacy results, the sites for inspection were chosen based on larger enrollment in the site (b) (4) were chosen for inspection. Table 5 summarizes the inspection results.

Table 5 DSI Inspection Results

Name of CI and site #	City, State	Protocol #	Insp. Date	EIR Received Date	Interim Classification	Final Classification
Robert E.Litman, M.D. site 031	Rockville, MD	F1D-MC-HGJZ	9/19/2007-9/27/2007	11/6/2007	N/A	VAI
Adam F.Lowy, M.D. site 032	Washington, DC	F1D-MC-HGJZ	11/26/07-11/30/07	pending	NAI	pending
Matthew Brams, M.D. site 016	Houston, TX	F1D-MC-HGJZ	7/31/2007-8/2/2007	8/17/07	N/A	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

There were no data integrity issues found at any of the sites. Observations for Dr. Lowy's site are based on communications from the field investigator. DSI reports that an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the Establishment Inspection Report (EIR).

4.5 Compliance with Good Clinical Practices

All studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.6 Financial Disclosures

(b) (6) received 31,600 Euros in payment of lecture fees and consulting fees. Two patients were randomized at his site (b) (6) which contributed (b) (4) of total patients in Study HGKA. The financial payments the investigator received were unlikely to influence the outcome of the study as the percentage of patients enrolled is negligible compared to the entire study population for the analyses.

(b) (6) received $100,000 in payment of lecture fees and consulting fees. At his site (b) (6) 9 patients were randomized which contributed (b) (4) of total patients in Study HGJZ. The financial payments the investigator received were unlikely to influence the outcome of the study for similar reason.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Andre Jackson, PhD. is the clinical pharmacology reviewer for this submission. Please refer to his review for pertinent information.

5.2 Pharmacodynamics

Andre Jackson, PhD. is the clinical pharmacology reviewer for this submission. Please refer to his review for pertinent information.

5.3 Exposure-Response Relationships

Andre Jackson, PhD. is the clinical pharmacology reviewer for this submission. Please refer to his review for pertinent information.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Lilly is submitting this NDA to gain approval for OP Depot for the indication of the treatment of schizophrenia.

Two studies were conducted to evaluate the efficacy and safety of OP Depot in the treatment of schizophrenia. These include one short-term (8 weeks), double-blind, randomized, placebo-controlled study (Study F1D-MC-HGJZ, HGJZ) and a long-term (24 weeks), double-blind, randomized, olanzapine-controlled study (Study F1D-MC-HGKA, HGKA). The efficacy data from both studies are reviewed in detail in the efficacy review section of this review. The efficacy review was performed in consultation with the statistical reviewer, George Kordzakhia, PhD.

George Kordzakhia, PhD concluded in his review that no statistical issues are identified in both studies.

6.2 Efficacy Review on Study F1D-MC-HGJZ

6.2.1 Methods

The clinical study report for the 8-week, placebo-controlled study, HGJZ, is the major data source used for this efficacy review.

6.2.2 General Discussion of Endpoints

The primary endpoint of Study HGJZ was the mean change from baseline to endpoint in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score. The PANSS is one of most commonly used instruments for measuring symptom reduction of schizophrenia patients in antipsychotic therapy trials. The PANSS is a 30-item rating instrument evaluating the presence/absence and severity of positive, negative and general psychopathology of

schizophrenia. The validation and use of the PANSS as a tool for assessing the efficacy of treatments for schizophrenia and other psychotic disorders is well documented.

6.2.3 Study Design

6.2.3.1 Investigators/Sites

Study HGJZ was conducted by 42 principle investigators at 42 study centers in three countries—the United States, Croatia, and Russia from 22 June 2004 to 26 April 2005.

A full list of clinical study sites and investigators for Study HGJZ is included in Appendices 10.1 List of Principle Investigators and Study Sites (see Table 27).

6.2.3.2 Objectives

Primary Objectives
The primary objective of Study HGJZ was to assess the acute efficacy (8-week) of OP Deport at doses of 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks in the treatment of schizophrenia.

Secondary Objectives
None of following secondary objectives was pre-specified as a key secondary objective.

- To assess the efficacy of OP depot treatment compared with placebo as measured by the Clinical Global Impression-Improvement of Illness (CGI-I) Scale.
- The earliest time point at which the percentage of patients with CGI-I score of ≤ 3.
- The mean change from baseline to endpoint in Clinical Global Impression-Severity of Illness (CGI-S) Scale.
- The mean change from baseline to endpoint in PANSS Positive, PANSS Negative, and PANSS General Psychopathology subscales.
- The mean change from baseline to endpoint in quality of life measured by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the Heinrichs-Carpenter Quality of Life Scale (QLS).
- The safety and tolerability of OP Depot treatments compared with placebo.
- PK of OP Depot following multiple doses at each of dosing regimens.

6.2.3.3 Subjects

Inclusion Criteria:

- Male or female patients, aged 18 to 75, who met the criteria for schizophrenia as defined by DSM-IV.
- PANSS-derived Brief Psychiatric Rating Scale (BPRS) score of ≥ 48 at Visit 1.

Exclusion Criteria:

- Patients who were considered to be treatment-resistant to olanzapine.

- Patients who had received treatment in the 30 days prior to Visit 1 with a drug that had not yet received regulatory approval or who had participated in a trial of another investigational drug.
- Patients who experienced clinically significant AEs while being treated with olanzapine.
- Patients who presents risks of suicide or homicide.
- Patients who had a serious, unstable medical conditions.

6.2.3.4 Overall Study Design

Study HGJZ was an 8-week, inpatient/outpatient, multiple center, randomized, double-blind, and parallel study to assess efficacy and safety of OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks compared with placebo/2 weeks in the treatment of patients with schizophrenia.

After a 2-7 day washout period, eligible patients were randomized into one of the following 4 groups at a 1:1:1:1 ratio: OP depot 300 mg/2 weeks, OP depot 405 mg/4 weeks, OP depot 210 mg/2 weeks, or placebo/2 weeks. During the first 2 weeks following randomization, patients remained inpatient and were assessed daily. During the rest of study period, patients were followed on weekly basis as outpatients.

6.2.3.5 Dose and Administration

After a washout period, patients entered an 8-week double-blind treatment period, during which they were assigned to one of four treatment injections (OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2 weeks or placebo/2 weeks) every two weeks. Patients who were randomized to 405 mg/4 weeks OP depot received a placebo injection at every other injection visit. All study medications were administered by gluteal intramuscular injection.

6.2.3.6 Statistical Analysis Plan

An intent-to-treat (ITT) principle was applied in the efficacy, safety, and health outcomes analyses. Efficacy analyses included all randomized patients (N=404) with baseline and postbaseline observations. Efficacy data were analyzed using the last-observation-carried-forward (LOCF) method. Continuous data were analyzed using ANOVA models. For analysis of proportions, Fisher's exact test was used. The primary comparisons of interest were the pairwise contrast of each OP depot treatment group versus placebo. The pairwise comparisons based on the hierarchical order of the fixed sequence procedure were specified a *priori*, so no further adjustment to the significance levels were necessary. All hypotheses were tested at a two sided α level of 0.05. In order to assess longitudinal effects, a likelihood-based repeated measures analysis was conducted on the post-baseline PANSS Total score and associated subscales.

6.2.4 Efficacy Findings

6.2.4.1 Disposition of Patients

A total of 466 patients were enrolled in the study and 62 patients failed screening. A total of 404 eligible patients were randomized in a 1:1:1:1 ratio to receive double-blind OP depot 300 mg/2 weeks, (n=100), OP depot 405 mg/4 weeks (n=100), OP depot 210 mg/2 weeks (n=106), or placebo (n=98). A total of 267 (66%) patients completed the study.

Table 6 summarizes overall patient disposition and reasons for discontinuation. The most common reasons for discontinuing the study were lack of efficacy (n=59) and patient decision (n=45). There was a higher discontinuation rate due to lack of efficacy in the placebo group. There were no statistically significant differences across treatment groups for overall reasons for discontinuation.

Table 6 Patient Disposition and Reasons for Discontinuation in Study HGJZ

Total Patients Enrolled: 466				
Total Patients Randomized: 404				
	OP Depot 300 mg/2 wks N (%)	OP Depot 405 mg/4 wks N (%)	OP Depot 210 mg/2 wks N (%)	Placebo N (%)
Randomized	100 (100.0)	100 (100.0)	106 (100.0)	98 (100.0)
Completed	67 (67.0)	72 (72.0)	72 (67.9)	56 (57.1)
p-values vs. placebo	0.268	0.114	0.213	
Discontinued	33 (33.0)	28 (28.0)	34 (32.1)	42 (42.9)
AEs	6 (6.0)	4 (4.0)	3 (2.8)	5 (5.1)
Lost to follow up	0 (0.0)	0 (0.0)	2 (1.9)	1 (1.0)
Protocol violation	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.0)
Subject decision	9 (9.0)	12 (12.0)	15 (14.2)	9 (9.2)
Physician decision	5 (5.0)	1 (1.0)	1 (0.9)	2 (2.0)
Sponsor decision	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Lack of efficacy	13 (13.0)	10 (10.0)	12 (11.3)	24 (24.5)

6.2.4.2 Demographic Characteristics

Table 7 summarizes baseline demographic characteristics in Study HGJZ for all randomized patients. The patients randomized were predominantly male (n=285, 70.5%) and Caucasian (n=226, 55.9%). This distribution is consistent with the distribution in the schizophrenic population. The average age of enrolled patients was 40 years, with a range of 18 to 74 years. There were no statistically significant differences across treatment groups with respect to these demographic characteristics.

Table 7 Baseline Demographic Characteristics in Study HGJZ

	300Q2W N=100	405Q4W N=100	210Q2W N=106	PLA N=98	Total N=404	p-Values			
						Overall	300Q2W Vs. PLA	405Q4W Vs. PLA	210Q2W Vs. PLA
Gender									
Female	28 (28.0)	27 (27.0)	27 (25.5)	37 (37.8)	119 (29.5)	0.217	0.144	0.106	0.059
Male	72 (72.0)	73 (73.0)	79 (74.5)	61 (62.2)	285 (70.5)				
Origin									
Caucasian	58 (58.0)	54 (54.0)	61 (57.5)	53 (54.1)	226 (55.9)	0.705	0.373	0.945	0.277
African	38 (38.0)	36 (36.0)	35 (33.0)	37 (37.8)	146 (36.1)				

	300Q2W N=100	405Q4W N=100	210Q2W N=106	PLA N=98	Total N=404	p-Values			
						Overall	300Q2W Vs. PLA	405Q4W Vs. PLA	210Q2W Vs. PLA
Hispanic	4 (4.0)	6 (6.0)	9 (8.5)	3 (3.1)	22 (5.4)				
Others	0 (0.0)	4 (4.0)	1 (0.9)	5 (5.1)	10 (2.5)				
Age (yrs)									
Mean	41.46	39.54	39.76	42.64	40.82	0.129	0.255	0.030	0.056
BMI	(n=99)		(n=105)		(n=402)				
Mean	28.9	29.42	28.72	28.26	28.82	0.627	0.671	0.196	0.585
Weight (kg)	(n=99)				(n=403)				
Mean	85.45	87.29	86.95	82.23	85.52	0.190	0.334	0.053	0.072

6.2.4.3 Disease Characteristics

There were no significant differences in disease characteristics (number of previous episodes or exacerbation in the last 2 years, age of onset, length of current episodes) across treatment groups. Two or more previous episodes or exacerbations of schizophrenia in the last 24 months were reported by 71% of the patients.

The three most frequently used previous antipsychotic therapies were risperidone (n=159, 39.4%), olanzapine (n=153, 37.9%), and haloperidol (n=104, 25.7%). There were no statistically significant differences in previous drug therapies across treatment groups.

Table 8 summarizes baseline severity of illness for all randomized patients. The treatment groups were comparable at baseline with respect to severity of illness. Baseline mean PANSS Total Score across all treatment groups was 101, and the mean score of the extracted BPRS Total (transformed from a 1-to-7 scale to a 0-to-6 scale) was 41. There were no statistically significant differences across treatment groups in baseline severity of illness scores.

Table 8 Baseline Severity of Illness Score in Study HGJZ

	300Q2W N=99 (Mean)	405Q4W N=100 (Mean)	210Q2W N=106 (Mean)	PLA N=98 (Mean)	Total N=403 (Mean)	p-Values			
						Overall	300Q2W Vs. PLA	405Q4W Vs. PLA	210Q2W Vs. PLA
PANSS Total	102.70	101.33	99.55	100.60	101.02	0.471	0.174	0.600	0.993
PANSS Positive Total	25.86	25.74	25.21	25.38	25.54	0.764	0.364	0.389	0.739
PANSS Negative Total	25.97	25.35	24.72	25.09	25.27	0.223	0.091	0.664	0.836
Extracted BPRS Total	41.53	41.07	40.45	40.40	40.86	0.715	0.268	0.389	0.549

6.2.4.4 Concomitant Medications

Lorazepam was the most frequently used concomitant medication, with 232 (57.4%) of the patients reporting its use. There were no statistically significant differences comparing OP depot arms with the placebo arm in regards to concomitant medication use or benzodiazepine use during the study.

6.2.4.5 Efficacy Results

Primary Variable

The primary objective of the study was to demonstrate superiority of the OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks compared to placebo in change from baseline to endpoint in the PANSS Total score in the treatment of patients with schizophrenia.

The mean changes from baseline to end point in PANSS Total Score for the OP depot treatment arms versus the placebo arm are presented in Table 9. Patients in the 300 mg/2 weeks, 405 mg/2 weeks, and 210 mg/2 weeks showed statistically significant improvements over placebo in the PANSS Total Score at endpoint (Week 8). The PANSS Total Scores at Week 8 were -26.32, -22.98 and -22.49 in the 300 mg/2 weeks, 405 mg/2 weeks, and 210 mg/2 weeks arms respectively, and −8.51 in the placebo arm using the LOCF analyses. The difference from placebo in mean change from baseline at Week 8 was −17.81 ($p < .001$) for the 300 mg/2 weeks arm and −14.47 ($p < .001$) for the 405 mg/4 weeks arm and -13.98 ($p < .001$) for the 210 mg/2 weeks arm.

The results of the OC analysis were consistent with the findings from the LOCF analyses. The difference between treatment arms and placebo arms in mean change from baseline to endpoint was -21.00 ($p < .001$) for the 300 mg/2 weeks arm, -12.97 ($p < .001$) for the 405 mg/2 weeks arm and -11.37 ($p < .001$) for the 210 mg/2 weeks arm (see Table 29 in 10.2 Appendix to Efficacy Review).

Table 9 Mean Change from Baseline to Endpoint in PANSS Total Score in Study HGJZ (LOCF) – Primary Efficacy Analysis

	300Q2W N=100	405Q4W N=100	210Q2W N=106	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (Mean)	102.58	101.33	99.55	100.60			
Mean Change (Mean)	-26.32	-22.98	-22.49	-8.51	<.001	<.001	<.001

Table 10 summarizes the visit-wise mean change from baseline to endpoint in PANSS total score (LOCF). Patients in OP depot 300 mg/2 weeks and 405 mg/4 weeks, showed significant improvement over placebo treatment after half-week. All three OP depot treatment groups were statistically superior to placebo in mean change of PANSS Total score from Week 1 through the completion of the study.

