*Psychopharmacologic Drugs Advisory Committee
Briefing Document*

Zyprexa® Olanzapine Pamoate (OP) Depot
(Olanzapine Long-Acting Injection)
Schizophrenia

Meeting Date: 06 February 2008

*United States Food and Drug Administration
Division of Psychiatry Products*

Answers That Matter.

Eli Lilly and Company

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table of Contents

Executive Overview

Unmet Medical Need

Patients with schizophrenia vary in their responsiveness to and/or ability to tolerate different antipsychotic medications. For this reason, no one treatment will be optimal for all patients. Although several oral antipsychotics are available, they have limitations. Because of the severity and chronicity of the disease, a broad range of treatment options is needed, including long-acting injectable formulations for the treatment of schizophrenia.

The American Psychiatric Association suggests the use of depot medications for those patients with schizophrenia who have recurrent relapses as a result of partial or full nonadherence to oral medications. Between 40% and 65% of patients with schizophrenia are nonadherent with oral medications and yet only 3 long-acting antipsychotics are approved for treatment in the US. Additional treatments would provide more options to this seriously ill population of patients, particularly those who have failed to achieve adequate symptom response from current medications or for whom adherence to oral medication is problematic.

Efficacy

Olanzapine (Zyprexa®) has been approved for the treatment of schizophrenia for more than 10 years and has been prescribed to more than 24 million people worldwide. Extensive clinical trial data has demonstrated that oral olanzapine is an effective treatment in this patient population. The efficacy of a long-acting formulation of olanzapine (Olanzapine Pamoate [OP] Depot) has recently been demonstrated in patients with schizophrenia in 2 double-blind, randomized, controlled studies (HGJZ and HGKA). Additional maintenance of treatment effect was demonstrated in 1 large, ongoing, open-label study (HGKB). In these studies, OP Depot provided the following clinical benefits to patients with schizophrenia or schizoaffective disorder:

- Efficacy in acutely ill and stabilized patients, representing different phases in the longitudinal course of schizophrenia

- Robust early efficacy and long-term maintenance of treatment effect without oral supplementation

- Efficacy for both the positive and negative symptoms of schizophrenia

- Low discontinuation rates over the long term

- Flexible doses and dosing intervals (2 or 4 weeks)

- Patient-reported greater satisfaction with OP Depot treatment, a preference for OP Depot compared with previous oral treatments, and fewer side effects with OP Depot treatment compared with previous oral medications

Safety

The safety evaluation included analyses of general safety parameters and special topics. In addition to the potential safety risks seen during treatment with oral olanzapine, 2 risks related to the route of administration—inadvertent intravascular (IAIV) injection events and injection-site–related adverse events (AEs) were further examined. Patients with IAIV injection events presented with signs and symptoms consistent with many of those seen with an olanzapine overdose. Key safety findings are summarized briefly below.

- The general safety evaluation of OP Depot treatment demonstrated an overall profile that is similar to that of oral olanzapine.

- The incidence of injection-site−related AEs during treatment with OP Depot was consistent with the incidence reported in the literature for another intramuscular (IM) medication. The most common injection-site−related AEs observed in patients treated with OP Depot were injection-site pain, injection-site erythema, and injection-site reaction.

- Patients experiencing IAIV injection events have presented with a range of signs and symptoms of varying degrees of severity, including sedation/somnolence, dizziness, confusion, and altered speech/dysarthria.

- Based on data available as of 30 November 2007, a total of 25 IAIV injection events have been identified in 24 patients during OP Depot clinical trials.

- Olanzapine plasma concentrations were higher than expected during IAIV injection events, suggesting that a portion of the OP Depot dose was released too quickly.

- Sixteen (16) of the 24 patients who experienced an IAIV injection event have continued to receive OP Depot injections.

- All patients experiencing IAIV injection events have fully recovered.

Benefits and Risks

Schizophrenia is a chronic and devastating mental illness with significant morbidity and mortality. No treatment is effective for every patient, and nonadherence with medication is common, so many treatment options are needed in order to effectively treat patients during the life cycle of the disease. The long-acting formulation of olanzapine combines the well-known effectiveness of olanzapine with the added benefits of a depot formulation.

Although there are potential risks during treatment with OP Depot that include the known safety concerns for oral olanzapine with the added risk of IAIV injections, many patients have decided that the risks are offset by robust symptom improvement, ensured medication delivery, and flexibility in the dose and dosing interval, as evidenced by the fact that 16 of the 24 patients experiencing an IAIV injection event chose to continue to

receive OP Depot injections. Although IAIV injections are serious, Lilly believes these relatively uncommon events can be safely managed with appropriate labeling and risk-minimization activities.

In clinical practice, benefit/risk decisions are made on an individual patient basis. Lilly's clinical data suggests that for many patients, the potential benefits of OP Depot use outweigh the potential risks. OP Depot will provide an important addition to the cache of available therapies in the treatment of patients with schizophrenia.

1.   Introduction

Eli Lilly and Company (Lilly) recently submitted a New Drug Application (NDA 22-173 Zyprexa® Adhera Olanzapine Long Acting Injection) to the US Food and Drug Administration (FDA). The NDA provides chemical, pharmaceutical, toxicological, and clinical documentation for a new parenteral long-acting formulation of olanzapine. The clinical performance of the product has been evaluated across a range of doses in clinical trials, and for treatment periods up to 2.6 years. Data from these trials provides evidence of the efficacy and safety of the long-acting intramuscular (IM) formulation compared to placebo and oral olanzapine, and during longer-term treatment of schizophrenia. The results of these trials are summarized in this briefing document that has been specifically prepared for the FDA Psychopharmacologic Drugs Advisory Committee.

The purpose of this document is to present the benefit and risk profile of the long-acting formulation of olanzapine in the context of its overall safety and efficacy findings. The long-acting formulation has demonstrated a robust efficacy profile and a safety profile, both similar to oral olanzapine. As with any drug given by IM injection, there are risks associated with the route of administration that include the possibility of inadvertent intravascular (IAIV) injection events and injection-site–related adverse events (AEs). Detailed information about these potential risks for the long-acting formulation of olanzapine is provided in this document.

Lilly believes that the benefit and risk profile of the long-acting formulation of olanzapine is favorable. This formulation combines the robust efficacy of oral olanzapine with the advantages of a depot formulation, and although there are important additional safety considerations associated with the injection, they are manageable with appropriate labeling and risk-minimization activities.

Presentation of Information

Before the efficacy, safety, and overall benefit-to-risk profile of OP Depot are presented in Section 3, Section 4, and Section 5, respectively, the targeted indication and population for depot formulations will be described, followed by a discussion of olanzapine. Information about the clinical development plan for OP Depot will also be provided (Section 2).

Throughout this document, the long-acting formulation of olanzapine, Olanzapine Pamoate Depot, will be referred to as OP Depot. It is anticipated that the commonly used name for this formulation will be olanzapine long-acting injection (OLAI).

1.1.   Targeted Indication and Associated Outcomes

Schizophrenia is a severe and complex disorder afflicting 1 in 100 adults, including more than 2 million people in the US (NIMH 2007). It is characterized by positive symptoms such as delusions, hallucinations, and grossly disorganized or catatonic behavior as well

as negative symptoms such as affective flattening, alogia, and avolition (APA 2000). Cognitive deficits are common and include impaired executive functioning, process deficits, attention impairments, and difficulties with long- and short-term memory (Harvey et al. 2000; Meyer 2007). The classic course of the disorder includes symptom exacerbations and symptom remissions. After exacerbations, patients generally fail to return to their baseline level of functioning, and further erosion in functioning may follow each successive exacerbation (Kaplan and Sadock 1998); therefore, it is critical to stop this cycle of exacerbations to preserve the patient's functional abilities over time.