Table 10 Visit-wise Mean Change from Baseline to Endpoint in PANSS Total Score in Study HGJZ (LOCF)

Visit	300Q2W N=100 (Mean)	405Q4W N=100 (Mean)	210Q2W N=106 (Mean)	PLA N=98 (Mean)	p-value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline	102.58	101.33	99.55	100.60			
Week 0.43	-8.64	-8.22	-7.58	-5.24	.011	.025	.056

Visit	300Q2W N=100 (Mean)	405Q4W N=100 (Mean)	210Q2W N=106 (Mean)	PLA N=98 (Mean)	p-value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Week 1	-14.8	-13.38	-13.68	-9.37	.001	.016	.005
Week 2	-19.61	-16.80	-16.51	-10.97	<.001	.004	.003
Week 3	-22.22	-18.84	-19.33	-10.69	<.001	<.001	<.001
Week 4	-22.68	-20.03	-20.63	-8.83	<.001	<.001	<.001
Week 5	-23.37	-21.77	-21.82	-8.74	<.001	<.001	<.001
Week 6	-24.80	-22.49	-22.76	-8.67	<.001	<.001	<.001
Week 7	-25.79	-22.98	-23.38	-8.64	<.001	<.001	<.001
Week 8	-26.32	-22.57	-22.49	-8.51	<.001	<.001	<.001

Mean change from baseline to endpoint in OP depot 300 mg/2 weeks (p=.005) arm was statistically superior to placebo at Visit 5 (day 3). Overall, all three OP depot treatment groups were statistically significantly superior to placebo at week 1 and through the remainder of the study.

Secondary Variables

No secondary variables in Study HGJZ were pre-specified as key secondary variables.

CGI-I Scores at Endpoint

Table 11 summarizes CGI-I scores at LOCF endpoint. All three OP depot treatment groups demonstrated statistically significant improvement on the CGI-I score compared with placebo at Visit 5 (day 3) and throughout the rest of Study (p<.001).

Table 11 CGI-I Score at Endpoint in Study HGJZ (LOCF)

	300Q2W N=99	405Q4W N=99	210Q2W N=105	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Day 1 (SE)	3.96 (0.05)	3.96 (0.04)	3.91 (0.04)	3.98 (0.05)			
Day 56 (SE)	2.92 (0.15)	2.96 (0.13)	3.01 (0.13)	4.05 (0.15)	<.001	<.001	<.001

Mean Change from Baseline to Endpoint in CGI-S

Table 12 summarizes mean change from baseline to endpoint in CGI-S Scores. All OP depot treatment groups demonstrated statistically significant improvement in CGI-S scores compared with placebo at Visit 9 (Day 7) and all subsequent visits of the study.

Table 12 Mean Change from Baseline to Endpoint in CGI-S in Study HGJZ (LOCF)

	300Q2W N=99	405Q4W N=99	210Q2W N=105	PLA N=98	P – value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (SE)	4.83 (0.07)	4.86 (0.08)	4.74 (0.07)	4.71 (0.07)			
Mean Change (SE)	-0.97 (0.12)	-0.92 (0.11)	-0.91 (0.10)	-0.28 (0.11)	<.001	<.001	<.001

Mean Change from Baseline to Endpoint in PANSS Subscale Scores

PANSS Positive Score
All three OP depot treatment groups (300 mg/2 weeks, p=.004; 405 mg/4 weeks, p=.001; 210 mg/2 weeks, p=.032) were statistically superior to placebo in mean change of the PANSS Positive score by Visit 5 (Day 3), and maintained significance through the remainder of the study. There were no statistically significant differences among the OP depot treatment groups. Table 13 summarizes the mean change from baseline to endpoint in PANSS Positive Score.

Table 13 Mean Change from Baseline to Endpoint in PANSS Positive Score in Study HGJZ (LOCF)

					P – value		
	300Q2W N=99	405Q4W N=99	210Q2W N=105	PLA N=98	300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (SE)	25.82 (0.49)	25.74 (0.50)	25.21 (0.49)	25.38 (0.54)			
Mean Change (SE)	-7.42 (0.79)	-7.18 (0.69)	-6.32 (0.66)	-1.99 (0.77)	<.001	<.001	<.001

PANSS Negative Score
All OP depot treatment groups demonstrated statistically significant improvement over placebo by Visit 17 (Week 3). Additionally, OP depot 300 mg/2 weeks showed statistically superior improvement over OP depot 405 mg/4 weeks at Visit 21 (Week 7), and over 405 mg/4 weeks and 210 mg/2 weeks at Visit 22 (Week 8). Table 14 summarizes the mean change from baseline to endpoint in PANSS Positive Score.

Table 14 Mean Change from Baseline to Endpoint in PANSS Negative Score in Study HGJZ (LOCF)

					P – value		
	300Q2W N=98	405Q4W N=100	210Q2W N=106	PLA N=98	300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline (SE)	26.02 (0.54)	25.35 (0.51)	24.72 (0.51)	25.09 (0.56)			
Mean Change (SE)	-6.28 (0.62)	-4.55 (0.54)	-4.79 (0.54)	-2.10 (0.59)	<.001	<.001	<.001

6.2.4.6 Subgroup Analyses

Subgroup analyses were performed to evaluate change from baseline to endpoint on the PANSS Total Score within subgroups based on age (<40 and ≥ 40), gender, race and region (US and Non-US). There was no subgroup for which there was a statistically significant therapy-by-subgroup interaction.

6.2.5 Clinical Microbiology

Clinical microbiology was not considered necessary for this product.

6.2.6 Efficacy Conclusions

The three OP depot treatment groups demonstrated superior improvement over placebo in reducing PANSS Total Score starting at week 1 and continuing through the end of the study.

6.3 Efficacy Review on Study F1D-MC-HGKA

6.3.1 Methods

The clinical study report for the 24-week Study HGKA is the major data source for this efficacy study review.

6.3.2 General Discussion of Endpoints

The primary endpoints of Study HGKA were:

- A comparison of pooled 2-Week OP Depot (300 mg/2 weeks and 150 mg/2 weeks) and oral olanzapine group with respect to rates of exacerbation of symptoms
- The pair-wise comparisons of time to exacerbation of symptoms for each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) versus the low OP Depot dose (45 mg/4 weeks)

Both exacerbation rates and time to exacerbation of symptoms are commonly used endpoints in long-term relapse prevention trials. In this study, the stabilization phase was relatively short, 4-8 weeks. However, since patients had been clinically stable before enrollment, the actual stabilization period was much longer than 4-8 weeks. The efficacy data from this trial can be used to support this submission.

6.3.3 Study Design

6.3.3.1 Investigators/Sites

Study HGKA was conducted by 113 principle investigators at 112 study sites in 26 countries from 6 July 2004 to 13 September 2006.

A full list of clinical study sites and investigators for Study HGKA is included in Appendices 10.1 List of Principle Investigators and Study Sites (see Table 28).

6.3.3.2 Objectives

Primary Objectives

- Non-inferior efficacy of pooled 2-week OP Depot (300 mg/2 weeks and 150 mg/2 weeks) versus oral olanzapine (10, 15 or 20 mg/d, flexible dosing) as measured by exacerbation rates after 24 weeks of maintenance treatment.

- Superior efficacy of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks OP Depot versus 45 mg/4 weeks OP Depot as measured by time to exacerbation of symptoms of schizophrenia after 24 weeks of maintenance treatment.

6.3.3.3 Subjects

Inclusion Criteria

- Male or female out-patients meeting DSM-IV criteria for schizophrenia, ages 18 to 75 years.
- Clinically stable on antipsychotics for at least 4 weeks preceding Visit 1 and BPRS Positive items score ≤ 4.
- If enrolled on parenteral antipsychotics, received their last injection at least 2 weeks (or 1-injection interval, whichever was longer) prior to visit 2.

Exclusion Criteria

- History of treatment-resistance to olanzapine
- Received treatment with an investigational drug or unapproved drug within 30 days prior to enrollment
- Had an allergic reaction to olanzapine or had experienced clinically significant adverse events while treated with olanzapine
- Had a significant suicidal or homicidal risk
- Were pregnant or breast feeding
- Had uncorrected narrow-angle glaucoma, hypo- or hyperthyroidism, history of agranulocytosis
- Had serious or unstable medical conditions
- Had substance dependency within the past 30 days
- Received treatment with remoxipride within 6 months, with clozapine within 4 weeks;
- Had previously participated in an OP depot study
- Required concomitant treatment with a medication with CNS activity other than those allowed in the protocol

6.3.3.4 Overall Study Design

Study HGKA was a randomized, double-blind, parallel group, 24-week maintenance-of-effect study comparing the efficacy and safety of OP Depot (150 mg/2 weeks, 300 mg/2 weeks, 405 mg/4 weeks) with oral olanzapine (10, 15, and 20 mg/day) and low dose OP Depot (45 mg/4 weeks) in clinically stabilized outpatients with schizophrenia. The study consisted of 4 study periods: a 2- to 9-day Lead-In/Screening Phase; a 4- to 8-week Conversion/Stabilization Phase; a 24-week Double-Blind Maintenance Phase; and an up to 24-week Open-Label Restabilization Phase for patients who were discontinued from double-blind therapy due to exacerbation of symptoms associated with schizophrenia. A separate datalock was conducted for the Open-Label Restabilization Phase data, and results from that study period were not included in this submission.

Patients who met the inclusion criteria were discontinued from their current antipsychotic medication (unless it was olanzapine) and converted to oral olanzapine monotherapy (at 10, 15 or 20 mg/d). To enter the double-blind phase of the study, patients had to be stabilized with oral olanzapine for at least 4 weeks. 1060 patients were randomized in a 2:1:1:1:2 ratio, into 1 of 5 treatment groups: 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks OP Depot, or oral olanzapine, respectively.

An unbalanced randomization scheme (2:1:1:1:2 ratio) was chosen to ensure that when pooled, an approximately equal number of patients at specific doses would be available for the following comparisons:

a) Primary efficacy comparison of Pooled 2-Week OP Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) versus oral olanzapine

b) Comparison of Pooled 2-Week OP Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) versus 405 mg/4 weeks OP Depot

c) To ensure that fewer patients received the very low dose of OP Depot (45 mg/4 weeks)

6.3.3.5 Dose and Administration

The doses of OP Depot administered in this study (IM buttock injection) were 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, and 45 mg/4 weeks. Doses of oral olanzapine were 10, 15, and 20 mg/day. The dosing schedule is presented in Table 15. No change in dose was permitted during the study.

Table 15 Dosage and Medication Schedule for Study HGKA

Treatment Group	Oral Olanzapine[a]	Oral Placebo[a]	Placebo Injection	OP Depot Injection
Oral olanzapine	Daily	Daily[b]	Every 2 weeks	N/A
OP Depot				
405 mg/4 weeks	N/A	Daily	Every 4 weeks[c]	Every 4 weeks[c]
300 mg/2 weeks	N/A	Daily	N/A	Every 2 weeks
150 mg/2 weeks	N/A	Daily	N/A	Every 2 weeks
45 mg/4 weeks	N/A	Daily	Every 4 weeks[c]	Every 4 weeks[c]

6.3.3.6 Statistical Analysis Plan

All analyses were conducted on an intent-to-treat (ITT) basis. Efficacy analyses included all randomized patients (N=1065) with baseline and postbaseline observations. Noninferiority

analyses were based on Kaplan-Meier estimated 24-week acumulative exacerbation rates. Exacerbation was defined as a BPRS Positive item score >4 (1-7 scale) either with an increase of ≥ 2 points since randomization or with a BPRS Positive subscale increase of ≥ 4 points since randomization, or as hospitalization due to worsening of positive symptoms. Noninferiority was assessed using the upper limit of a two-sided 95% confidence limit for the difference between estimated exacerbation rates, with noninferiority declared if the absolute value of the upper limit was <.20. For time-to-relapse analyses, Kaplan-Meier curves were compared using a log-rank test. Baseline to endpoint analyses used last-observation-carried-forward (LOCF) methodology unless otherwise specified. Analysis of variance (ANOVA) models were used to evaluate continuous data and generally included terms for treatment and investigator or geographic region. The analysis of covariance (ANCOVA) on the LOCF mean change from baseline to endpoint in PANSS Total score included baseline PANSS Total score as a continuous covariate as well as terms for treatment and investigator. Type III sums of squares were used to test for significant effects for all ANOVA/ANCOVA models. For analysis of proportions, the Fisher's exact test was used unless otherwise specified. All hypotheses were tested at a two-sided α level of 0.05.

6.3.4 Efficacy Findings

6.3.4.1 Disposition of Patients

Of the 1205 patients entering the Conversion/Stabilization Phase, 1065 eligible patients were randomized during the Double-Blind Maintenance Phase. A total 753 of the 1065 eligible patients (70.7%) completed Study HGKA. Table 16 presents a summary of patient disposition following randomization into the Double-Blind Maintenance Phase.

Table 16 Summary of Patient Disposition in Study HGKA

	OP Depot 405 mg/4 wks N (%)	OP Depot 300 mg/2 wks N (%)	OP Depot 150 mg/2 wks N (%)	OP Depot 45 mg/4 wks N (%)	Oral Olanzapine 10, 20 or 30 mg N (%)
Randomized	318 (100.0)	141 (100.0)	140 (100.0)	144 (100.0)	322 (100)
Completed	222 (69.8)	107 (75.9)	90 (64.3)	76 (52.8)	258 (80.1)
Discontinued	96	34	50	68	64
AEs	10 (3.1)	4 (2.8)	7 (5.0)	6 (4.2)	8 (2.5)
Clinical relapse	39 (12.3)	7 (5.0)	22 (15.7)	42 (29.2)	23 (7.1)
Lack of efficacy	2 (0.6)	2 (1.4)	4 (2.9)	2 (1.4)	4 (1.2)
Lost to follow up	5 (1.6)	2 (1.4)	3 (2.1)	2 (1.4))	2 (0.6)
Physician decision	8 (2.5)	3 (2.1)	2 (1.4)	3 (2.1)	4 (1.2)
Protocol violation	5 (1.6)	4 (2.8)	3 (2.1)	1 (0.7)	3 (0.9)
Sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)
Subject decision	27 (8.5)	12 (8.5)	9 (6.4)	10 (6.9)	20 (6.2)
Entering open-label phase	39	7	22	42	23

Other than those patients who entered the Open-Label Restabilization Phase due to exacerbation, no treatment group showed >8.5% discontinuation for any reason. The most common reason for discontinuing the study during this period was patient decision (n=78). There was a statistically

significant difference (p<.001) across treatment groups for all-cause discontinuation. Statistically significant between-group comparisons were as follows:

- A statistically significantly greater percentage of patients treated with oral olanzapine completed the Double-Blind Maintenance Phase compared with patients in all other treatment groups except 300 mg/2 weeks OP Depot (300 mg/2 weeks OP Depot [p=.324]; 405 mg/4 weeks OP Depot [p=.003]; 150 mg/2 weeks OP Depot [p<.001]; and 45 mg/4 weeks OP Depot [p<.001]).

- A statistically significantly greater percentage of patients in all treatment groups, other than 150 mg/2 weeks OP Depot, completed the Double-Blind Maintenance Phase compared with 45 mg/4 weeks OP Depot (300 mg/2 weeks OP Depot [p<.001]; 405 mg/4 weeks OP Depot [p<.001]; 150 mg/2 weeks OP Depot [p=.055]; and oral olanzapine [p<.001]).