In addition to the educational, employment, and social difficulties associated with schizophrenia (Kaplan and Sadock 1998), patients with this disorder suffer disproportionately from general medical illness, increased mortality (especially due to suicide), and other psychiatric afflictions such as substance abuse (Green et al. 2007) relative to the general population (Herings and Erkens 2003). The mortality rate for patients with schizophrenia has been estimated to be 2 to 4 times greater than in the general population (APA 2004). Suicidal behavior is very common in this population; approximately 50% will attempt suicide at least once in their lifetime, and over a 20-year period, approximately 10% to 15% will die by suicide (Kaplan and Sadock 1998). Untreated patients with schizophrenia have much higher mortality rates: up to tenfold that of treated patients (Tiihonen et al. 2006).

In 2002, the direct healthcare cost of schizophrenia in the US was $22.7 billion, with 12% of the costs resulting from hospitalizations and 35% from long-term care (Wu et al. 2005). The most common reason for hospitalization among this population is relapse, which is one of the most devastating and costly outcomes in schizophrenia (Almond et al. 2004). Furthermore, the most common causes of relapse are nonadherence and partial adherence to antipsychotic medications (Love and Conley 2004; Schooler 2006); relapse accounts for 25% of all healthcare costs in schizophrenia care (Robinson et al. 1999; Perkins 2002; Valenstein et al. 2002; Fleischhacker et al. 2003). Unfortunately, nonadherence and partial adherence are very common: Between 40% and 65% of patients with schizophrenia are poorly adherent to antipsychotic treatment at any given time (Valenstein et al. 2006; Perkins 2002). Medication nonadherence is associated with greater risk of arrest, violence, victimization, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems (Ascher-Svanum et al. 2006). Avoidance of nonadherence is thus an important treatment goal not only because of the relationship between relapse and progressively poorer outcomes in patients with schizophrenia but also because of the associated higher healthcare costs.

Treatment with antipsychotic medications is the first line of care for patients with schizophrenia, but continued use of oral antipsychotic medications may have limited effectiveness in patients who are nonadherent or partially adherent to their medication.

1.2. Unmet Medical Need and the Role of Long-Acting (Depot) Formulations

Although many antipsychotics are available in the US today, no single medication is effective for all patients with schizophrenia. The severity of this mental illness is such that a broad range of treatment modalities is needed and especially important because between 20% and 45%, of patients fail to show a satisfactory response to antipsychotic medications (Lambert 2006; Conley and Kelly 2001; Kane 2006). Treatment of chronic illnesses like schizophrenia requires new therapies and delivery systems to increase the proportion of patients who achieve sustained improvements in function.

Limitations associated with currently available oral and depot antipsychotics that may contribute to this lack of satisfactory response are described below.

Oral antipsychotics. Although oral antipsychotics are efficacious for many patients, they have some limitations:

- Patients treated with oral atypical antipsychotics also continue to have high treatment discontinuation rates, as demonstrated by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, in which 64% to 82% of patients treated with oral atypical antipsychotics discontinued their assigned treatment by 18 months (Lieberman et al. 2005).

- There is wide variability in the tolerance of and efficacy achieved with any given treatment, and stopping or changing medications is cited as a frequent occurrence with oral antipsychotics (Weiden et al. 2004; Kane et al. 1998).

- Patients taking oral medications still have a high rate of nonadherence (Keith et al. 2004), and because nonadherence is difficult to detect, patients may suffer relapse before it is detected (Kane 2006). Although greater tolerability—and thus greater adherence—was predicted for atypical relative to typical oral antipsychotics, nonadherence continues to be a problem (Mahmoud et al. 1997; Kane 2006).

Depot antipsychotics. Long-acting injectable antipsychotics were introduced in the 1960s and were generally accepted to confer greater benefit than oral antipsychotics (Ayd 1975; Johnson 1977; Heres et al. 2006). Some of the benefits of depot antipsychotics are summarized below.

- *Prevention or delay of relapse.* A meta-analysis across 36 outpatient studies found a significant reduction in relapse rates with depot compared to oral antipsychotics (Davis et al. 1994). By preventing or delaying relapse, consistent treatment can improve patients' overall cognitive function, insight, and quality of life; reduce hospitalization rates; potentially reduce the risk of suicidality; and lead to an overall reduction in the cost of care by preempting the need for hospitalization (Meltzer 1999; Hawton et al. 2005; McEvoy 2006).

- *Regular interactions between patient and healthcare provider (HCP).* Regular injections provide the opportunity for ongoing contact and the development of relationships between patients and healthcare professionals, which can have beneficial effects on long-term clinical outcomes (Dursun 2005).

- *Controlled administration.* Administration of each dose of medication by a healthcare professional reduces the potential for intentional or accidental overdose/self-poisoning with that drug (Patel and David 2005).

- *Improved global functioning.* A systematic meta-analysis demonstrated that patient global functioning appears to be significantly better with depot antipsychotics compared to oral agents (Adams et al. 2001).

- *Improved adherence.* Adherence to treatment is improved by ensuring medication delivery. If a patient misses an injection, nonadherence is immediately apparent and can be brought to the attention of relevant parties (Kane 2006).

- *Stable plasma levels of the drug.* Long-acting injectable antipsychotics provide predictable and stable plasma levels of active drug (Kane et al. 1998).

- *Patient convenience.* Depot antipsychotics can be administered every few weeks, freeing the patient from having to take daily medication. When given a choice, many patients prefer this freedom not offered by oral medication (Kane 2003, 2006).

Currently only 2 typical long-acting injectable antipsychotic medications (haloperidol decanoate and fluphenazine decanoate) and 1 atypical long-acting injectable antipsychotic medication (risperidone long-acting injection) are approved by the FDA. Although numerous studies have shown robust efficacy during treatment with these approved long-acting antipsychotics, not all patients achieve clinical improvement with these drugs (Fleischhacker et al. 2003; Kane et al. 2003; Hosalli and Davis 2007; Keks et al. 2007). Some of the limitations of these currently approved long-acting antipsychotics are noted below.

- Supplementation with oral antipsychotics may be needed in early treatment with long-acting antipsychotics (APA 2004; Kane et al. 1998).

- Movement disorders are associated with long-acting antipsychotic treatments. Although such disorders are less likely in treatment with risperidone long-acting, a recent study found a trend toward greater incidence of movement disorders at higher doses of risperidone (Hosalli and Davis 2007; Lindenmayer et al. 2007).

- Risk of tardive dyskinesia is associated with the typical long-acting antipsychotics (APA 2004).

- Presumed patient compliance with oral medications may lead clinicians to decide that long-acting antipsychotics are not needed (Heres et al. 2006); however, both patients and clinicians have been found to overestimate treatment compliance in patients with schizophrenia (Byerly et al. 2005).

- Currently approved long-acting antipsychotics have limited options for dosing intervals (Kane et al. 1998; APA 2004)

- Refrigeration requirements of risperidone long-acting injection may limit use in some settings (Risperdal PI).