- A statistically significantly greater percentage of patients treated with 300 mg/2 weeks OP Depot completed the Double-Blind Maintenance Phase compared with patients treated with 150 mg/2 weeks OP Depot (p=.038).

There was also a statistically significant difference between treatment groups for discontinuation due to clinical relapse (p<.001). No other reasons for discontinuation were statistically different across treatment groups.

6.3.4.2 Demographic Characteristics

Table 17 summarizes baseline physical characteristics (gender, ethnic origin, age, BMI, and weight) for all randomized patients. The patient population was predominantly male (65.4%) and Caucasian (71.8%), which is consistent with the distribution of schizophrenia population. Patients' age ranged from 18 to 71 years with a mean age of 39 years at baseline. There were no statistically significant differences across treatment groups with respect to baseline physical characteristics.

Table 17 Baseline Demographic Characteristics of Study HGKA

	OPD405Q4W N=318	OPD300Q2W N=141	OPD150Q2W N=140	OPD45Q4W N=144	Oral OLZ N=322	Total N=1065
Gender						
Female	106 (33.3)	46 (32.6)	56 (40.0)	48 (33.3)	113 (35.1)	369 (34.6)
Male	212 (66.7)	95 (67.4)	84 (60.0)	96 (66.7)	209 (64.9)	696 (65.4)
Origin						
Caucasian	230 (72.3)	99 (70.2)	96 (68.6)	106 (73.6)	234 (72.7)	765 (71.8)
African	12 (3.8)	7 (5.0)	8 (5.7)	5 (3.5)	13 (4.0)	45 (4.2)
Hispanic	51 (16.0)	25 (17.7)	26 (18.6)	21 (14.6)	53 (16.5)	176 (16.5)
Others	25 (7.9)	10 (7.1)	10 (7.1)	12 (8.4)	22 (6.9)	79 (7.4)
Age (yrs)						
Mean	39.00	39.54	37.71	39.47	38.98	38.96

	OPD405Q4W N=318	OPD300Q2W N=141	OPD150Q2W N=140	OPD45Q4W N=144	Oral OLZ N=322	Total N=1065
BMI Mean	(n=317) 26.96	26.5	27.20	27.13	(n=321) 26.76	(n=1063) 26.89
Weight (kg) Mean	77.89	75.30	78.40	78.44	76.95	77.41

6.3.4.3 Disease Characteristics

With respect to historical illness characteristics, approximately 37% of patients reported 2 or more previous episodes or exacerbations of schizophrenia in the last 24 months; approximately 32% of patients reported 1 such episode in the last 24 months, and approximately 31% of patients reported no such episodes in the last 24 months. No statistically significant differences were observed across treatment groups. No statistically significant differences were observed in historical illness characteristics between the Pooled 2-Week OP Depot and the oral olanzapine treatment groups.

Table 18 presents baseline severity of illness scores. The mean PANSS Total score for all randomized patients was 55.87. Statistically significant differences across treatment groups were observed for the PANSS Total (p=.048), PANSS Negative Total (p=.027), and Extracted Brief Psychiatric Rating Scale (BPRS) Negative (p=.014). On each of these measures, the 45 mg/4 weeks OP Depot group had the highest mean scores, while the 150 mg/2 weeks group had the lowest mean scores. Baseline Clinical Global Impression-Severity of Illness (CGI-S) scores were also statistically significantly different across treatment groups (p=.016), again with the 45 mg/4 weeks group having the highest mean score, but with the 300 mg/2 weeks group having the lowest mean score. Although statistically significant, these baseline differences between groups were small—within a range of 3.42 points on the PANSS Total, 1.06 points on the PANSS Negative, 0.62 on the BPRS Negative, and 0.19 on the CGI-S. The small differences are not likely to be clinically significant.

No statistically significant differences were observed between the Pooled 2-Week OP Depot and the oral olanzapine treatment groups with respect to baseline severity of illness Scores.

Table 18 Baseline Severity of Illness Scores in Study HGKA

	OPD405Q4W N=99 (Mean)	OPD300Q2W N=100 (Mean)	OPD150Q2W N=106 (Mean)	OPD45Q2W N=98 (Mean)	Oral OLZ N = 322 (Mean)	Total N=403 (Mean)
PANSS Total	55.06	56.81	54.33	57.75	56.08	55.87
PANSS Positive Total	11.12	11.07	11.15	11.63	11.23	11.22
PANSS Negative Total	15.94	16.66	15.82	16.88	16.67	16.37
Extracted BPRS Total	12.10	12.84	11.54	13.42	12.45	12.41
Extracted BPRS Negative	3.44	3.72	3.20	3.82	3.77	3.60
Extracted BPRS Positive	3.21	3.12	3.17	3.65	3.32	3.29

6.3.4.4 Concomitant Medications

A total of 54.1% of patients took at least one concomitant medication during this study. The concomitant medications used by at least 5% of patients during the double-blind phase were lorazepam (11.6%), clonazepam (9.9%), diazepam (7.3%), biperiden (5.6%), and paracetamol (4.9%). There were no statistically significant differences across all treatment groups in concomitant medication use (either overall or for individual drugs listed above) during double-blind treatment phase.

6.3.4.5 Efficacy Results

Superiority Analysis

The superiority analysis assessed the pairwise comparisons of time to exacerbation of symptoms for each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) versus the low OP Depot dose (45 mg/4 weeks). In order to control the Type I error, these pairwise tests were conducted sequentially as follows: (1) 300 mg/2 weeks versus 45 mg/4 weeks, (2) 405 mg/4 weeks versus 45 mg/4 weeks, and (3) 150 mg/2 weeks versus 45 mg/4 weeks. Thus, the 405 mg/4 weeks versus 45 mg/4 weeks test would be declared significant only if both this comparison and the first comparison (300 mg/2weeks versus 45 mg/4 weeks) were statistically significant. The 150 mg/2 weeks versus 45 mg/4 weeks comparison would be declared statistically significant only if all 3 comparisons were statistically significant.

Each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4 weeks dose with respect to time to exacerbation of symptoms (p-values: <.001, <.001, and =.006, respectively; Figure 1).

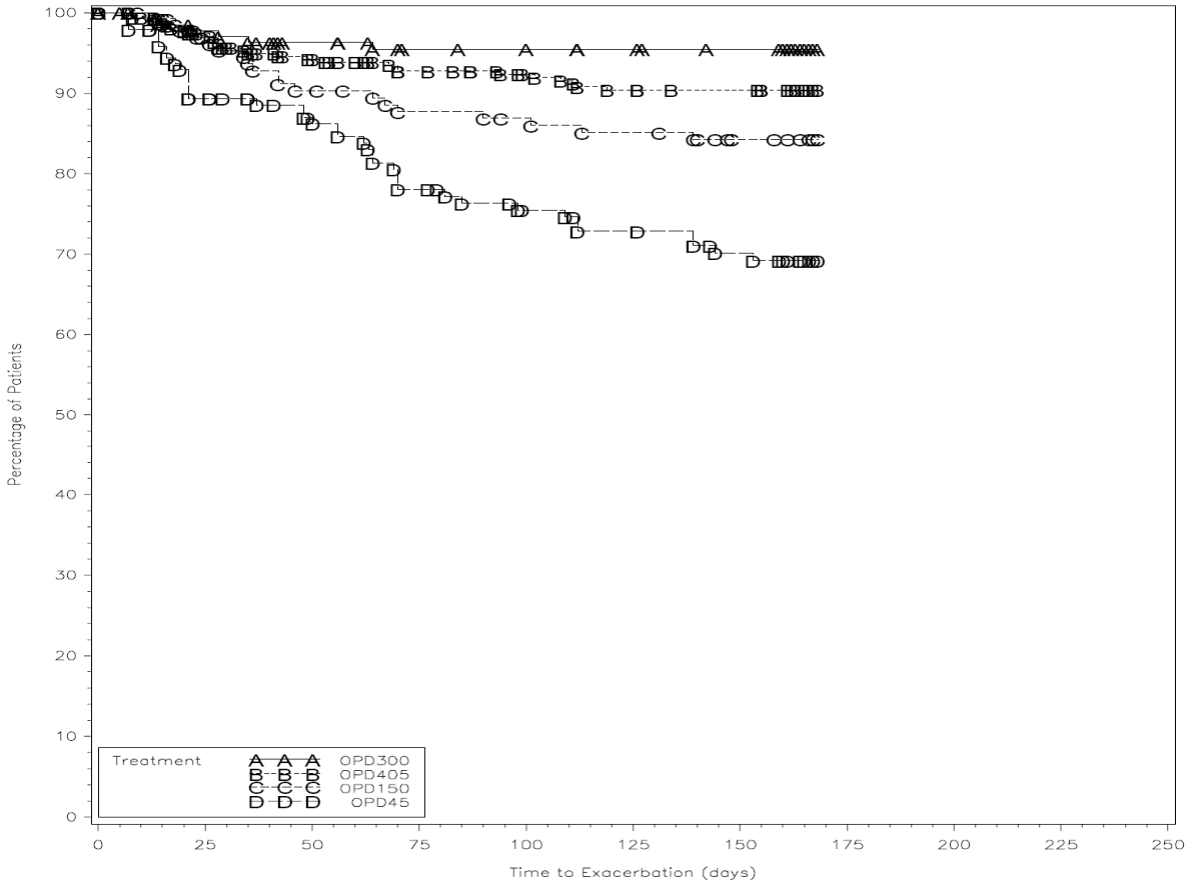

Figure 1 Time to Exacerbation for the Double-Blind Maintenance Phase in Study HGKA

Non-inferiority Analysis

The primary non-inferiority analysis in Study HGKA was a comparison of the Pooled 2-Week OP Depot and the oral olanzapine treatment groups with respect to exacerbation rates. Non-inferiority between these 2 treatment groups was assessed by comparing the Kaplan-Meier estimated exacerbation rates at 24 weeks after randomization.

Ninety percent of the Pooled 2-week OP Depot patients remained free of exacerbation during the 24-week double-blind maintenance period compared to 93% of oral olanzapine patients, for a difference of 3% (Table 19). Per a *priori* criteria specified, the Pooled 2-Week OP Depot treatment group would be declared noninferior to the oral olanzapine treatment group if the 95% confidence interval (CI) excluded a difference of 0.20 (20%). Using this criterion, the Pooled 2-Week OP Depot treatment group was non-inferior to the oral olanzapine treatment group with respect to exacerbation rates at 24 weeks after randomization. Comparison of the 95% CIs indicated that the Pooled 2-week OP Depot survival rate was in the range of 86% to 94%, while the oral olanzapine survival rate was in the range of 90% to 96%, with the likely difference between these rates ranging from -2% to +8%. This finding was also confirmed across regions (US, East Europe, West Europe, and Other).

Table 19 Exacerbation Rates for Pooled 2-Week OP Depot vs. Oral Olanzapine at 24 weeks in Study HGKA (Kaplan-Meier Estimates)

Therapy	Survival Rate	Standard Error	95% CI
OLZ	0.93	0.015	(0.90, 0.96)
OPD2WK	0.90	0.019	(0.86, 0.94)
OLZ – OPD2WK	0.03	0.024	(-0.02, 0.08)

Analysis of time to exacerbation also revealed no statistically significant differences between the Pooled 2-Week OP Depot treatment group and the oral olanzapine treatment group (log-rank test p-value=.167).

6.3.5 Clinical Microbiology

Clinical microbiology was not considered necessary for this product.

6.3.6 Efficacy Conclusions

In Study HGKA, the 3 higher dose OP Depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups demonstrated positive maintenance of effect over 24 weeks for stabilized patients with schizophrenia.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

General safety parameters and special safety topic analyses are summarized using the following 3 databases:

- **Placebo-Controlled Database**: This database includes safety data from patients randomized to OP Depot or placebo for up to 8 weeks in the double-blind, placebo-controlled study (HGJZ) in 404 patients with schizophrenia. Data for the 3 OP Depot treatment groups were pooled for all analyses.
- **Olanzapine-Controlled Database**: This database includes safety data from patients randomized to OP Depot or oral olanzapine for up to 24 weeks in the double-blind maintenance of effect study (HGKA) in 921 patients with schizophrenia. Data for 3 OP Depot treatment groups were pooled for all analyses. This database provides direct comparisons to oral olanzapine.

- **OP Depot Integrated Database**: This database includes safety data from all patients (N=1918) treated with OP Depot in the 2 double-blind comparator studies described above and in 6 open-label studies. These studies were conducted in patients with schizophrenia or schizoaffective disorder.

Table 20 presents the databases and analyses discussed throughout this safety review. The updated safety information from the 4 Months Safety Update submitted on 8 August 2007 (data cut-off date of 31 January 2007) was also integrated into this review. The safety data from Placebo-Controlled Database are reviewed in detail in this safety review. The data from the Olanzapine-Controlled Database were used to compare the safety profile of OP Depot with that of oral olanzapine. Overall Integrated Database were used to detecting deaths, rare, unexpected or serious AEs, or any pattern changes of common adverse events.

Table 20 Databases Reviewed for the Integrated Review of Safety

Databases/Description of Databases	Studies	Treatment Groups	Analyses
Placebo-Controlled Database/contains safety data from 404 patients randomized to OP Depot (306) or placebo (98)	HGJZ	Pooled OP Depot treatment groups (210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) Placebo	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and special topic[a] for injection-site–related AEs.
Olanzapine-Controlled Database/contains safety data from 921 patients randomized to OP Depot (599) or oral olanzapine (322)	HGKA	Pooled OP Depot treatment groups[b] (150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) excluding 45 mg/4 weeks Oral Olanzapine (10, 15, and 20 mg)	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: (IAIV) injection events, cardiovascular events, metabolic parameters and weight gain, and hepatic measures.
Overall Integrated Database/contains safety data from patients who received treatment with OP Depot in any clinical trial conducted in patients with schizophrenia or schizoaffective disorder	HGJW LOBE LOBO LOBS HGJZ HGKA HGKB	Pooled OP Depot treatment groups[c]	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: IAIV injection events, cardiovascular events, metabolic parameters and weight gain, hepatic measures, and injection-site–related AEs.

7.1.1 Deaths

Three deaths (3/1918, 0.2%) have been reported in patients assigned to OP Depot as of the data cut-off date on 31 January 2007. One death was reported in the original submission (HGKA-

HGKB-442-8542). The other 2 deaths occurred after the data cut-off date for the integrated database that was presented in the NDA and were reported in the 4 Month Safety Update. Each death is briefly summarized below:

- Patient HGKA-HGKB-442-8542, a 33-year-old Caucasian female with a history of chronic alcoholism, received her first dose of 210 mg/2 weeks OP Depot in Study HGKB on (b) (6). Nine days later she was found dead, and the autopsy revealed that the cause of death was acute heart failure with associated toxic/alcoholic heart damage (cardiomyopathy).

- Patient HGKA-HGKB-182-7321, a 30-year-old male of African descent, first received 300 mg/2 weeks OP Depot in Study HGKB on 07 December 2005. On (b) (6) he experienced the SAE of severe leptospirosis and died 5 days later.