Additional treatment options, including long-acting injectable formulations, are therefore needed. A larger cache of treatment options would allow clinicians to customize care to the individual patient, potentially alleviating the distress associated with the debilitating symptoms of schizophrenia.

1.3. Target Population for Depot Antipsychotics

Schizophrenia patients with medication adherence problems are generally thought to be the subpopulation who is most likely to benefit from long-acting injectable antipsychotics (Schooler 2003; APA 2004). Using data from the US Schizophrenia Care and Assessment Program (US-SCAP), Shi and colleagues (2007) found that patients receiving long-acting antipsychotics differed from those who received oral antipsychotics; patients given long-acting antipsychotics had greater clinical and social dysfunction and were more likely to have been hospitalized in the year before enrollment, to use alcohol and illicit substances, to have been arrested, and to show greater psychopathology. As noted by Glazer (2007), of the estimated 50% of patients with schizophrenia in the US who have problems with treatment adherence, only about 10% to 15% are currently receiving a long-acting antipsychotic.

It is within the context of the need for more treatment options for this seriously ill patient population that Lilly has submitted for the approval of a long-acting formulation of olanzapine for the treatment of schizophrenia.

1.4. Olanzapine

Oral olanzapine is a potent serotonin 5-$HT_{2A/2C}$, dopamine D_{1-4} antagonist with affinity for muscarinic receptors. Its mechanism of action, as with other drugs having efficacy in schizophrenia, 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. An atypical antipsychotic agent, oral olanzapine (Zyprexa) was initially approved by the FDA in 1996. Table 1.1 lists other formulations of olanzapine and their approval years.

Table 1.1.   **FDA Approval Dates for Olanzapine Formulations**

First Approval (Year)	Formulation Name	Indications
1996	Zyprexa (olanzapine tablets)	Schizophrenia, acute manic or mixed episodes of bipolar I disorder, maintenance treatment in bipolar disorder
2000	Zyprexa Zydis (olanzapine orally disintegrating tablets)	Schizophrenia, acute manic or mixed episodes of bipolar I disorder, maintenance treatment in bipolar disorder
2004	Zyprexa IntraMuscular (olanzapine for injection; rapid-acting intramuscular [RAIM] injection)	Agitation associated with schizophrenia and bipolar I mania

Although OP Depot and rapid-acting intramuscular olanzapine [RAIM] are both intramuscular injectable formulations of olanzapine, they are substantially different, based on their absorption characteristics and physical form. RAIM is a solution of olanzapine (base) that is immediately available and is completely absorbed within a few hours after injection. OP Depot, on the other hand, is a crystalline salt formulation, olanzapine pamoate monohydrate, which is composed of olanzapine and pamoic acid. The micron-sized salt crystals are suspended in an aqueous vehicle and injected into muscle tissue; the salt slowly dissolves and, in solution, dissociates into the separate molecular entities of olanzapine (base) and pamoic acid at the site of injection. Both olanzapine and pamoic acid are then absorbed into the systemic circulation. The slow dissolution of the olanzapine pamoate salt provides continuous absorption of olanzapine over a period of weeks. Thus, RAIM is intended for the immediate, acute treatment of an agitated patient with schizophrenia or bipolar I mania, whereas OP Depot is intended for long-term, sustained treatment of a patient with schizophrenia.

Efficacy and Safety of Oral Olanzapine

The efficacy and safety of olanzapine in the treatment of schizophrenia have been extensively studied in both Lilly- and externally-sponsored clinical trials, and findings from these studies have been reported in the scientific literature (for example, Beasley et al. 1996a, 1997, 2003; Tollefson et al. 1997; Lieberman et al. 2005; Haro et al. 2006a, 2006b). In these studies, olanzapine was associated with clinically meaningful efficacy. The CATIE study compared the effectiveness of 5 antipsychotic drugs (4 atypical and 1 typical) and found that oral olanzapine had the lowest discontinuation rates for any reason (referred to as all-cause treatment discontinuation) relative to all of the other

antipsychotics studied during 18-month treatment (Lieberman et al. 2005). In a meta-analysis that included 16 studies in the primary survival analysis, Beasley et al. (2007) found that patients treated with olanzapine had a lower all-cause discontinuation rate relative to haloperidol, risperidone, ziprasidone, or quetiapine during acute, 12-week treatment. All-cause discontinuation is considered a leading indicator of treatment effectiveness, as this measure encompasses both efficacy and tolerability.

The safety of oral olanzapine has also been well characterized, and safety considerations have been incorporated into the warnings and precautions sections of the Zyprexa product label and include the potential risks of hyperglycemia, hyperlipidemia, hemodynamic effects (orthostatic hypotension and syncope), hyperprolactinemia, elevations in transaminases, and weight gain. Somnolence/sedation is a common AE observed during treatment with oral olanzapine.

2.   Overview of Clinical Plan of Development

2.1.   Overview of Development Plan

Lilly met with the FDA on 10 occasions between 1999 and 2007 to obtain regulatory input regarding the clinical development plan for OP Depot. Key recommendations and agreements regarding OP Depot clinical trials are summarized below.

- FDA agreed with Lilly's planned number of safety exposures for OP Depot, with the understanding that agreement was based on the extensive human exposures with oral olanzapine.

- FDA agreed that a single, positive, clinical trial (HGJZ) would be sufficient to support registration of OP Depot.

- FDA reconfirmed the efficacy and safety clinical plan to support the registration of OP Depot. Comments were provided on the overall proposed study designs for Studies HGJZ (efficacy, safety, and pharmacokinetics) and HGKA (maintenance of effect and safety).

Based on discussions with the FDA, the focus of the clinical development plan was to evaluate OP Depot within the context of the well-studied efficacy and safety profiles of oral olanzapine. An oral olanzapine treatment arm was also included in the large maintenance-of-effect trial, HGKA.

2.2.   Overview of OP Depot Studies

Table 2.1 presents an overview of the important design features of all studies that were included in the clinical development plan for OP Depot. The efficacy and safety of OP Depot in the treatment of schizophrenia were evaluated in a total of 8 controlled and open-label studies:

- Controlled studies: One (1) double-blind, placebo-controlled, fixed-dose study (HGJZ) and 1 double-blind, oral olanzapine-controlled, fixed-dose study (HGKA) were conducted to evaluate the efficacy and safety of OP Depot.

- Open-label studies: Six (6) open-label studies were conducted at varying phases of clinical development for OP Depot.

Two additional studies not shown in Table 2.1 were conducted in healthy volunteer subjects: Study LOAZ was conducted in 18 healthy volunteer subjects who were given a single, very low dose of OP Depot (10 to 40 mg) before OP Depot was tested in patients with schizophrenia. Study LOBQ was conducted in 6 healthy volunteer subjects and characterized pamoic acid exposure resulting from the administration of a marketed pamoate salt, hydroxyzine pamoate; the study did not involve OP Depot but provided reference information on pamoic acid exposure.

Appendix 1 presents a summary of preclinical studies with OP Depot.

Table 2.1.   **Overview of Studies in the Clinical Plan of Development for OP Depot**

Study ID/ Study Status	Study Length	# Enroll or Rand	Dose	Study Design and Objective
LOBE/ Concluded	Up to 24 weeks	282 Enroll	**OP Depot**: single dose 50 to 450 mg; multi-dose 100 to 405 mg/2 to 4 weeks	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 weeks **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, or 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.
HGJZ/ Concluded	8 weeks	404 Rand	**OP Depot**: 210 mg/2 weeks, 300 mg/2 weeks, or 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, or 300 mg/2 weeks **Oral OLZ**: 10, 15, or 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	**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 have previously completed an OP Depot clinical trial (HGJZ, HGKA, or LOBS).
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 who are at risk for relapse.