- Patient HGJZ-HGKB-804-8852, a 52-year-old Caucasian male with a 23-year history of essential hypertension, received his first dose of 210 mg/2 weeks OP Depot in Study HGKB on 26 April 2005. The patient was reported to have died of hypertension on (b) (6) (b) (6) 26 days after the last dose of study drug, while away on a fishing trip. Over the course of the study, the patient had been diagnosed with heart failure, ischemic heart disease, and aortic aneurysm; according to the investigator, these diagnoses were not related to the primary reason for death. According to relatives of the patient, the sudden death was described as very quick and without symptoms. The cause of death provided by the investigator was reported to be essential hypertension, probably hypertension stroke, but autopsy results were not available to confirm this.

7.1.2 Other Serious Adverse Events

A total of 19 (4.7%) patients reported serious AEs in the placebo-controlled database: 14 patients (4.6%) from an OP depot treatment group and 5 patients (5.1%) from the placebo treatment group. There were no statistically significant differences across all four treatment groups in patients reporting SAEs. Psychotic disorder (n=4) was the only SAE reported by more than 1 OP Depot–treated patient. Of the 14 patients on OP depot, 8 patients reported SAEs that were likely to be related to the underlying diagnosis of schizophrenia. A summary of all reported SAEs is presented in Table 21.

Table 21 Serious Adverse Events in the Placebo-Controlled Database

Event Term	300Q2W (N=100) n (%)	405Q4W (N=100) n (%)	210Q2W (N=106) n (%)	PLA (N=98) n (%)	TOTAL (N=404) n (%)
Patients with >= 1 SAE	5 (5.0)	3 (3.0)	6 (5.7)	5 (5.1)	19 (4.7)
Psychotic disorder	0 (0.0)	2 (2.0)	2 (1.9)	0 (0.0)	4 (1.0)
Schizophrenia	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.0)	2 (0.5)
Agitation	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)
Anxiety	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Depressed level of consciousness	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Pneumonia	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory acidosis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Schizophrenia, paranoid type	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Social problem	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)

No statistically significant between-group differences in the incidence of SAEs were observed in the Placebo-Controlled Database and the Olanzapine-Controlled Database. In the Overall Integrated Database, a total of 159 patients (8.9%) reported one or more SAEs. The most commonly reported events (in 5 or more patients) were consistent with symptoms of the underlying disease (psychotic disorder, schizophrenia, agitation, suicidal ideation, anxiety, auditory hallucination, paranoia, paranoid schizophrenia, and suicide attempt).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Eighteen patients (4.5%) discontinued due to an AE in the placebo-controlled database: 13 patients (4.5%) from an OP depot treatment group and 5 patients (5.1%) from the placebo treatment group. Overall, there were no statistically significant differences across all four treatment groups in patients reporting discontinuing due to AEs.

Discontinuations due to adverse events (AEs) were ≤ 5.1% in all databases. In the controlled databases, no statistically significant between-group differences were observed in the overall incidence of discontinuations due to AEs. In addition, no statistically significant differences were observed between treatment groups in the incidence of any specific AE as a reason for study discontinuation.

7.1.3.2 Adverse events associated with dropouts

Table 22 presents incidence of patient discontinuation due to an AE in the placebo-controlled database. There were 18 patients who discontinued due to an AE, of which the most frequently reported AEs were psychotic disorder (n=4), hepatic enzyme abnormalities (n=3; enzyme increased [n=2] and ALT increased [n=1]), and sedation (n=2).

Table 22 Incidence of Discontinuation Due to Adverse Event in the Placebo-Controlled Database

Event Term	300Q2W (N=100) n (%)	405Q4W (N=100) n (%)	210Q2W (N=106) n (%)	PLA (N=98) n (%)	TOTAL (N=404) n (%)
Patients discontinued	6 (6.0)	4 (4.0)	3 (2.8)	5 (5.1)	18 (4.5)
Psychotic disorder	0 (0.0)	2 (2.0)	1 (0.9)	1 (1.0)	4 (1.0)
Hepatic enzyme increased	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Sedation	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	2 (0.5)
Agitation	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Alanine aminotransferase increased	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Depressed level of consciousness	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
Respiratory acidosis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Schizophrenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)

In the Overall Integrated Database, AEs most commonly reported as reasons for discontinuation (reported in 5 or more patients) were consistent with the underlying disease (psychotic disorder and schizophrenia) or with events historically reported in patients treated with oral olanzapine (sedation, somnolence, and weight gain).

7.1.3.3 Other significant adverse events

As of 4 September 2007, 25 cases of the excessive sedation with signs and symptoms consistent with those observed in an olanzapine overdose and temporally related to the injection of OP Depot had been reported in 24 patients. No excessive sedation events were reported in the Placebo-Controlled Database. Two cases (HGKA-532-4011, HGKA-571-4437) were reported in the Olanzapine-Controlled Database. Twenty two of 25 events occurred in Study HGKB, and 1 event was reported in Study LOBE. More discussion regarding the excessive sedation events can be found in section 7.1.12 Special Safety Studies.

7.1.4 Other Search Strategies

No other search strategies were considered to be warranted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

During every study, AEs were collected at every visit, regardless of relationship to study drug. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) terms by blinded Lilly clinical personnel.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were appropriately categorized and coded with preferred terms.

7.1.5.3 Incidence of common adverse events

Across all OP depot treatment groups in the Placebo-Controlled Database, the most frequently reported AEs included headache (n=44, 14.4%), insomnia (n=33, 10.8%), and sedation (n=25, 8.2%). The following treatment-emergent adverse events (TEAEs) occurred in at least 2% of OP depot-treated patients and at a rate of at least twice the placebo rate: sedation, nausea, dry mouth, increased appetite, musculoskeletal stiffness, toothache, arthralgia, abdominal pain (upper), injection site pain, and muscle spasms.

Overall, sedation was the only TEAE reported statistically significantly more often by patients treated with OP Depot than by patients treated with placebo. In the Olanzapine-Controlled Database, no clinically meaningful differences between patients treated with OP Depot and patients treated with oral olanzapine were observed with respect to TEAEs. In the Integrated Database, except for injection-site pain (expected with an injectable product) and headache, all other AEs are consistent with events observed historically in patients treated with oral olanzapine or with symptoms of the disease state under treatment.

7.1.5.4 Common adverse event tables

Table 23 summarizes common adverse events in the Placebo-Controlled Database.

Table 23 TEAEs of 2% or More among OP Depot -Treated Patients in the Placebo-Controlled Database

(Percentage of Patients Reporting Adverse Reaction)

Body System/Adverse Reaction	Placebo (N=98)	Olanzapine Pamoate 405 mg/4 wks (N=100)	Olanzapine Pamoate 210 mg/2 wks (N=106)	Olanzapine Pamoate 300 mg/2 wks (N=100)
Ear and Labyrinth Disorders				
Ear pain	2	1	1	4
Gastrointestinal Disorders				
Abdominal pain	1	2	0	1
Abdominal pain upper	1	1	3	3
Diarrhea	4	2	7	5
Dry mouth	1	2	6	4
Flatulence	0	2	2	1
Nausea	2	5	5	4
Toothache	0	3	4	3
Vomiting	2	6	1	2

General Disorders and Administration Site Conditions				
Fatigue	2	4	2	3
Injection site pain	0	2	3	2
Pain	0	0	2	3
Pyrexia	0	2	0	0
Infections and Infestations				
Nasopharyngitis	2	3	6	1
Tooth abscess	0	2	0	0
Tooth infection	0	2	0	0
Upper respiratory tract infection	2	3	1	4
Viral infection	0	0	0	2
Injury, Poisoning and Procedural Complications				
Procedural pain	0	2	0	0
Investigations				
Alanine aminotransferase increased	1	3	0	1
Aspartate aminotransferase increased	1	2	0	1
Electrocardiogram QT-corrected interval prolonged	1	0	0	2
Gamma-glutamyltransferase increased	0	2	1	0
Hepatic enzyme increased	0	0	0	2
Weight increased	5	5	6	7
Metabolism and Nutrition Disorders				
Increased appetite	0	4	1	6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0	3	3	3
Back pain	4	4	3	5
Muscle spasms	0	3	1	2
Musculoskeletal stiffness	1	1	4	4
Nervous System Disorders				
Dizziness	2	4	4	1
Dysarthria	0	0	1	2
Headache	8	11	15	17
Sedation	2	8	7	10
Somnolence	5	6	1	3
Tension headache	0	2	0	1
Tremor	1	3	0	1
Psychiatric Disorders				
Abnormal dreams	0	0	0	2
Hallucination, auditory	2	3	1	0
Restlessness	2	2	3	1
Sleep disorder	1	0	0	2
Thinking abnormal	1	3	0	0
Reproductive System and Breast Disorders				
Vaginal discharge	0	0	4	4

Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	5	9
Nasal congestion	1	1	1	3
Pharyngolaryngeal pain	2	2	3	3
Sinus congestion	2	1	0	4
Sneezing	0	0	0	2
Skin and subcutaneous tissue disorders				
Acne	0	2	0	2
Vascular Disorders				
Hypertension	0	3	2	0

7.1.5.5 Identifying common and drug-related adverse events

Common and drug-related adverse events were identified by 1) the rate of AEs for OP Depot-treated patients was at least 2%, and 2) the rate of AEs was at least twice that of placebo.

7.1.5.5 Additional analyses and explorations

Subgroup Analyses

Subgroup analyses by age, geographic region, and ethnic origin in the Placebo-Controlled Database showed no statistically significant differences of clinical relevance.

Differences in gender were found in paranoia: no more than one female reported paranoia in each of the treatment groups, but no differences were observed between the four treatment groups. However, male patients in OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks treatment groups (1.4%, 1.4%, and 1.3%, respectively) reported significantly less paranoia compared with male patients in the placebo treatment group (11.5%).

Extrapyramidal Symptoms (EPS)

In the Placebo-Controlled Database, patients treated with OP Depot had mean decreases on all EPS rating scales—Simpson-Angus Scale (SAS) total score, Barnes Akathisia Scale (BAS) global scores, and the Abnormal Involuntary Movement Scale (AIMS) total scores, but only the 405 mg/4 weeks treatment group showed a statistically significant reduction compared with the placebo group (p=.023). Patients in the 405 mg/4 weeks and 210 mg/2 weeks treatment groups had statistically significantly reduced mean BAS global scores from baseline compared with placebo (p=.037 and p=.023, respectively). Patients in the 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks treatment groups had statistically significantly reduced mean AIMS total scores from baseline compared to placebo (p=.018, p<.001, and p=.037, respectively). The categorical analyses of the SAS, BAS, and AIMS found no statistical differences across all treatment groups.

In the Olanzapine-Controlled Database, there were no statistically significant differences between OP Depot and oral olanzapine in mean change on any of SAS, BAS and AIMS measures. Mean scores decreased from baseline, though these changes were very small (less than half a point) for either treatment group on any of the 3 scales.

7.1.6 Less Common Adverse Events

The excessive sedation events were identified as a serious safety concern in these studies. More discussion can be found in section 7.1.12 Special Safety Studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

During these studies, blood samples were collected at regular intervals per protocol for standard laboratory tests, including chemistry, hematology, and urinalysis panels. Urine drug screens, thyroid function tests, and urine pregnancy tests (if applicable) were completed at baseline. In addition, hepatic safety was assessed and monitored throughout the studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study HGJZ is the only placebo-controlled study submitted to his NDA. Therefore, only the laboratory data from Study HGJZ were reviewed in detail in this review and the laboratory data from other OP Depot trials (the Olanzapine-Controlled Database and the Overall Integrated Database) were used to detect rare, unexpected, serious and clinically significant laboratory abnormalities.

7.1.7.3 Standard analyses and explorations of laboratory data

In all 3 databases, there were no patterns in laboratory analyses suggesting clinically relevant differences between OP Depot and the known safety profile of oral olanzapine. Differences among OP Depot treatment groups with respect to prolactin (mean change) and fasting triglycerides (normal to high) were observed.

7.1.7.3.1 Analyses focused on measures of central tendency

Chemistry Laboratory Parameters

Compared to patients on placebo in the Placebo-Controlled Database, patients on 300 mg/2 weeks OP depot demonstrated statistically significant increases in AST, ALT, and CPK; and statistically significant decreases in calcium, potassium, albumin, and direct bilirubin. Patients on 405 mg/4 weeks OP depot demonstrated statistically significant increases in alkaline phosphatase, cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides; and statistically significant decreases in urea nitrogen, potassium, and prolactin, compared with

patients on placebo. Patients on 210 mg/2 weeks OP depot demonstrated statistically significant increases in cholesterol and triglycerides, and statistically significant decreases in calcium, albumin, and prolactin, compared with patients on placebo.

Though the difference in serum prolactin between groups was not statistically significant, OP Depot-treated patients showed a significant within-group decrease of -5.80 μg/L and placebo-treated patients showed a non-significant within-group decrease of -4.11 μg/L in serum prolactin. Many patients in this database received previous antipsychotic medications (39.4% with risperidone and 25.7% with haloperidol) prior to randomization to OP Depot or placebo, which may have affected their serum prolactine levels during the studies.

Hematology Laboratory Parameters

Compared with patients on placebo in the Placebo-Controlled Database, patients on 300 mg/2 weeks OP depot demonstrated statistically significant increases in monocytes and basophils, and statistically significant decreases in mean cell hemoglobin concentration. Compared with patients on placebo, patients on 405 mg/4 weeks OP depot demonstrated statistically significant increases in platelets, while patients on 210 mg/2 weeks OP depot demonstrated statistically significant increases in lymphocytes, eosinophils, and platelets.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Treatment-emergent significant changes in glucose and lipid levels were found in the Placebo-Controlled Database. Compared to placebo-treated patients, more patients on 300 mg/2 weeks OP depot demonstrated shifts from normal baseline LDL cholesterol levels to borderline high post-baseline levels (p=.038) and from normal baseline triglyceride levels to high post-baseline levels (p=.016). Compared to placebo-treated patients, more patients on 405 mg/4 weeks OP depot demonstrated shifts from normal baseline total cholesterol levels to borderline high Post-baseline levels (p=.005). Compared to placebo-treated patients, more patients on 210 mg/2 weeks OP depot demonstrated shifts from normal baseline triglyceride levels to high post-baseline levels (p=.029).

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were 3 OP Depot-treated patients discontinued from Study HGJZ due to “hepatic enzyme increased”—1 case of ALT increased (405 mg/4 week group) and 2 cases of hepatic enzyme increased (300 mg/2 week group). None of these cases were reported as SAEs and no cases met the criteria of Hy’s Law (ALT ≥ 3 times upper limit of normal [ULN] and TBILI ≥ 1.5 times ULN). Transient, asymptomatic elevations of the hepatic transaminases ALT (alanine transaminase) and AST (aspartate transaminase) have been commonly reported in clinical studies of oral olanzapine, especially during early treatment. Asymptomatic elevations of hepatic transaminases and alkaline phosphatase are included in the Warnings and Precautions section of current olanzapine labeling.

One patient in OP Depot 210 mg/2 week group discontinued Study HGJZ due to "moderate blood glucose increased".

7.1.7.4 Additional analyses and explorations

Hepatic-Related Adverse Events

Special analyses of hepatic-related adverse events were conducted by the sponsor.

In the Placebo-Controlled Database, changes ≥ 3 x ULN in ALT (SGPT) values were observed in 2.7% (8/291) of patients treated with OP Depot compared with 3.2% (3/94) of patients treated with placebo. None of these patients experienced jaundice.

In the Olanzapine-Controlled Database, no statistically significant differences were observed between Olanzapine Pamoate (OP) Depot and oral olanzapine in the incidence of patients with one or more hepatic-related AEs overall (p=.577) or for any specific event. The incidence of hepatic-related AEs was 1.3% in the OP Depot treatment group, 1.9% in the oral olanzapine treatment group, and 1.5% overall. In the Overall Integrated Database, the incidence of hepatic-related AEs was 1.6% (29 of 1779 randomized patients). The most commonly reported elevated liver function test was increased alanine aminotransferase, which occurred in 13 patients (0.7%).

7.1.7.5 Special assessments

No special assessments were warranted in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

During these studies, blood pressure (systolic and diastolic), pulse rate, weight, and temperature were collected at regular intervals per protocol.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The vital sign data from Study HGJZ (the placebo-controlled database) were examined in detail in this review and the vital sign data from other OP Depot trials (the Olanzapine-Controlled Database and the Overall Integrated Database) were examined to detect rare, unexpected, serious and clinically significant vital sign abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Patients treated with OP Depot 300 mg/2 weeks exhibited a mean increase in standing systolic blood pressure (+3.735 mm HG, p=.018), supine pulse (+3.316 bpm, p=.030) and weight (+3.861 kg, p<.001). Patients treated with OP Depot 405 mg/4 weeks demonstrated a mean increase in supine systolic blood pressure (+3.870 mm HG, p=.003), standing systolic blood pressure (+3.360 mm HG, p=.024), supine pulse (+3.010 bpm, p=.020), and weight (+2.763 kg, p<.001). Patients treated with OP Depot 210 mg/2 weeks exhibited a mean increase in weight (+3.819 kg, p<.001). In addition to being statistically significant within each treatment group, the mean increases in weight were statistically significant compared to placebo for each of the OP Depot treatment groups.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no statistically or clinically significant differences in vital sign measurements among any of the treatment groups. However, differences in weight gain and weight loss were statistically significant between the OP-depot treatment groups compared with the placebo group. Each of the OP-depot treatment groups had a statistically significant greater percentage of patients gaining at least 7% of their baseline weight (35.4%, p<.001; 27.0%, p=.012; and 23.6%, p=.046 for 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks, respectively) compared to the placebo group (12.4%). Similarly, the placebo group had a statistically significantly higher percentage of patients losing at least 7% of their baseline weight (12.4%) compared to the OP depot groups (2.0%, p=.005; 1.0%, p=.001; and 2.8%, p=.014 for 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks, respectively).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no patients discontinued from Study HGJZ due to abnormal vital signs or weight gain.

7.1.8.4 Additional analyses and explorations

Metabolic Parameters and Weight Gain

The purpose of these analyses is to assess changes in weight and metabolic parameters in patients treated with OP Depot and to compare these changes to those seen in patients treated with oral olanzapine.

The analyses of mean changes from baseline to endpoint for weight, fasting glucose & lipids, clinically significant weight gain (at least 7% from baseline) and on incidence rates of treatment-emergent weight gain-related AEs in the Olanzapine-Controlled Database and in the Overall Integrated Database were conducted.

The findings from these analyses show that patients treated with OP Depot doses of 150 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks (in the Olanzapine-Controlled Database) did not experience a statistically significant higher incidence of weight gain or a statistically significant higher incidence of undesirable changes in lipids parameters when compared to patients treated

with oral olanzapine. In addition, the types of weight gain-, diabetes- and dyslipidemia-related adverse events (AEs) in the patients treated with OP Depot were similar to those seen in the patients treated with oral olanzapine.

Statistically significant dose responses were found for the incidence of potentially clinically significant (PCS) weight gain and elevated triglycerides (from normal to high) in the Olanzapine-Controlled Database. The highest incidence of PCS weight gain and elevated triglycerides (from normal to high) were observed in patients treated with 300 mg/2 weeks OP Depot compared to other OP Depot treatment groups.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

During these studies, twelve-lead ECGs were collected at regular intervals per protocol. Each ECG was reviewed by a qualified physician to determine whether any findings were clinically significant. If a clinically significant increase from baseline in the QTc interval is observed during the trial, the patient was assessed by the investigator for symptoms (such as palpitations, near syncope, syncope).

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The ECG data from Study HGJZ (the placebo-controlled database) were examined in detail in this review and the ECG data from other OP Depot trials (the Olanzapine-Controlled Database and the Overall Integrated Database) were examined to detect rare, unexpected, serious and clinically significant ECG abnormalities.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Statistically significant changes from baseline were observed in all OP depot treatment arms in the Placebo-Controlled Database. Patients in the 300 mg/2 weeks treatment group had statistically significant increases in heart rate (5.00 bpm, p=.003), QTc Bazett's (7.673 msec, p<.001), and QTc Fredericias (3.353 msec, p=.039). Patients in the 405 mg/4 weeks treatment group had statistically significant increases in QTc Bazett's (5.13 msec, p=.019). Patients in the 210 mg/2 weeks treatment group had statistically significant increases in heart rate (4.095 bpm, p=.002), QTc Bazett's (7.952 msec, p<.001), and QTc Fredericias (4.316 msec, p=.008). Even these QT elongations are statistically significant, the changes are small and the clinical significance is unclear. Olanzapine associated mild tachycardia has been addressed in current olanzapine labeling.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no statistically or clinically significant differences between OP depot and placebo in potentially clinically significant ECG observations in the Placebo-Controlled Database.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Although there were no statistically significant differences in clinically significant outliers across treatment groups in the Placebo-Controlled Databse, there were 8 patients with potentially clinically significant QTc observations. One patient randomized to OP depot 300 mg/2 weeks had a reported QTc Bazett's interval ≥500 msec. Six patients randomized to OP depot treatment groups showed a QTc Bazett's interval increase ≥60 msec. One patient in the placebo treatment group had a QTc Fredericias interval increase ≥60 msec.

None of those patients were reported as SAEs and none of them discontinued from the study due to the AE. There was one patient in placebo group discontinued because of atrial fibrillation.

7.1.9.4 Additional analyses and explorations

Cardiovascular Safety

Lilly conducted separate analyses of cardiovascular events for the Olanzapine-Controlled Database and the Overall Integrated Database. In addition, an analysis was conducted comparing treatment-emergent cardiovascular-related AEs and syncope-related AEs between patients treated with OP Depot and patients treated with oral olanzapine.

The analyses of cardiovascular measures did not reveal any new safety findings during treatment with OP Depot that had not been previously reported during treatment with oral olanzapine. The key safety findings are discussed below.

- No statistically significant differences were observed between patients treated with OP Depot and patients treated with oral olanzapine in the incidence of treatment-emergent cardiovascular-related AEs or syncope-related events.

- No statistically significant treatment differences in mean changes at endpoint in vital signs, ECG heart rate, or QT-corrected Fridericia formula (QTcF) were observed between any OP Depot doses in the fixed-dose study HGKA.

- No evidence was found to indicate that patients treated concomitantly with benzodiazepines experienced clinically significant changes in cardiovascular or hemodynamic function as a result of a drug interaction; however, caution is necessary in patients who receive treatment with OP Depot and other drugs having effects that can induce hypotension, bradycardia, and respiratory or central nervous system (CNS) depression.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not required.

7.1.12 Special Safety Studies

The Excessive Sedation Events

1. Summary of the Excessive Sedation Events

Summary of Related Clinical Data

As of 30 November 2007, a total of 25 of these events had been reported in 24 patients. A total of 36,856 injections had been given to 1915 patients in OP Depot clinical trials. Therefore, the incidence of these excessive sedation events is 0.07% of injections and 1.3% of patients.

Adverse event reports have demonstrated 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, and weakness. However, orthostatic hypotension, arrhythmias, cardiac arrest were not observed in these cases.

The majority of initial signs and symptoms of the excessive sedation events have occurred within 1 hour of injection (21/25; 84%, median time of onset is 20 min.). However, the time onset of the excessive sedation events has ranged from immediately post injection to up to 3 hours after the injection.

Most events occurred after the patient had received several months of injections (mean number of injections was 18.5) and ranged in occurrence from 1 event at the first injection to 1 event at the 40th injection. The mean number of days (from starting treatment with OP Depot) to an event was 278 days. Only one patient experienced two events.

Patients have fully recovered from the excessive sedation events within 3 to 72 hours and without permanent sequelae. The majority of patients (17/24; 68%) who experienced an event continued to receive OP Depot.

Table 30 (10.3 Appendix to Safety Review) summarizes all 25 cases that had been identified as of 30 November 2007. Among these cases, 20 were hospitalized for monitoring or treatment during excessive sedation events. The profound sedation ranged from “drowsiness”, “deep sleep”, “unarousable for hours”, to “altered consciousness” (1 case), “loss of consciousness” (2 cases) and “coma” (2 cases: one was in coma for 13 hours and another one had bilateral miosis, no photomotroic reflex and left side Babinski). Two patients were intubated, which the sponsor described as preventive measures (one for tonic clonic convulsions and one for severe agitation).

Delirious symptoms were reported in 2 cases and tonic clonic convulsions were observed in two cases. One patient experienced increased blood pressure (190/110 mmHg, 60 min post injection).

The Possible Cause of the Excessive Sedation Events

The mechanism underlying these events is not clear. However, all the available information from investigations suggested that an excessive amount of olanzapine enters the systemic circulation faster than intended for this IM controlled-release depot form. The olanzapine concentrations in the 7 cases where plasma concentrations were measured further support this etiology. Lilly characterized that these events as most likely related to accidental intravascular injection of a portion of the OP Depot dose, but the exact mechanism producing the excessive sedation events has not been determined.

To address accidental intravascular injection problems which may have been responsible for the excessive sedation events, Lilly retrained their study personnel to reinforce proper IM injection technique and extended the post-injection observation period to 3 hours in their ongoing OP Depot clinical trials in July 2007. However, the incidence of the excessive sedation events didn't change and ten additional cases were reported after then.

Characteristic of Patients Experiencing the Excessive Sedation Events

Table 24 summaries the characteristics of patients experiencing the excessive sedation events.

Table 24 Summary of Excessive Sedation Patients Characteristics

Variable	OP Depot Patients (N = 1918)	IAIV Patients (N = 24)
Gender		
Male	1306 (68.1)	18 (75.0)
Origin		
Caucasian	1260 (65.7)	20 (83.3)
African	291 (15.2)	2 (8.3)
Hispanic	247 (12.9)	2 (8.3)
Age in years		
Mean	39.41	43.13
Median	39.59	
Maximum	74.12	63.49
Minimum	18.10	23.84
Standard Dev.	11.02	11.21

Logistic Regression for Identification of Factors in the Excessive Sedation Events

Lilly analyzed excessive sedation event data for factors that might be associated with a greater risk of an event. An analysis of data for the 25 excessive sedation events was performed. The

logistic regression model identified higher dose (p=0.037), greater age (p=0.055), and lower BMI (p=0.052) as potential risk factors for an excessive sedation event. But, the events have also occurred in patients without these specific risk factors. A statistically significantly increased potential risk of an excessive sedation event was found at higher dose. It is 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.

2. Investigations to Determine the Cause of the Excessive Sedation Events

Solubility of Olanzapine Pamoate Monohydrate

The low aqueous solubility of the practically insoluble crystalline salt, olanzapine pamoate monohydrate, in muscle tissues is the means by which the release of olanzapine is sustained over a period of weeks when OP Depot is injected intramuscularly. It is reasonable to believe that olanzapine pamoate may be more soluble in certain biological fluids or under certain physiological conditions. Therefore, as a preliminary investigation, in vitro experiments that evaluated the solubility of olanzapine pamoate in plasma or blood were performed by the sponsor. The in vitro solubility experiment demonstrated that the amount of Olanzapine Pamoate Monohydrate dissolved in human blood was much higher (35 – 68% within roughly half an hour) than anticipated for the practically insoluble olanzapine pamoate crystalline salt. The equilibrium solubility experiment demonstrated that the solubility of olanzapine pamoate monohydrate in plasma is about 167 times (plasma 0.5 mg/mL, aqueous buffer 0.003 mg/mL) higher than that in an aqueous medium which is assumed to putatively reflect the solubility of olanzapine pamoate in extracellular fluid of muscle tissue.

PK Investigations

Olanzapine plasma concentrations were measured in 7 of the 25 the excessive sedation events. In each of these events, a much higher olanzapine plasma concentration was observed than would have been expected. Olanzaopine plasma concentrations obtained during the excessive sedation events were presented in Table 31 (10.3 Appendix to Safety Review).

Figure 2 from the sponsor's submission illustrates the olanzapine plasma concentration profile after 6 different OP Depot injections in one patient who experienced an excessive sedation event after the second injection. Higher than expected olanzapine plasma concentrations occurred after the second 300 mg OP Depot injection as marked in the graph by an arrow at the point at which the excessive sedation event was experienced. This patient also received five other injections (one 300 mg dose before and four 200 mg doses after the excessive sedation event) all of which exhibited a typical plasma concentration profile associated with the OP Depot regimen.

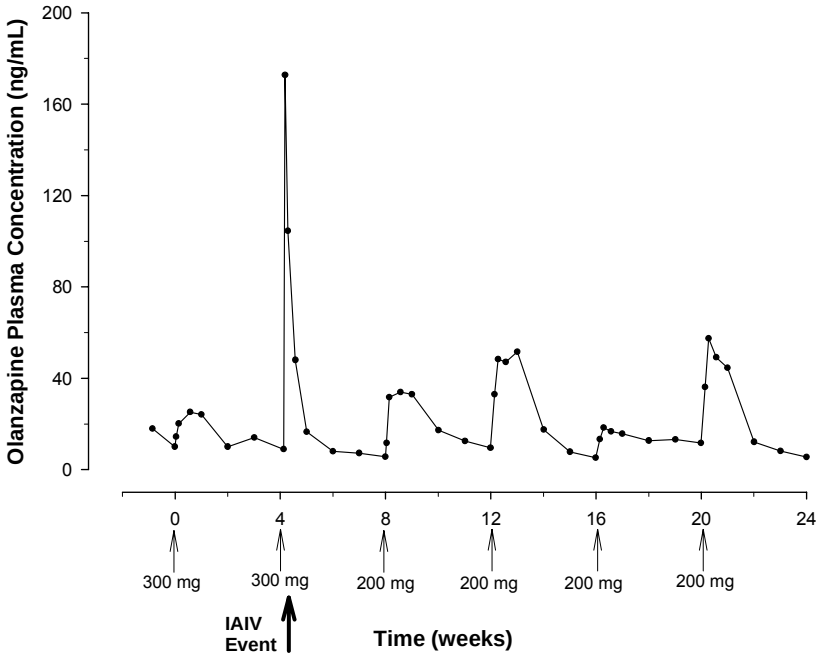

Figure 2 Olanzapine Plasma Concentration vs Time Profile During an Excessive Sedation Event

Olanzapine concentrations for 4 out of the 7 events demonstrated a very similar finding, where the olanzapine concentrations during the excessive sedation event were unexpectedly elevated compared to those drawn after injections where no excessive sedation event had occurred. In the remaining 2 of the 7 events, patients did not have any other blood samples drawn for pharmacokinetic analysis.