Abbreviations: # = number; Approx = approximately; Enroll = enrolled; ID = identification; OLZ = olanzapine; OP = olanzapine pamoate; PET = positron emission tomography; PK = pharmacokinetic(s); PQBP = product quality bioavailability performance; PSD = particle size distribution; RAIM = rapid-acting intramuscular; Rand = randomized.

Page 15

3. Efficacy

This section provides evidence of the robust efficacy of OP Depot demonstrated in the treatment of adult patients with schizophrenia based on 2 randomized, double-blind, controlled trials, Study HGJZ and Study HGKA. Efficacy assessments also occurred in the open-label Study HGKB, and although that study was designed primarily to assess safety, it provides additional support for long-term maintenance of effect. The efficacy of OP Depot in the treatment of schizophrenia is further supported by extrapolation from the established effectiveness of the oral formulation of olanzapine.

Therapeutic Dosages of OP Depot

The therapeutic OP Depot dosages are 150, 210, 300, and 405 mg, representing the amount of active ingredient, olanzapine. The sustained-released performance of olanzapine from an OP Depot injection delivers a consistent systemic olanzapine exposure over a period of weeks at levels that are comparable to those associated with once-daily oral administration of olanzapine. OP Depot doses are therefore designed to provide an olanzapine steady-state exposure that corresponds to daily doses of 10 to 20 mg olanzapine, as shown below (Table 3.1).

Table 3.1.   **Dose Correspondence between OP Depot and Oral Olanzapine at Steady State**

Dose of Oral Olanzapine	Approximate Corresponding Dose of OP Depot given every 2 weeks	Approximate Corresponding Dose of OP Depot given every 4 weeks
10 mg/day	150 mg	300 mg
15 mg/day	210 mg	405 mg
20 mg/day	300 mg	-

Key efficacy findings from Studies HGJZ, HGKA, and HGKB are described below.

3.1. Acute Efficacy: Study HGJZ

Study HGJZ was designed to assess the acute efficacy of OP Depot in patients with schizophrenia based on baseline-to-endpoint mean change in Positive and Negative Syndrome Scale (PANSS) Total score after 8 weeks of double-blind treatment. In this inpatient/outpatient, multicenter, parallel study, acutely ill patients with schizophrenia were randomized in a 1:1:1:1 ratio into 4 treatment groups: (1) 300 mg/2 weeks OP Depot, (2) 405 mg/4 weeks OP Depot, (3) 210 mg/2 weeks OP Depot, and (4) placebo (placebo injection/2 weeks). No supplementation with oral antipsychotic therapy was permitted at any stage during the study. This study was conducted according to a protocol agreed on with the FDA. Figure 3.1 provides an illustration of the study design.
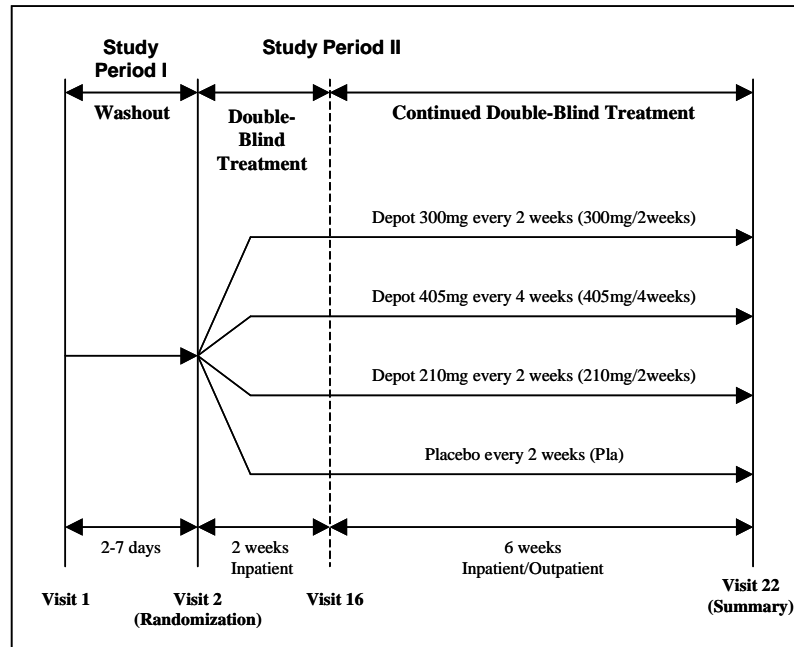
Figure 3.1.   **HGJZ study design.**

The majority of randomized patients in Study HGJZ were male (70.5%) and Caucasian (55.9%), with a mean age of 40 years. The mean baseline PANSS Total score across all treatment groups was 101, and the mean Brief Psychiatric Rating Scale (BPRS) score was 41 (items scored on a scale of 0 to 6), indicative of "moderate" to "markedly ill" patients and consistent with interpretation of PANSS and BPRS scores in the literature (Leucht et al. 2005).

Primary Efficacy Analysis. In the primary efficacy analysis, all 3 OP Depot dosages (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically significantly superior to placebo (all p-values <.001) with respect to mean change from baseline to endpoint in PANSS Total score (-26.32, -22.57, and -22.49 versus -8.51, respectively).

Visitwise analyses indicated that by Day 3, patients in the 300 mg/2 weeks and 405 mg/4 weeks OP Depot treatment groups had statistically significantly greater reductions in PANSS Total scores compared to patients in the placebo (p<.05) treatment group. By the end of Week 1, patients in all 3 OP Depot treatment groups showed statistically significantly greater improvement than patients in the placebo (p<.05) treatment group. These statistically significant improvements in all OP Depot dose groups over placebo were maintained throughout the study (p<.001 for all treatments from 3 weeks onward). These results demonstrate robust efficacy for OP Depot without the use of oral antipsychotic supplementation.

Figure 3.2 illustrates the visitwise mean change from baseline to endpoint in PANSS Total score.