Figure 3 from the sponsor's submission illustrates the plasma concentration profiles obtained during the excessive sedation events from all 7 excessive sedation events on a common scale (Lilly refers the excessive sedation events as IAIV events). More detailed PK review can be found in Dr. Andre Jackson's (clinical pharmacology) review.

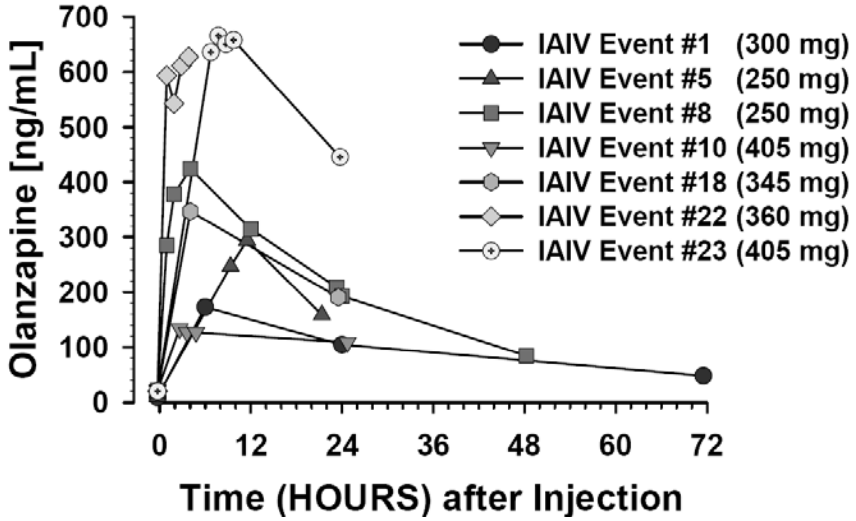

Figure 3 Olanzapine Plasma Concentrations Observed During an Excessive Sedation Event-Data for All Seven Cases

Chemistry, Manufacturing, & Control Investigations

The physicochemical properties of olanzapine salt (crystal form), such as the particle size or surface area, can affect the rate of release. The drug product particle size distribution (PSD) defines the surface area available for dissolution. Significant amounts of small particles giving rise to a very large surface area could potentially result in too rapid an initial dissolution and drug release.

Review of manufacturing data for the clinical trial lots used for these events demonstrated that all lots met the established standards for CM&C during their manufacturing. CM&C approval and stability data were comparable to data from other clinical trial lots in which sedation was not observed. Clinical trial lot CM&C data used to approve the release of the lots for clinical use indicate that there have been no lots with significant amounts of small particles. Furthermore, it has been shown that the PSD does not change upon storage. Homogeneity of the drug product PSD from vial-to-vial has been demonstrated.

Analysis of the residual suspension remaining in the drug product vials after administration of OP Depot was performed for 11 vials. Ten vehicle vials were also tested to confirm the identity of the vehicle. Results of testing demonstrated that the residual suspension exhibited the expected physicochemical properties (potency, related substances, pH, particle size, morphology).

3. Overall Summary and Conclusions

The key findings regarding excessive sedation events can be briefly summarized as follows:

- As of 30 November 2007, a total of 25 excessive sedation events have been identified in 24 patients during OP Depot clinical trials.
- Signs and symptoms reported with excessive sedation events are consistent with AEs reported in patients experiencing oral olanzapine overdose.
- 20 of the 24 patients were hospitalized for monitoring or treatment. Alteration of consciousness was reported in 5 cases which included two cases of coma. Two patients were intubated.
- Higher dose (also corresponding to an increased injection volume), greater age, and low BMI have been identified as potential risk factors of an excessive injection event, based on logistic regression analysis; but the events have also occurred in patients without these specific risk factors.
- The time to onset for 21 of the 25 events was within 1 hour of the injection and within 3 hours of the injection for the 4 remaining events.
- Olanzapine plasma concentrations were higher than expected in the 7 excessive sedation events where samples were collected.
- Preliminary equilibrium solubility experiment demonstrated that the solubility of olanzapine pamoate monohydrate in plasma is about 167 times higher than that in an aqueous medium.
- The incidence of the excessive sedation events didn't change after Lilly retrained their study personnel and reinforced IM injection technique in July 2006. Ten additional cases were reported after then.
- All patients who experienced an excessive sedation event were fully recovered from the event, and the majority (17/24) continued in the study.

The excessive sedation events raised a serous 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 1.3% of patients).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The current existing clinical trial information does not demonstrate specific risks related to discontinuation or abuse of OP Depot.

7.1.14 Human Reproduction and Pregnancy Data

Women who were pregnant or breast feeding and women of childbearing potential who were not using a medically accepted means of contraception were excluded from enrolling in all clinical studies presented in this application. However, four incidences of pregnancy were identified in OP Depot clinical trials.

Three patients (LOBE-101-1152, HGJZ-HGKB-23-5727, and HGKA-HGKB-570-8634) had elective abortions during OP Depot clinical trials. In these cases, the decision was made by the investigator, in consultation with a Lilly CRP, to continue the patient in the study because the abortions had been confirmed.

In the 4th event, the patient (HGKA-HGKB-224-7595) received an OP Depot injection (300 mg/2 weeks, after total of 189 days on OP Depot) on the same visit in which the positive pregnancy test was obtained. The patient was discontinued from the study because of noncompliance with protocol procedures. Upon follow-up, the investigator reported the pregnancy outcome was a normal birth.

7.1.15 Assessment of Effect on Growth

No pediatric patients were enrolled in these studies. Therefore, the effect of OP Depot on growth was not studied.

7.1.16 Overdose Experience

Because OP Depot is administered intramuscularly by health care professionals, no OP Depot-related intentional overdose cases were reported.

7.1.17 Postmarketing Experience

Because OP Depot has not been approved for marketing, no postmarketing data specific to OP Depot are available as this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 25 summarizes the studies included in OP Depot integrated safety review.

Table 25 Description of Studies Included in the Integrated Safety Database

Databases/Description of Databases	Studies	Treatment Groups	Analyses
Placebo-Controlled Database/contains safety data from 404 patients randomized to OP Depot (306) or placebo (98)	HGJZ	Pooled OP Depot treatment groups (210 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) Placebo	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and special topic[a] for injection-site–related AEs.
Olanzapine-Controlled Database/contains safety data from 921 patients randomized to OP Depot (599) or oral olanzapine (322)	HGKA	Pooled OP Depot treatment groups[b] (150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) excluding 45 mg/4 weeks Oral Olanzapine (10, 15, and 20 mg)	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: (IAIV) injection events, cardiovascular events, metabolic parameters and weight gain, and hepatic measures.
Overall Integrated Database/contains safety data from patients who received treatment with OP Depot in any clinical trial conducted in patients with schizophrenia or schizoaffective disorder	HGJW LOBE LOBO LOBS HGJZ HGKA HGKB	Pooled OP Depot treatment groups[c]	Safety data: Exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS, and the following special topics: IAIV injection events, cardiovascular events, metabolic parameters and weight gain, hepatic measures, and injection-site–related AEs.

7.2.1.2 Demographics

Although a few statistically significant differences were seen (age and gender) in the Placebo-Controlled Database, actual mean differences between groups were small. Patients in both treatment groups of the Olanzapine-Controlled Database were comparable with respect to baseline demographics and physical characteristics at baseline. At baseline, patients in the Overall Integrated Database had a mean age of 39.2 years; 66.0% were Caucasian, and 68.1% were male.

As a whole, baseline Positive and Negative Syndrome Scale (PANSS) scores indicated that patients in the Placebo-Controlled Database were clinically more acutely ill (mean baseline PANSS Total Score = 101), while patients in the Olanzapine-Controlled Database were clinically stable (mean baseline PANSS Total Score = 55).

Discontinuations due to adverse events (AEs) were ≤ 5.1% in all databases.

7.2.1.3 Extent of exposure (dose/duration)

Table 26 summarizes exposure information for all patients who had received at least one injection of OP Depot. Cumulative exposure represents a maximum length of 951 days (approximately 2.6 years).

Table 26 Summary of Patient Exposure to All OP Depot doses (Overall Integrated Database)

	N=1915[a]				
	Min	**Med**	**Mean**	**Max**	**Total**
Number of injections [b]	1	8	14.21	68	27,210
Days of OP Depot exposure	14	168	278.64	951	533,599
Total patient years of exposure:	1460.91				

Abbreviations: Max = maximum; Med = median; Min = minimum; N = Number of patients with OP Depot exposure; OP = olanzapine pamoate.

a A total of 1918 patients have been assigned to OP Depot, however, 2 patients discontinued study participation before the first injection and 1 patient received the first injection after datalock in an ongoing study (HGLQ). Thus, only 1915 patients have received at least one injection of OP Depot.

b All depot dose levels are included in the calculations of the number of injections and days of exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were conducted to evaluate the safety of OD Depot for this submission.

7.2.2.2 Postmarketing experience

Because OP Depot has not been approved for marketing, no postmarketing data specific to OP Depot are available as this time.

7.2.2.3 Literature

A worldwide literature search was conducted on 8 February 2007 using the following databases: Biosis Previews (1989 to 2007 Week 9), Embase (1988 to 2007 Week 5), Ovid Medline (1950 to 2007 Week 5), and Ovid Medline In-Process & Other Non-Indexed Citations (7 February 2007). No citations were identified related to olanzapine pamoate depot, olanzapine and pamoic acid, or olanzapine pamoate. This literature search did not reveal any important new safety information.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate to evaluate the efficacy and safety of OP Depot.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal study was conducted in this submission. In vitro solubility tests were conducted to explore the causality of the excessive sedation events. Details of these solubility tests can be found in section 7.1.12 Special Safety Studies.

7.2.5 Adequacy of Routine Clinical Testing

Generally speaking, routine clinical testing in this submission was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A detailed review of metabolism, clearance and interaction workup can be found in Dr. Andre Jackson's review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Overall evaluation for potential adverse events for OP Depot was adequate.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of data were acceptable.

7.2.9 Additional Submissions, Including Safety Update

A four month safety update was submitted by Lilly on 8 August 2007 (data cut-off date on 31 January 2007). The updated safety information has been incorporated into the integrated safety review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Other than excessive sedation events and injection site-related AEs, the profile of drug-related adverse events in OP Depot is consistent with that of oral olanzapine. No important limitations of data were found.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Both the Placebo-Controlled Database and the Olanzapine-Controlled Database are comprised of only one study in each database. The Overall Integrated Database included 8 OP Depot clinical trials.

7.4.1.2 Combining data

The Overall Integrated Database combined 8 OP Depot clinical trials.

7.4.2 Explorations for Predictive Factors

No further explorations for predictive factors were conducted in these studies.

7.4.3 Causality Determination

Adverse events were considered as generally treatment-related only if the AE rate occurred in at least 2% of OP Depot treated patients and at a rate of at least twice that of placebo.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Both the short-term (HGJZ) and long-term (HGKA) controlled studies were fixed dose studies. In Study HGJZ, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2 weeks and placebo. In Study HGKA, the dose regimen was OP Depot 300 mg/2 weeks, 405 mg/4 weeks, 150 mg/2 weeks, 45 mg/4 weeks and oral olanzapine (flexible doses 10 to 20 mg/d). All OP Depot was administered by gluteal intramuscular injection.

8.2 Drug-Drug Interactions

The existing olanzapine labeling addresses safety outcomes related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

8.3 Special Populations

The existing olanzapine labeling addresses safety outcomes as they relate to the pediatric population, geriatric population, nursing mothers and pregnant women. There have been no new data generated on these topics that have not already been addressed in the labeling.

8.4 Pediatrics

Lilly requested a full waver of OP Depot pediatric studies for indication in the treatment of schizophrenia. This waiver requested covers ages from birth to 17 years old. Lilly's main justification for the request is that OP Depot is unlikely to be used in a substantial number of pediatric patients, for several reasons, including that it does not represent a meaningful therapeutic benefit over existing therapies for the pediatric population.

Briefly, schizophrenia is less common overall in children and adolescents than in adults; compliance issues that make depot formulations attractive are less common in pediatric populations than in adult populations; and generally accepted clinical practice guidelines for treatment of schizophrenia in children and adolescents recommend only limited use of depot antipsychotics.

I find Lilly's arguments persuasive. In addition, olanzapine is associated with significant adverse events including metabolic syndrome, weight gain and increased risk of diabetes, which will pose additional risk to children if pediatric trials are conducted. The excessive sedation events occurred in adult OP Depot trials could be life threatening to children. Therefore, I recommend a full waiver of pediatric studies if the agency decides to grant OD Depot an approval status.

8.5 Advisory Committee Meeting

This NDA will be presented to the Psychopharmacologic Drug Advisory Committee (PDAC) on 6 February 2008 because of a significant safety issue—the excessive sedation events (see 7.1.12 Special Safety Studies). A addendum to this review with final recommendation will be filed after the PDAC meeting.

8.6 Literature Review

A worldwide literature search was conducted on 8 February 2007 using the following databases: Biosis Previews (1989 to 2007 Week 9), Embase (1988 to 2007 Week 5), Ovid Medline (1950 to 2007 Week 5), and Ovid Medline In-Process & Other Non-Indexed Citations (7 February 2007).

The following search was performed:
[{olanzapine}] and [{pamoate}] and [{depot}]

Additional search using above databases with similar timeline was conducted to search following key words: [{olanzapine}] and [{pamoic acid}], [{olanzapine}] and [{pamoate}].

No citations were identified regarding olanzapine pamoate depot, olanzapine and pamoic acid, or olanzapine pamoate. This literature search did not reveal any important new safety information.

8.7 Postmarketing Risk Management Plan

This application will be presented to the PDAC on Feb. 6, 2008. A risk management plan may be recommended after the meeting.

8.8 Other Relevant Materials

The plasma concentration data in patients who experienced the excessive sedation events were provided by Lilly upon the requests of clinical pharmacology reviewer.

9 OVERALL ASSESSMENT

9.1 Conclusions

In the short-term acute efficacy and safety study (HGJZ), the three OP depot treatment groups showed superiority to placebo in reducing PANSS Total Score from baseline to endpoint starting at week 1 and continuing through the end of the study.

In the long-term maintenance study (Study HGKA), the 3 higher dose OP Depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups demonstrated positive maintenance effect over 24 weeks for stabilized patients with schizophrenia.

The safety evaluation of OP Depot demonstrated that the safety profile is similar to that of oral olanzapine for most parameters that were measured, with the exception of injection-related adverse events and excessive sedation events.

Excessive sedation events are a serious safety concern because of the severity of excessive sedation, the unpredictable characteristics, and relatively high incidence—0.07% of injections and 1.3% of patients.

9.2 Recommendation on Regulatory Action

Since this NDA will be presented to Psychopharmacologic Drug Advisory Committee on February 6, 2008, decisions on final regulatory action will be defined until after the committee recommendations are considered.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The development of a risk management plan will depend on the outcome and conclusions of the PDAC to take place on Feb. 6, 2008.

9.3.2 Required Phase 4 Commitments

To be determined based on regulatory action to be decided after the PDAC meeting.

9.3.3 Other Phase 4 Requests

To be determined.

9.4 Labeling Review

Since this NDA will be presented to advisory committee on February 6, 2008 and no regulatory action is recommended, labeling review is not deemed necessary at this time.

9.5 Comments to Applicant

None at this time.

10 APPENDICES

10.1 List of Principle Investigators and Study Sites

Table 27 List of Principle Investigators in Study HGJZ

Investigator 010 Scott Tyler Aaronson, MD Director of Clinical Research Programs Sheppard Pratt Health System 6501 N. Charles Street Baltimore, MD 21285-6815	Investigator 012 Steven J. Glass, MD Psychiatric Medical Director 130 White Horse Pike Clementon, NJ 08021	Investigator 013 Mohammed A. Bari, MD VP/Director, Clinical Research Synergy Clinical Research Center 1908 Sweetwater Road National City, CA 91950
Investigator 014 Louise M. Beckett, MD Chief Executive Officer and Medical Director IPS Research Company 1111 North Lee, Suite 400 Oklahoma City, OK 73103	Investigator 015 Terrance J. Bellnier Chairman GPI, Inc. 36 Forest Meadow Tr. Rochester, NY 14624	Investigator 016 Matthew Brams, MD Principal Investigator Bayou City Research Corp. 550 Westcott, Suite 310 Houston, Texas 77007
Investigator 017 Ronald Brenner, MD President and CEO Neurobehavioral Research, Inc 371 Central Ave Lawrence, NY 11559	Investigator 018 Menahem Krakowski, MD Research Psychiatrist Nathan Kline Psychiatric Research Institute 140 Old Orangeburg Road Orangeburg, NY 10962	Investigator 020 Carlos M. Figueroa, MD Principal Investigator Advanced Psychiatric Group 4619 N Rosemead Blvd. Rosemead, CA 91770
Investigator 022 Steven E. Holroyd, MD Staff Psychiatrist West Hills Hospital 1240 East Ninth Street Reno, Nevada 89512	Investigator 023 Robert L. Horne, MD Medical Director Montevista Hospital 2915 W. Charleston Blvd. Las Vegas, NV 89102	Investigator 024 Richard L. Jaffe, MD Research Psychiatrist Belmont Center for Comprehensive Treatment 4200 Monument Road Philadelphia, PA 19131
Investigator 025 Andrew J. Cutler, MD Medical Director, President, and Investigator CORE Research, Inc 2020 26th Avenue East Bradenton, FL 34208	Investigator 026 James A. Knutson, MD Private Practice Physician 512 6th Street South, Suite 101 Kirkland, WA 98033	Investigator 027 John Lauriello, MD Executive Medical Director The University of New Mexico Department of Psychiatry 943 Stanford Dr. Northeast Albuquerque, New Mexico 87131-5326

Investigator 028 Zinaida Lebedeva, MD Principal Investigator 13207 Ravenna Road, Suite 400 Chardon, OH 44024	Investigator 029 Mark Lerman, MD Director of Clinical Research Program and Principal Investigator Alexian Brother's Behavioral Health Hospital 1721 Moon Lake Blvd, Suite 109 Hoffman Estates, IL 60194	Investigator 030 Michael T. Levy, MD Chairman, Department of Behavioral Sciences Behavioral Medical Research of Staten Island, PC 1361 Hylon Blvd Staten Island, NY 10305
Investigator 031 Robert Enoch Litman, MD Medical Director CBH Health, LLC 9605 Medical Center Drive Main Office: Suit 250 Rockville, MD 20850	Investigator 032 Adam F. Lowy, MD Investigator Psychiatric Institute of Washington 4228 Wisconsin Avenue, NW Washington, DC 20016	Investigator 033 Gerald A. Maguire, MD Attending Physician UC Irvine Medical Center Department of Psychiatry 101 City Drive South, Route 88 Orange, California 92868
Investigator 034 Denis Mee-Lee, M.D. Principal Investigator Hawaii Clinical Research Center 1750 Kalakaua Avenue, Suite 2602 Honolulu, Hawaii 96826 Investigator 039 John G. Sonnenberg, PhD Executive Director Uptown Research Institute, LLC 4755 N. Kenmore Avenue Chicago, IL 60640	Investigator 035 Ricky S. Mofsen, MD Medical Director Clinical Research Inc 2639 Miami Street St. Louis, MO 63118 Investigator 042 Roger William Sommi, Jr, PharmD Director Western Missouri Mental Health Center 2411 Holmes M3-C19 Kansas City, MO 64108	Investigator 038 Michael G. Plopper, MD Medical Director Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, California 92123 Investigator 043 Marshall R. Thomas, MD Associate Professor, Medical Director, Vice President and Medical Director 4455 East 12th Avenue Box A-011-99 Denver, CO 80220
Investigator 044 Cherian Verghese, MD Principal Investigator Keystone Clinical Studies, LLC 1401 Dekalb Street, Suite 201 Norristown, PA 19401	Investigator 045 Kashinath G. Yadalam, MD Medical Director, Institute for Neuropsychiatry Institute for Neuropsychiatry 1770 3rd Avenue, Suite 340, Lake Charles, LA 70601	Investigator 046 Adrian Leibovici, MD Attending Psychiatrist Strong Memorial Hospital 300 Crittenden Boulevard Rochester, NY 14642
Investigator 047 Saroj Brar, MD Windsor Hospital 115 East Summit Street Chargrin Falls, OH 44022	Investigator 048 Himasiri De Silva, MD FAPA Medical Director Clinical Office 801 North Tustin, Suite 600 Santa Ana, CA 92705	Investigator 049 Jean-Pierre Hans Peter Lindenmayer, MD Clinical Director Psychopharmacology Research Program Manhattan Psychiatric Center, Meyer 10A – Wards Island New York, NY 10035

Investigator 050 Kenneth Lovko, MD Principal Investigator CBH Health at Maryview Behavioral Medicine Center 3636 High Street Portsmouth, VA 23703	Investigator 501 Dr. Vera Folnegovic-Smalc Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090, Croatia	Investigator 502 Dr. Darko Perusic Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090, Croatia
Investigator 503 Dr. Vlado Jukic Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090, Croatia	Investigator 800 Prof. Sergey N Mosolov Moscow Research Institute of Psychiatry of the Ministry of Health of the Russian Federation , Federal Scientific Centre for Therapy of Mental Disorders Poteshnaya 3, Moscow, Russia, 107076	Investigator 801 Prof. Vladislav Shamrey Department of Psychiatry Military Medical Academy ul. Botkinskay, 17 Saint Petersburg, Russia , 194044
Investigator 802 Prof. Nikolaj G Neznanov St.-Petersburg State Medical University Obvodniv Kanal, 13 St. Petersburg, 193167, Russia	Investigator 803 Prof. Yuri Popov St. Petersburg Bekhterev Psychoneurologycal Recearch Institute Per Matveeva, 3 Saint Petersburg, 190121, Russia	Investigator 804 A/Prof Mikhail Ivanov St. Petersburg Bekhterev Psychoneurologycal Recearch Institute ul. Bekhtereva, 3 Saint Petersburg, 192019, Russia

Table 28 List of Investigators and Key Individuals in Study HGKA

Investigator 016 Dr. Matthew Brams Bayou City Research Corporation Suite 310 550 Westcott Houston, TX 77007 United States	Investigator 026 Dr. James Knutson Eastside Therapeutic Resources 830 6th Street South Kirkland, WA 98033 United States	Investigator 130 Dr. Miguel A. Ramirez Instituto Psicoterapeutico De Puerto Rico Hostos Avenue 405 San Juan PR 00918 Puerto Rico
Investigator 131 Dr. Juan J. Fumero Hospital San Juan Capestrano State Road #877 KM1.6 Camino Las Lomas Rio Piedras 00926 Puerto Rico	Investigator 132 Dr. Pedro Fernandez Hospital Perea #15 Dr. Basora Street Mayaguez PR 00680 Puerto Rico	Investigator 133 Dr. Osvaldo Caro Unidad De Medicina Conductual First Hospital Panamericano Hospital Damas 8th Floor 2213 Ponce By Pass Ponce PR 00731-7779 Puerto Rico
Investigator 134 Dr. Luis A. Franco Ponce Medical School CAIMED (Lot #4) Calle Monterrey #280 Street A Ponce 00732 Puerto Rico	Investigator 140 Dr. Francisco Paez Instituto Jalischiense De Salud Mental Col Zoquipan, CP45170 Planta Alta Av. Zoquipan #1000 Colonia Zoquipan Guadalajara Jalisco 45170 Mexico	Investigator 141 Dr. M. E. Herrera-Estrella Hospital Psiquiatrico Fray Bernardino Alvarez Col. Thalpan 3er piso BUENAVENTURA Y NINO JESUS S/N TLALPAN Mexico City 14000 Mexico
Investigator 142 Dr. Ricardo Chapa Centro Avanzado De Salud Animica (C.A.S.A.) Col Centro CP 64000 Dra Quiroga PADRE MIER 1015 PONIENTE ESQ. MIGUEL NIETO COL CENTRO Monterrey Nuevo Leon 64000 Mexico	Investigator 143 Dr. Juan Rosales Clincal Psiquiatrica San Refael INSURGENTES SUR NO 4177 TLALPAN Mexico City 14420 Mexico	Investigator 144 Dr. Eric Landa Hospital San Juan De Dios Av. De los Laureles #55 Col El Capullo Zapopan Guadalajara 14150 Mexico

Investigator 160 Dr. Ricardo M. Corral Centro De Neuropsiquiatria Marcelo T. De Alvear 2430 Buenos Aires C1122AAN Argentina	Investigator 161 Dr. Rodolofo D. Fahrer Hospital De Clinicas Av Cordoba 2351 Ciudad De Buenos Aires 1120 Argentina	Investigator 162 Dr. Perdro Gargoloff Clinica San Juan Calle 115 No.231 La Plata Buenos Aires 1900 Argentina
Investigator 163 Dr. Juio J. Herrera Centro De Psiquiatria Biologica Pedro Molina 249 Mendoza M5500GAC Argentina	Investigator 164 Dr. Carlos Nunez Clinica San Jorge Eva Peron 1536 Lanus Este Buenos Aires B18241BR Argentina	Investigator 165 Dr. Miguel Marquez Hospital Frances La Roija 951 Ciudad De Buenos Aires 1221 Argentina
Investigator 180 Dr. Sandra I. Ruschel Hospital Mario Kroeff A/C Dra. Sandra Ruschel-Psiquiatria Rue Mage 326 – Penha Circular Rio De Janeiro RJ 21020-130 Brazil	Investigator 181 Dr. Joao O. Campos Clinica Psiquiatrica Pax A/C Dr. Joao Campos BR 153 Km 9,0 Aparecida De Goiania GO 74922-810 Brazil	Investigator 182 Dr. Irismar R. Oliveira Sanatorio Sao Paulo Ladeira Do Aquidaban, 91 Salvador BA 40301500 Brazil
Investigator 200 Prof. Antonio P. Palha Casa de Saude Do Bom Jesus Rua Antonio Alves Palha Braga 4710-200 Portugal	Investigator 201 A/Prof Marques Teixeira Centro Hospitalar Conde De Ferreira Rua de Costa Cabral, 1211 Porto 4200-272 Portugal	Investigator 202 Dr. Joaquim M. Cabecas Hospital Sobral Cid Apartado 1 Ceiro-Coimbra 3031801 Portugal
Investigator 203 Prof. M. Luisa Figueira Hospital De Santa Maria Servico de Psiquiatria, Piso 3 AVENIDA PROF EGAS MONIZ Lisboa 1649-035 Portugal	Investigator 204 Prof. Elsa Lara Hospital Ingles De Lisboa R. Saraiva De Carvalho N49 Lisboa 1250 Portugal	Investigator 205 Dr. Ana Grilo Hospital Julio De Matos Residencia Psiquiatrica 1, Pavilhao 16 Avenida Do Brasil 53 Lisboa 1749002 Portugal

10.2 Appendix to Efficacy Review

Table 29 Visitwise Mean Change from Baseline to Endpoint in PANSS Total Score in Study HGJZ (OC)

Visit	300Q2W N=100 (LS Mean)	405Q4W N=100 (LS Mean)	210Q2W N=106 (LS Mean)	PLA N=98 (LS Mean)	p-value		
					300Q2W vs. PLA	405Q4W vs. PLA	210Q2W vs. PLA
Baseline	102.58	101.33	99.55	100.60			
Week 0.43	-9.14	-8.45	-7.70	-5.24	.005	.017	.046
Week 1	-15.84	-14.57	-14.10	-9.72	<.001	.009	.010
Week 2	-21.33	-18.86	-16.87	-12.67	<.001	.007	.013
Week 3	-25.34	-21.18	-19.79	-12.95	<.001	<.001	<.001
Week 4	-26.54	-23.19	-21.72	-12.89	<.001	<.001	<.001
Week 5	-29.55	-25.84	-24.06	-14.44	<.001	<.001	<.001
Week 6	-33.94	-26.71	-26.69	-15.23	<.001	<.001	<.001
Week 7	-35.56	-29.33	-28.50	-16.65	<.001	<.001	<.001
Week 8	-36.82	-28.79	-27.19	-15.82	<.001	<.001	<.001

10.3 Appendix to Integrated Safety Review

Table 30 Summary of Excessive Sedation Events Occurring Through 4 September 2007

Patient ID (Reg Subj ID)	Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
LOBE-100-1039 (LOBE-100-1039)	Case 1	31-year-old male	Inj #2 17 Apr 2001	300 mg/4 weeks 45 min	No	45 min after inj, pt experienced AEs of severe sedation, moderate akathisia (described as tension in legs), and mild dizziness. Pt also described feeling weakness. Pt given biperiden. 6 hours after inj, pt still sleepy but felt better. **Recovered approx 48 hr; Continued in study**
HGKA-532-4011 (HGKA-532-4011)	Case 2	32-year-old male	Inj #1 21 Dec 2004	405 mg/4 weeks 10 min	Yes	10 min after inj, experienced dizziness and bad general state. Speech progressively altered and somnolence appeared. After 1.5 hr, stopped responding to verbal stimuli. After 2 hr, profound sedation, bilateral miosis with no photomotor reflex, automatic movements, babinski on left side, no response to pain or verbal stimuli. Hospitalized. Tests neg. Treated with fluids, mannitol, lucetam (piracetamum), and infesol and cerebrolysin. Able to speak a little but with difficulty next morning. **Recovered approx 60 hr; Discontinued study**
HGKA-571-4437 (HGKA-571-4437)	Case 3	63-year-old male	Inj #2 27 Dec 2004	405 mg/4 weeks 15–20 min	Yes	15–20 min post inj, appeared pale, yellowish, not standing steady, and a little confused. 30 min post inj, felt bad, disoriented, with seizures in hands and legs. Walked into a wall; suffered superficial injuries. Experienced spasms which began in shoulders and hands. Appeared to want to sleep but remained awake, responded to questions, drank some. Sent to hospital. Tests neg. Treated with midazolam, ranitidine, diazepam, haloperidol, and promethazine. Hospital diagnosed as tonic clonic convulsions with partial consciousness. Ventilated as preventive measure. Extubated shortly thereafter. **Recovered approx 60 hr; Discontinued study**
HGKB-088-6257	Case 4	30-year-old male	Inj #4 21 Mar 2005	405 mg/4 weeks Approx 60 min	Yes	Patient appears to have presented himself at hospital. Approx. 1 hr post inj, pt experienced sedation. Became drowsy and irritable, disoriented