*p<.05 Type III Sum of Squares (ANOVA): Full model: (Therapy) + (Inv)
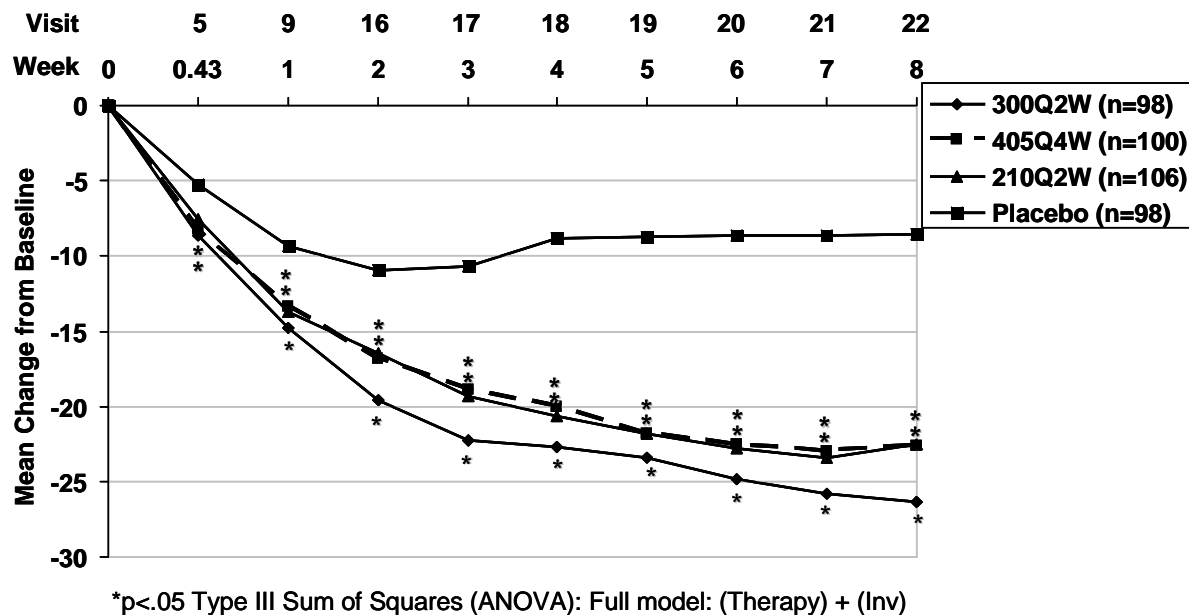
Abbreviations: 210Q2W = 210 mg/2 weeks OP Depot; 300Q2W = 300 mg/2 weeks OP Depot; 405Q4W = 405 mg/4 weeks OP Depot; ANOVA = analysis of variance; Inv = investigator; LOCF = last observation carried forward; OP Depot = Olanzapine Pamoate Depot; PANSS = Positive and Negative Syndrome Scale.
Week 0.43 = Day 3.

Figure 3.2. **Visitwise mean change from baseline to LOCF endpoint in PANSS Total score, Study Period II, Study HGJZ.**

Additional Analyses. Other secondary efficacy analyses included assessment of response rate and baseline-to-endpoint mean change in PANSS Positive, Negative, and General Psychopathology subscales; BPRS Total score; Clinical Global Impressions–Improvement (CGI-I), and Clinical Global Impressions–Severity (CGI-S). These findings also demonstrated the superiority of OP Depot to placebo in the acute treatment of schizophrenia. Specifically, all 3 OP Depot doses were statistically significantly superior to placebo (all p-values <.001) with respect to mean change from baseline to endpoint in PANSS Positive, Negative, and General Psychopathology subscale scores; BPRS Total score; CGI-I; and CGI-S.

Comparison with Historical Oral Olanzapine Studies. Historical oral olanzapine Study HGAD (Beasley et al. 1996b) was used as a model for OP Depot Study HGJZ. As a result, both studies have highly similar designs and patient populations. Both studies were randomized, double-blind, placebo-controlled studies examining the efficacy of fixed doses of oral olanzapine or OP Depot in patients diagnosed with schizophrenia with an acute exacerbation and a minimum BPRS Total score. Although the double-blind phase of OP Depot Study HGJZ lasted for 8 weeks and the double-blind phase of oral olanzapine Study HGAD lasted for 6 weeks, efficacy results can be compared across the studies through Week 6 (Table 3.2). At baseline, patients across all active drug dose groups in Studies HGAD and HGJZ had BPRS Total scores from 40.45 to 42.8 on a 0 to 6 scale. At Week 6, patients treated with oral olanzapine in Study HGAD experienced mean reductions in BPRS Total scores from 6.7 to 15.2 across dose groups, yielding effect sizes from 0.17 to 0.72 compared to placebo. In Study HGJZ, patients treated with OP Depot experienced BPRS Total score reductions from 14.15 to 15.35 for effect sizes from 0.42 to 0.48 compared to placebo across doses at Week 6.

Table 3.2. **Comparison of OP Depot Study HGJZ and Oral Olanzapine Study HGAD**

Study	ORAL OLANZAPINE STUDIES (Doses in mg/day)					OP DEPOT STUDY (Doses in mg/wk)			
	HGAD					HGJZ			
	Pla	Oral Hal	Oral Olanzapine			Pla	OP Depot		
Dose	0	15±5	5±2.5	10±2.5	15±2.5	0	405/4	210/2	300/2
Patients	n=68	n=69	n=65	n=64	n=69	n=98	n=100	n=106	n=100
Mean daily dose (mg/d)	0	16.4	6.6	11.6	16.3	0	14.5	15.0	21.4
BPRS (0 to 6)									
Mean Baseline	39.7	41.8	41.2	42.8	42.6	40.40	41.07	40.45	41.44
6-wk Change	-3.1	-12.9	-6.7	-12.6	-15.2	-6.07	-14.15	-14.40	-15.35
Effect Size[a]		**0.57**	**0.17**	**0.54**	**0.72**		**0.42**	**0.45**	**0.48**

Abbreviations: BPRS = Brief Psychiatric Rating Scale; d = day; Hal = haloperidol; LOCF = last observation carried forward; mg = milligram; n = number of patients; OP = Olanzapine Pamoate; Pla = placebo; wk = week.

[a] Effect size for each treatment arm compared to placebo.

Note: All scores represent mean values using LOCF methodology. Mean daily dose represents mean modal daily dose.

Conclusion. The efficacy analyses for Study HGJZ demonstrated rapid and robust clinical efficacy of all 3 OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) compared with placebo in the acute treatment of patients with schizophrenia without the need for supplementation with oral antipsychotic therapy. Efficacy was observed for both positive and negative symptoms.

The acute efficacy results of Study HGJZ are of the same magnitude of effect as those demonstrated in an oral olanzapine study and support the plan to evaluate OP Depot within the context of the well-studied efficacy profile of oral olanzapine.

3.2.   Maintenance of Effect: Study HGKA

Study HGKA was designed to assess the efficacy of OP Depot as a maintenance treatment over 24 weeks of double-blind treatment for adult outpatients with schizophrenia. In this multicenter, double-blind, parallel study, patients entered, clinically stable on antipsychotic medications, and were then switched to oral olanzapine monotherapy and had to remain stable for at least 4 weeks before they were eligible for randomization. Patients were randomized in a 2:1:1:1:2 ratio into 5 treatment groups: (1) 405 mg/4 weeks OP Depot, (2) 300 mg/2 weeks OP Depot, (3) 150 mg/2 weeks OP Depot, (4) 45 mg/4 weeks OP Depot, or (5) 10, 15, or 20 mg/day oral olanzapine. The therapeutic doses (150 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks OP Depot) were selected to correspond to oral doses of 10, 15, and 20 mg/day,

respectively. A low dose of OP Depot (45 mg/4 weeks) was included to serve as a comparator for the superiority analysis to therapeutic doses of OP Depot. No supplementation with oral antipsychotic therapy was permitted after randomization to treatment. This study was designed in accordance with the European Medicines Agency (EMEA) guidance on the clinical development of depot antipsychotic preparations (EMEA 2003).

Figure 3.3 provides an illustration of the study design.
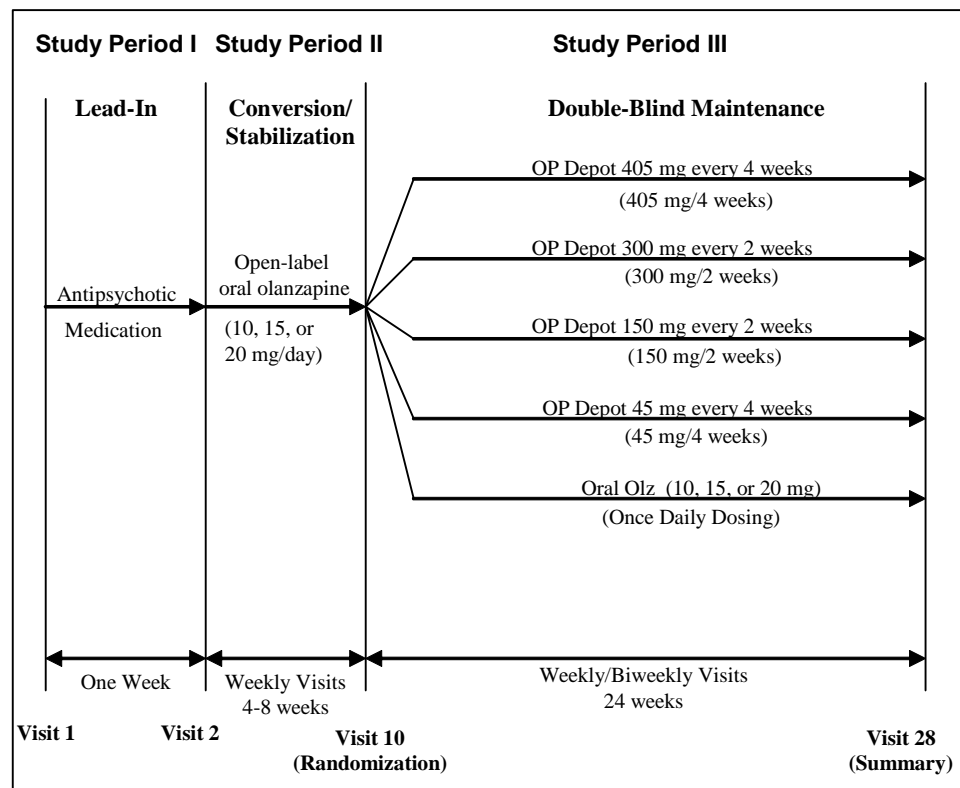
Figure 3.3.   HGKA study design.

A total of 1065 patients were randomized in the study. The majority of randomized patients were male (65.4%) and Caucasian (71.8%), with a mean age of 39 years. Mean PANSS Total score at time of randomization was 56, indicating a population that was stable and minimally symptomatic.

Primary Efficacy Analyses. There were 2 primary a priori efficacy endpoints in Study HGKA:

- The superiority primary objective was to demonstrate the superiority of the 3 therapeutic OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) over a low OP Depot dose (45 mg/4 weeks) in terms of time to exacerbation of symptoms.

- The noninferiority primary objective was to demonstrate the noninferiority of the 2-week OP Depot dosing regimen (150 mg/2 weeks pooled with 300 mg/2 weeks) to oral olanzapine in terms of exacerbation rate after 24 weeks of maintenance treatment.

Exacerbation was defined as worsening of positive symptoms as measured by the BPRS or hospitalization due to worsening of positive psychotic symptoms (see Appendix 2 for the detailed definition of exacerbation and the rationale for the definition).

In the superiority primary analysis, results indicated that each of the therapeutic 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 ($p<.001$, $p<.001$, and $p=.006$, respectively; Figure 3.4). This finding was confirmed by the visitwise PANSS Total scores, which showed that the 3 therapeutic doses of OP Depot were effective in maintaining a response for the 24-week duration of the study (Figure 3.5), while the 45 mg/4 weeks OP Depot dose showed a statistically significant worsening of Total PANSS scores over the 24 weeks ($p<.001$).

Time to exacerbation for the double−blind maintenance phase by using log−rank test
OPD150, OPD300, OPD405 vs OPD45
F1D−MC−HGKA: Study Period III
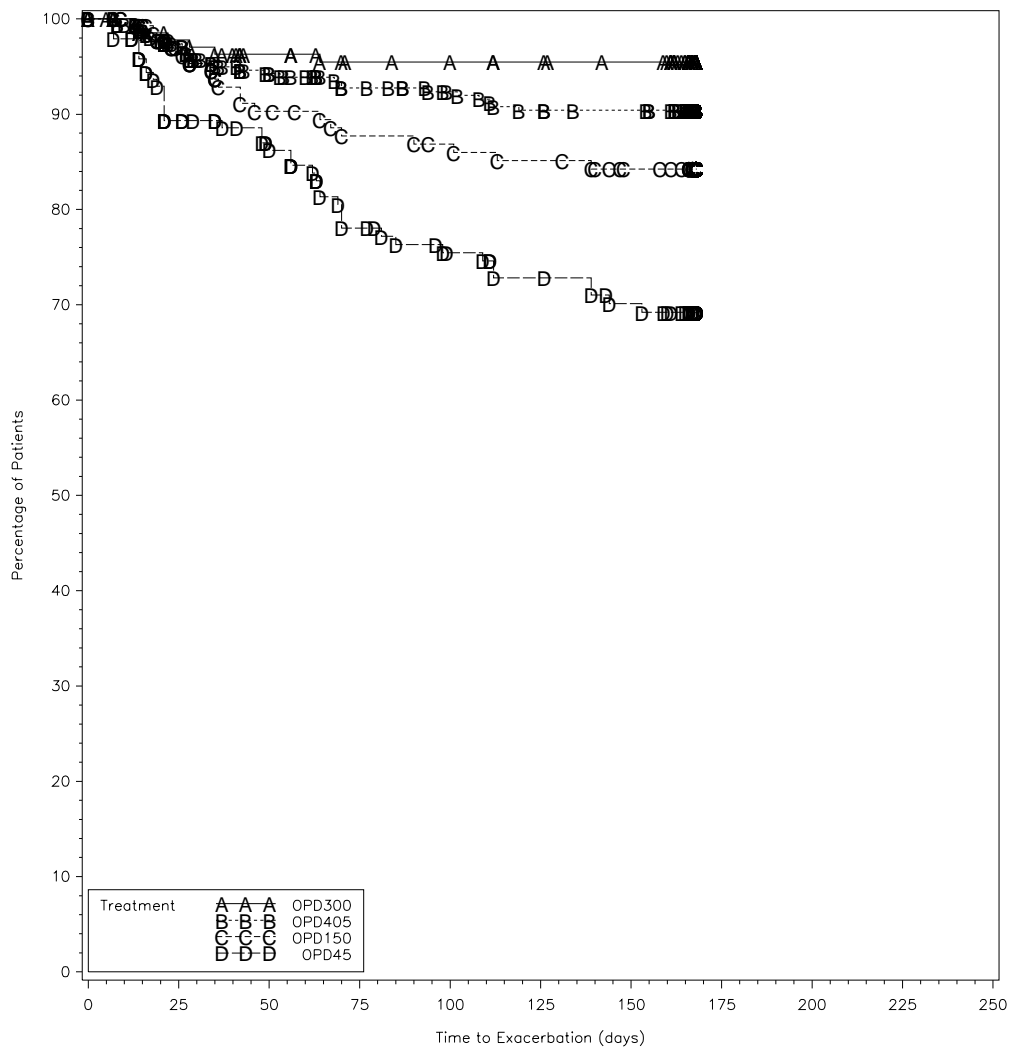
P−value from Log−rank test: <.001
P−value from Log−rank test for OPD300 vs OPD45 : <.001
P−value from Log−rank test for OPD405 vs OPD45 : <.001
P−value from Log−rank test for OPD150 vs OPD45 : .006