(LOBS-HGKB-88-6257)						times 3. Also felt stiff and weak in legs. Stated that he passed out for a while, was very confused. Was slightly febrile (100.6 F). **Recovered approx 24 hr; Continued in study**
HGKB-035-5910-A (LOBS-HGKB-35-5910)	Case 5	49-year-old male	Inj #22 24 Oct 2005	250 mg/2 weeks Within 60 min	Yes	Historical conditions of mixed substance abuse, diabetes, hypertension, rheumatoid arthritis. Pt returned to site about 1 hr post inj and appeared in drunken state. Speech was slurred, gait unsteady. Sent to hospital for evaluation. All tests neg. Difficulty ambulating, incontinent of urine while at hospital. Admitted to drinking ¾ pint whiskey the evening before the inj. **Recovered approx 48 hr; Continued in study**
HGKB-182-7318 (HGKA-HGKB-182-7318)	Case 6	51-year-old male	Inj #24 28 Dec 2005	300 mg/2 weeks Within 50 min	Yes	Pt stayed 10 min post inj without complaint, then left site. 50 min post inj, found in coma at bus stop. Sent to hospital. Tests neg. In coma 13 hours post inj. Pt later described not feeling well before he lost consciousness. Patient noted by investigator to abuse alcohol. **Recovered approx 24 hr; Continued in study**
HGKB-412-8428 (HGKA-HGKB-412-8428)	Case 7	31-year-old female	Inj #11 26 Jan 2006	300 mg/3 weeks 30 min	Yes	30 min post inj, experienced drowsiness and washy speech. Admitted to psych hospital. Also experienced slight confusion (nonserious). **Recovered approx 24 hr; Continued in study**
HGKB-035-5910-B (LOBS-HGKB-35-5910)	Case 8	49-year-old male	Inj #35 24 Apr 2006	250 mg/2 weeks 15 min	Yes	15 min post inj, began to have slurred speech and unsteady gait. Progressed to point where couldn't speak clearly or ambulate without assistance. Taken to hospital for evaluation. Tests neg. **Recovered approx 72 hr; Discontinued study**
HGKB-141-6928 (HGKB-141-6928)	Case 9	34-year-old male	Inj #29 17 May 2006	300 mg/4 weeks 5 min	Yes	Pt. diabetic. 5 min post inj, became increasingly sedated, like just woke up from anesthesia. In and out of consciousness. Site assumed low glucose and gave pt Coke to drink. Pt confused, disoriented, ataxic (as if drunk). 30 min post inj, glucose was 275 mg/dL. Site laid pt down in ward where he was in and out of sleeping state. When would try to get up, was restless and had slurred speech. Given fluids and insulin. Glucose cont'd to increase to 360. Temp 37 C. Given haloperidol. Released but readmitted next day due to cont'd problems with alertness and glucose. Sleepy & disoriented, delirious, with slight rigidity in

						extremities. High glucose with slight hypokalemia. Tests indicated hepatic steatosis. **Recovered approx 72 hrs; Continued in study**
HGKB-235-7685 (LOBS-HGKB-235-7685)	Case 10	43-year - ld male	Inj #20 13 Jun 2006	405 mg/4 weeks 30 min	Yes	Pt returned to work soon after injection. A few minutes later (30 min post inj), felt bad a*-nd so drank a juice. Coworkers contacted site due to pt's irritability. Pt returned to the site about 60 min post inj in a sedated state. Sent to hospital for observation. **Recovered approx 24 hr; Continued in study**
HGKB-521-8460 (LOBS-HGKB-521-8460)	Case 11	43-year-old female	Inj #27 14 Jun 2006	100 mg/2 weeks 10 min	Yes	10 min post inj, experienced weakness, dizziness, slurred speech, & profound sedation (described as slightly decreased level of consciousness). **Recovered approx 48 hr; Continued in study**
HGKB-481-8734 (HGKA-HGKB-481-8734)	Case 12	57-year-old male	Inj #2 13 Jun 2006	210 mg/2 week Unspecified. Within 3 hr	No	3 hr post inj, felt weak. Pt was at home. Wife contacted site, reported that pt experiencing profound sedation, weakness, slurred speech. Not unconscious. Event ended after 3 hours. **Recovered approx 3 hr; Continued in study**
HGKB-252-7885 (HGKA-HGKB-252-7885)	Case 13	23-year-old male	Inj #12 27 June 2006	270 mg/4 weeks Immediately post injection	Yes	Immediately post inj, pt complained of feeling weak, dizzy, with headache. Stated that he'd been working outside all day in warm weather without eating or drinking. Stayed at site 45 min but then left per investigator instructions to get something to eat. Pt got sandwich on street and as starting to eat felt unwell. Began staggering; attempted to go into bar but was turned away as appeared drunk. Sat on road and shopkeeper called emergency medical services. 3 hours post inj, admitted to hospital confused and dizzy. Tests neg. **Recovered approx 24 hr; Continued in study**
HGKB-245-7791 (HGKA-HGKB-245-7791)	Case 14	56-year-old female	Inj #25 04 Jul 2006	210 mg/4 weeks Unspecified. Within 75 min	Yes	Elevated WBC at lab draw prior to inj. Complained of hunger, thirst due to fasting. Refused to stay at site. Left 20–25 min post inj. Experienced malaise in the street 1 hr 15 min post inj and admitted to hospital with loss of consciousness. There experienced alternating agitation and somnolence, with dysarthria and sweating. Mild tachycardia (114 bpm) and QTc=421 msec. Blood culture positive for gram +. Due to persistence of agitation, given sedatives and intubated and ventilated to

						perform tests. Temp was 38.1 C. Oliguria noted overnight. Given furosemide. Urine test next day showed bacterial infection. Pt extubated and released. **Recovered approx 48 hr; Continued in study**
HGKB-491-9513 (HGKA-HGKB-491-9513)	Case 15	40-year-old male	Inj #7 11 Jul 2006	300 mg/3 weeks 15 min	Not reported	15 min post inj, became confused and weak. 1 hr 15 min post inj, condition worsened; pt was stunned, had deep sedation, with loss of consciousness. Recovered after 3 hours. (Seen by anesthetist, so assume pt was hospitalized.) **Recovered approx 3 hr; Discontinued from study**
HGKB-242-7758 (HGKA-HGKB-242-7758)	Case 16	36-year-old male	Inj #17 06 Dec 2006	405 mg/4 weeks 90 min	Yes	1 hour 30 min post inj, pt experienced somnolence (during 3-hr observation period). 2.5 to 3 hr post inj, experienced major fatigue, inconsistent speech, mumbling, and automatism (picking invisible things on floor/pseudo-delirium). Hospitalized overnight for observation. Pt later admitted to drinking 1 liter of beer prior to the injection. **Recovered approx 24 hr; Continued in study**
HGKB-143-6958 (HGKA-HGKB-143-6958)	Case 17	59-year-old female	Inj #27 19 Jan 2007	300 mg/2 weeks 2 hours and 45 min	Yes	2 hr 45 min post inj, pt experienced significant somnolence. Pt took 4 mg unprescribed clonazepam 8 hr prior to injection (but did not appear drowsy when arrived at site). 20 min after start of somnolence, experienced difficulty with speech; had motor restlessness, worrying about things she needed to do. Remained alert and oriented. 6 hr 15 min post inj, presented with profound sedation; unarousable for 8 hours. Responsive to pain. Awoke next morning. **Recovered approx 12 hr; Continued in study**
HGKB-406-8350 (HGKA-HGKB-406-8350)	Case 18	26-year-old male	Inj #17 16 Mar 2007[a]	345 mg/4 weeks 30 min	Yes	30 min post inj, pt experienced dizziness, gummy legs, and insecurity while standing. Symptoms slowly increased, progressing to deep sedation, reported to be like deep sleep but pt could always be aroused by speaking to him loudly. Hospitalized for monitoring and hydration. **Recovered approx 24 hr; Continued in study**
HGKB-476-8620 (LOBS-HGKB-476-8620)	Case 19	38-year-old female	Inj #16 12 Jan 2007	390 mg/4 weeks 5 min	No	5 min post inj, experienced somnolence that worsened gradually, but pt was oriented and able to communicate although had dysarthria. PI did not call it an SAE but CRA had him designate it as serious. At end of 3-hr observation, pt was sent home with a friend in an improved but still slightly somnolent state. **Recovered approx 72 hr; Discontinued from study**

HGKB-200-7420 (HGKA-HGKB-200-7420)	Case 20	48-year-old female	Inj #15 4 Oct 2006	405 mg/4 weeks 20 min	No	20 min post inj, experienced dizziness. 45 min post inj, was severely sedated but always conscious, was disoriented to place and time, with dysarthria and confusion. All nonserious AEs. Site was attached to psych unit where patient lived for social reasons so pt was able to be observed by staff there until recovered. **Recovered approx 16 hr; Continued in study**
HGKB-202-7446 (HGKA-HGKB-202-7446)	Case 21	52-year-old male	Inj #35 23 May 2007[a]	210 mg/2 weeks 15 min	Yes	15 min post inj, became confused, somnolent, with blurred vision, dizziness. All events considered nonserious. 2.5 hr post inj, sent to hospital for monitoring. Remained conscious throughout. Vital sign data do not indicate any decrease in BP or HR. **Recovered approx 11 hr 30 min; Continued in study**
HGKB-476-8622 (LOBS-HGKB-476-8622)	Case 22	52-year-old male	Inj #20 06 Jun 2007[a]	360 mg/4 weeks 10 min	Yes	10 min post inj, became somnolent, confused, and cramps developed. Pt slept for 30 min. Arousable but couldn't answer questions correctly. Disoriented with altered consciousness but not unconscious. Experienced retention of urine. Sent to hospital after 3 hr observation. Pt did not urinate despite attempts so was catheterized. Cramps of moderate severity localized in arms & legs. **Recovered approx 24 hr; Discontinued from study**
HGKB-222-7568 (HGKA-HGKB-222-7568)	Case 23	47-year-old male	Inj #17 19 Jun 2007[a]	405 mg/4 weeks 15 min	Yes	Pt complained of dizziness prior to injection, probably due to fasting. Symptoms reportedly worsened. Pt ate 15–30 min post inj and while eating began to feel nervous and experienced abnormal movements like tonic convulsion in his arms. Sporadic at first and then increasing. 2 hr post inj, began to present somnolence and dysarthria but nervous and with abnormal movements so unable to fall asleep. Pt given 1 mg lorazepam (his usual daily dose). No loss of consciousness at any time. Sent to hospital at 4 hr post inj due to continued symptoms. **Recovered approx 24 hr; Discontinued study**
HGKB-571-8643 (HGKA-HGKB-571-8643)	Case 24	55-year-old male	Inj # 40 15 Jul 2007[a]	330 mg/4 weeks 30 min	Yes	Pt had BP 140/90 prior to inj and felt good but had not eaten anything that day or the day prior. 30 min post inj, BP increased to 180/90, HR 96. 45 min post inj, pt complained of headache and stomach ache; BP 160/100. 60 min post inj, pt was confused, ataxic, restless; BP 190/110, HR 100, and glucose 125. Site attempted to treat with captopril but no change. Also treated with enalapril maleate and paracetamol. Pt sent to emergency room and admitted for confusion. BP remained elevated.

						Diagnosed with urinary tract infection; treated with cefuroxime axetil. Pt also treated with large amount of benzodiazepines and slept thereafter. **Recovered approx 48 hr; Continued in study**
HGKB-160-7119 (HGKA-HGKB-160-7119)	Case 25	36-year-old male	Inj #36 13 Aug 2007[a]	405 mg/4 weeks 15 min	Yes	Pt started experiencing dizziness, dysarthria, and gait disturbance 15 min post inj with progressive deepening of sedation over the next 10 min. Patient was sent to the emergency room 6 hours 40 min post inj where pt remained sedated, disoriented, and confused. Vitals were normal and stable. Patient was discharged fully recovered 3 days later. **Recovered approx 48 hr; Continued in study**

Table 31 Olanzapine Plasma Concentrations Obtained During an Excessive Sedation Event

Study	Date (YYYYMMDD)	Time (Days on Study)	Dose	Time of Sample From Last Dose (hours)	Olanzapine Concentration (ng/mL)
Patient LOBE-100-1039	**IAIV Event #1** 20010417		300 mg OP Depot		
LOBE	20010417	29.25		6 hours	172.75
LOBE	20010418	30.00		24 hours	104.48
LOBE	20010420	31.98		72 hours	47.96
Patient HGKB-035-5910	**IAIV Event #5** 20051024		250 mg OP Depot		
HGKB	20051024	294.27		9.4 hours	246.78
HGKB	20051024	294.36		11.5 hours	293.84
HGKB	20051025	294.77		21.4 hours	158.45
Patient HGKB-035-5910	**IAIV Event #8** 20060424		250 mg OP Depot		
HGKB	20060424	475.93		1 hours	284.80
HGKB	20060424	475.97		2 hours	377.79
HGKB	20060424	476.06		4 hours	423.80
HGKB	20060424	476.39		12 hours	314.43
HGKB	20060425	476.86		23.2 hours	208.64
HGKB	20060425	476.89		24 hours	192.82
HGKB	20060426	477.90		48.2 hours	84.27
Patient HGKB-235-7685	**IAIV Event #10** 20060613		405 mg OP Depot		
HGKB	20060613	480.03		2.7 hours	133.47
HGKB	20060613	480.07		3.7 hours	127.07
HGKB	20060613	480.12		4.7 hours	126.73
HGKB	20060614	480.95		24.6 hours	108.77
Patient HGKB-406-8350	**IAIV Event #18** 20070316		345 mg OP Depot		
HGKB	20070316	282.17		4 hours	346.56
HGKB	20070317	282.98		23.5 hours	190.38

Study	Date (YYYYMMDD)	Time (Days on Study)	Dose	Time of Sample From Last Dose (hours)	Olanzapine Concentration (ng/mL)
Patient HGKB-476-8622	**IAIV Event #22** 20070606		360 mg OP Depot		
HGKB	20070606	455.00		1 hour	593.03
HGKB	20070606	455.04		2 hours	542.19
HGKB	20070606	455.08		3 hours	611.13
HGKB	20070606	455.12		4 hours	627.18
Patient HGKB-222-7568	**IAIV Event #23** 20070619		405 mg OP Depot		
HGKB	20070619	424.18		6.75 hours	635.54
HGKB	20070619	424.22		7.75 hours	664.96
HGKB	20070619	424.26		8.75 hours	650.04
HGKB	20070619	424.30		9.75 hours	657.32
HGKB	20070620	424.89		23.75 hours	445.08

Abbreviations: IAIV = inadvertent intravascular; OP = olanzapine pamoate.

REFERENCES

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/s/

Jing Zhang
1/7/2008 04:40:30 PM
MEDICAL OFFICER

Gwen Zornberg
1/7/2008 06:32:09 PM
MEDICAL OFFICER
I concur with Dr. Zhang, the exception to the olanzapine safety profile are the OP depot overdose-type ADRs that are unpredictable with respect to person, place, and time (1.25% of patients) despite RN training. Efficacy is satisfactory, no dose-response.