Figure 3.4.   **Time to exacerbation for the double-blind maintenance phase (individual OP Depot groups versus low-dose Depot; log rank test).**

PANSS Total Score (y-axis), Weeks (x-axis)

Legend:
- Oral OLZ (n=322)
- OPD300 (n=140)
- OPD405 (n=316)
- OPD150 (n=140)
- OPD45 (n=144)

*p-value at Visit 28/Week 24:
300mg/2wks vs. 45mg/4wks p<.001   405mg/4wks vs. 45mg/4wks p<.001
150mg/2wks vs. 45mg/4wks p<.001   OLZ vs. 45mg/4wks p<.001
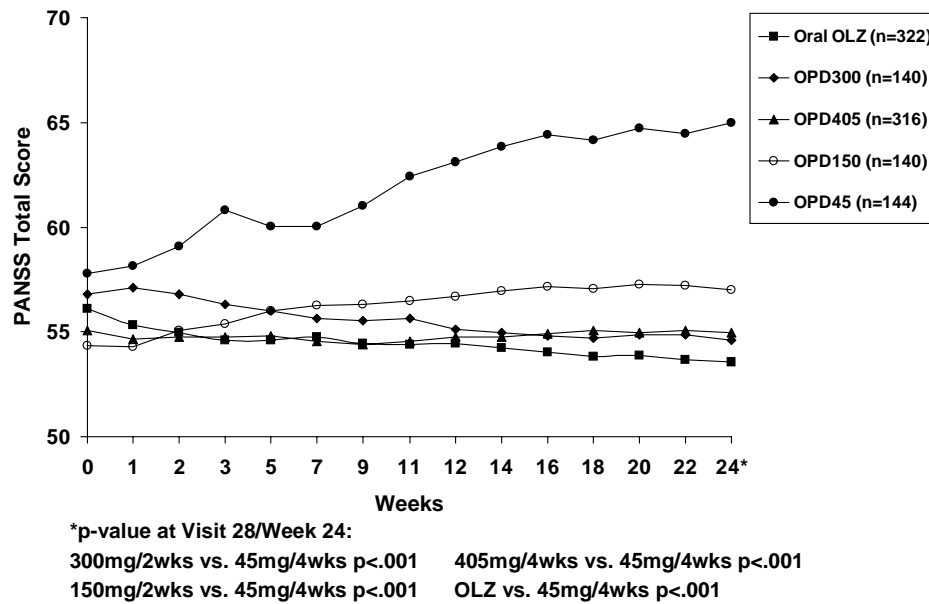
Figure 3.5.   Visitwise PANSS Total scores during double-blind treatment, Study HGKA.

In the noninferiority primary analysis, the pooled 2-week OP Depot dosing regimen was found to be noninferior to the oral olanzapine treatment group in terms of nonexacerbation rate (Table 3.3). The cumulative 24-week nonexacerbation rate was 90% for the pooled 2-week OP Depot dosing regimen and 93% for the oral olanzapine treatment group. The upper limit of the 95% confidence interval around the difference between these 2 rates was 8%, which was less than the a priori cut-off limit of 20% and therefore confirmed noninferiority. Appendix 2 includes an explanation of the noninferiority criteria.

Table 3.3.   **Noninferiority Analysis of Kaplan–Meier Estimates of Nonexacerbation Rates for Pooled 2-Week OP Depot versus Oral Olanzapine at 24 Weeks Study HGKA Double-Blind Maintenance Phase**

```
-----------------------------------------------------------------
                        Survival     Standard
Therapy                   Rate        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)
-----------------------------------------------------------------
```
Abbreviations: OLZ = Oral Olanzapine; OPD2WK = Pooled 2-Week Olanzapine Pamoate Depot.

Both primary objectives were met without the use of oral antipsychotic supplementation.

Additional Analyses. Each of the therapeutic OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) demonstrated noninferiority to oral olanzapine with respect to rates of exacerbation of symptoms. The 405 mg/4 weeks OP Depot treatment group was noninferior to oral olanzapine and the pooled 2-week OP Depot dosing regimen. These results support the efficacy of the 4-week dosing regimen.

Additional secondary efficacy measures included PANSS Total score; PANSS Positive, Negative subscales; BPRS Total; and CGI-S. The results of the mean change analyses of these measures demonstrated overall positive maintenance of effect for the 3 therapeutic OP Depot doses over 24 weeks of treatment (Table 3.4), based on small mean changes at endpoint on each measure.

Table 3.4. **PANSS Total and Subscale Scores, BPRS Total, and CGI-S Mean Change from Baseline to Endpoint (LOCF) 24-Week Double-Blind Maintenance Phase Study HGKA**

	Baseline	Mean Change	Within-Group p-Value
PANSS Total			
150 mg/2 weeks	54.34	2.66	.037
405 mg/4 weeks	55.06	-0.09	.907
300 mg/2 weeks	56.81	-2.19	.051
PANSS Positive			
150 mg/2 weeks	11.15	1.29	.003
405 mg/4 weeks	11.13	0.56	.019
300 mg/2 weeks	11.08	0.16	.626
PANSS Negative			
150 mg/2 weeks	15.82	-0.06	.857
405 mg/4 weeks	15.94	-0.69	<.001
300 mg/2 weeks	16.66	-0.95	.009
BPRS Total			
150 mg/2 weeks	11.54	2.29	.004
405 mg/4 weeks	12.10	0.34	.468
300 mg/2 weeks	12.84	-0.97	.134
CGI-S			
150 mg/2 weeks	3.10	0.06	.447
405 mg/4 weeks	3.05	-0.01	.896
300 mg/2 weeks	3.03	-0.09	.144

Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI-S =Clinical Global Impression-Severity;
   LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale.

Comparison with Historical Oral Olanzapine Studies. Because of similar design features among OP Depot Study HGKA, oral olanzapine Study HGGI (Beasley et al. 2003), and the maintenance phases of oral olanzapine Studies HGAD, HGAJ, and E003 (Dellva et al. 1997; Tran et al. 1998), maintenance–of-effect results can be compared across these studies. Studies HGKA and HGGI were both double-blind, randomized relapse-prevention studies of clinically stable patients (BPRS positive items scores ≤4) who had been stabilized on oral olanzapine prior to randomization. Patients who achieved clinical response in the acute phases of Studies HGAD, HGAJ, and E003 were eligible to continue blinded treatment in long-term extensions of ≥46 weeks. Control groups for the studies included low-dose OP Depot (45 mg/4 weeks; Study HGKA), placebo (Study HGGI), haloperidol (Study HGAJ), placebo (Study HGAD), and low-dose oral olanzapine (1 mg/day; Study E003).

A comparison of 6-month cumulative estimated relapse rates for therapeutic olanzapine groups and control groups from OP Depot Study HGKA and the 4 oral olanzapine studies suggests a high degree of consistency among the studies (Table 3.5). All of the Kaplan–

Meier cumulative estimated 6-month exacerbation rates for therapeutic doses of oral olanzapine and OP Depot fell in the range of 5% to 11%. Six-month estimates of exacerbation for subtherapeutic low-dose treatment groups were similar for both oral olanzapine (31.8%) and OP Depot (31%). Lastly, 6-month exacerbation estimates for placebo were consistently around 55%. This consistency among studies and the clear pattern of findings lend validity to the findings of Study HGKA.

Table 3.5.   **Summary of Kaplan–Meier 6-Month Risk of Relapse/Exacerbation OP Depot and Oral Olanzapine Maintenance Studies**

Study	Treatment Group	Mean Modal Dose	N	6-Month Risk[a]
Therapeutically Treated Patients				
HGKA	Oral olanzapine	14.3 mg/d	322	7%
HGGI	Oral olanzapine	13.4 mg/d	224	5.5%
HGAD, HGAJ, E003 (Pooled)	Oral olanzapine	13.6 mg/d	627	11.3%
HGKA	OP Depot 405 mg/4 weeks	Corresponds to 14.5 mg/d	318	10%
HGKA	2-Week Pooled OP Depot (300 & 150 mg/2 weeks)	-	281	10%
Control Groups				
HGKA	Low-dose OP Depot (45 mg/4 weeks)	Corresponds to 1.6 mg/d	144	31%
E003	Low-dose olanzapine	1 mg/d	14	31.8%
HGGI	Placebo	0	102	55.2%
HGAD	Placebo	0	13	54.9%

Abbreviations: d = day; mg = milligram; n = number of patients; OP = Olanzapine Pamoate.

a   Kaplan–Meier cumulative estimated 6-month risk of relapse/exacerbation.

Conclusion. The results of Study HGKA demonstrated the efficacy of all 3 therapeutic OP Depot doses (150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) over 24 weeks.

- All 3 therapeutic OP Depot doses (150 mg/2 weeks, 300 mg/2 weeks and 405 mg/4 weeks) were superior to the low OP Depot dose (45 mg/4 weeks).

- All 3 therapeutic OP Depot doses (150 mg/2 weeks, 300 mg/2 weeks and 405 mg/4 weeks) were noninferior to oral olanzapine in symptom exacerbation and showed positive maintenance of effect over 24 weeks in visitwise comparisons.

- The maintenance-of-effect results of Study HGKA were of the same magnitude of effect as those demonstrated in 4 oral olanzapine studies and support the strategy of evaluating OP Depot within the context of oral olanzapine.

3.3. Long-Term, Open-Label Treatment: Study HGKB

Study HGKB was designed to assess the long-term safety and efficacy of OP Depot (ranging from 45 to 405 mg at intervals ranging from 2 to 4 weeks) in the treatment of schizophrenia or schizoaffective disorder over a period of up to 4 years. Patients were treated in a way that would mimic clinical practice, with flexible dosing and supplementation with oral olanzapine (up to 20 mg/day) permitted in the study. Patients had to have completed 1 of 3 previous OP Depot studies (LOBS, HGJZ, or HGKA) prior to entering Study HGKB and were initiated at a dose of 210 mg/2 weeks for the first injection period, with flexible dosing within the range of 45 to 405 mg OP Depot and injection intervals within a range of 2 to 4 weeks thereafter. Figure 3.6 provides an illustration of the study design.
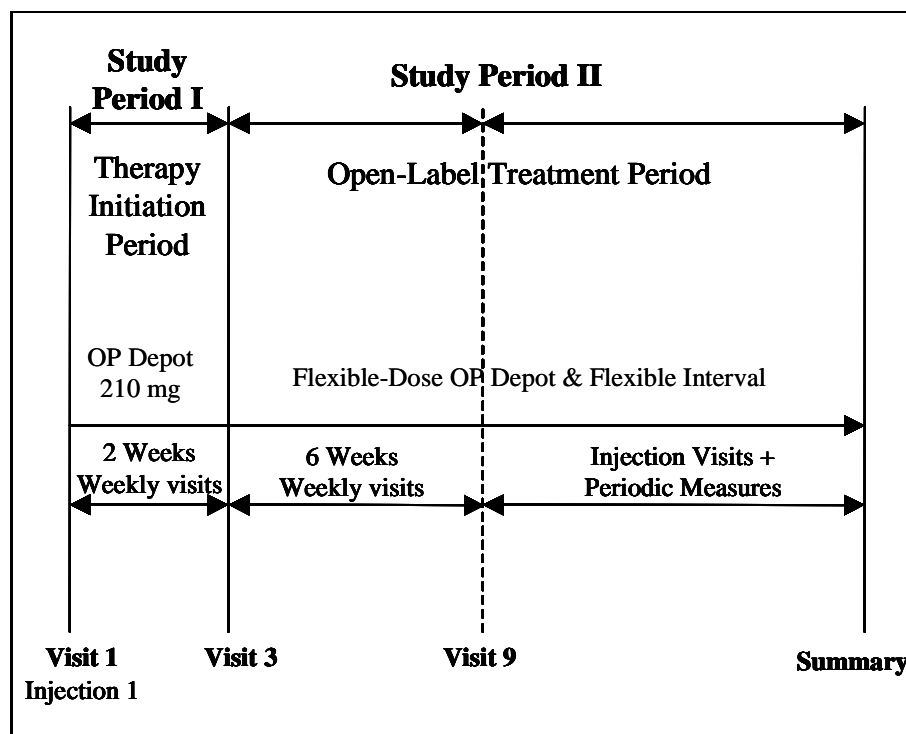
Figure 3.6.   **HGKB study design.**

Study HGKB doses were chosen to allow for continuity from all eligible feeder studies. The study is ongoing; however, results from an interim datalock with a data cutoff date of 30 June 2006 were provided to the FDA and included patients with up to 22 months of OP Depot treatment.

The primary objective of Study HGKB is to assess the long-term safety of OP Depot. The long-term efficacy of OP Depot was assessed based on the PANSS Total and Positive, Negative, and General Psychopathology subscales scores and on CGI-S score.

Analysis of study results thus far provides supportive evidence for the long-term efficacy of OP Depot.

A total of 880 patients were included in the interim report for Study HGKB. The majority of patients were male (66.7%) and Caucasian (66.7%), with a mean age of 39 years. The mean PANSS Total score at baseline was 56, indicating a population that was stable and minimally symptomatic.

Efficacy Analysis. In the efficacy analysis, maintenance of the clinical stability that was achieved during the patient's previous OP Depot study (LOBS, HGJZ, or HGKA) was demonstrated by changes from baseline to endpoint on the PANSS Total score and CGI-S scores. Overall, patients in Study HGKB showed mean improvements from baseline to endpoint on these measures:

- At endpoint, a statistically significant decrease from 56.28 to 54.90 was observed in PANSS Total score (p=.013), demonstrating that patients remained stable and minimally symptomatic.

- Analyses of CGI-S scores over time demonstrated persistence of effect, with CGI-S scores throughout the study ranging from 2.91 to 2.78, indicating minimal to mild illness severity.

Time to All-Cause Discontinuation as a Measure of Effectiveness. All-cause discontinuation of treatment is widely accepted as a measure of treatment effectiveness (Beasley et al. 2007) because it integrates patients' and physicians' overall evaluation of efficacy, safety, and tolerability into a global measure of the balance of benefits and risks. This measure was used as the primary outcome measure in the CATIE study (Lieberman et al. 2005).

Time to all-cause discontinuation in Study HGKB is presented below (Figure 3.7) using data up to 31 January 2007. Based on the Kaplan–Meier estimates, 27.8% of patients had discontinued from the study at one year. At 18 months, 34.0% of patients had discontinued.

PRODUCTION DATA – TEST MODE

Kaplan–Meier Time to Discontinuation
F1D–MC–HGKB: Data through 31JAN2007
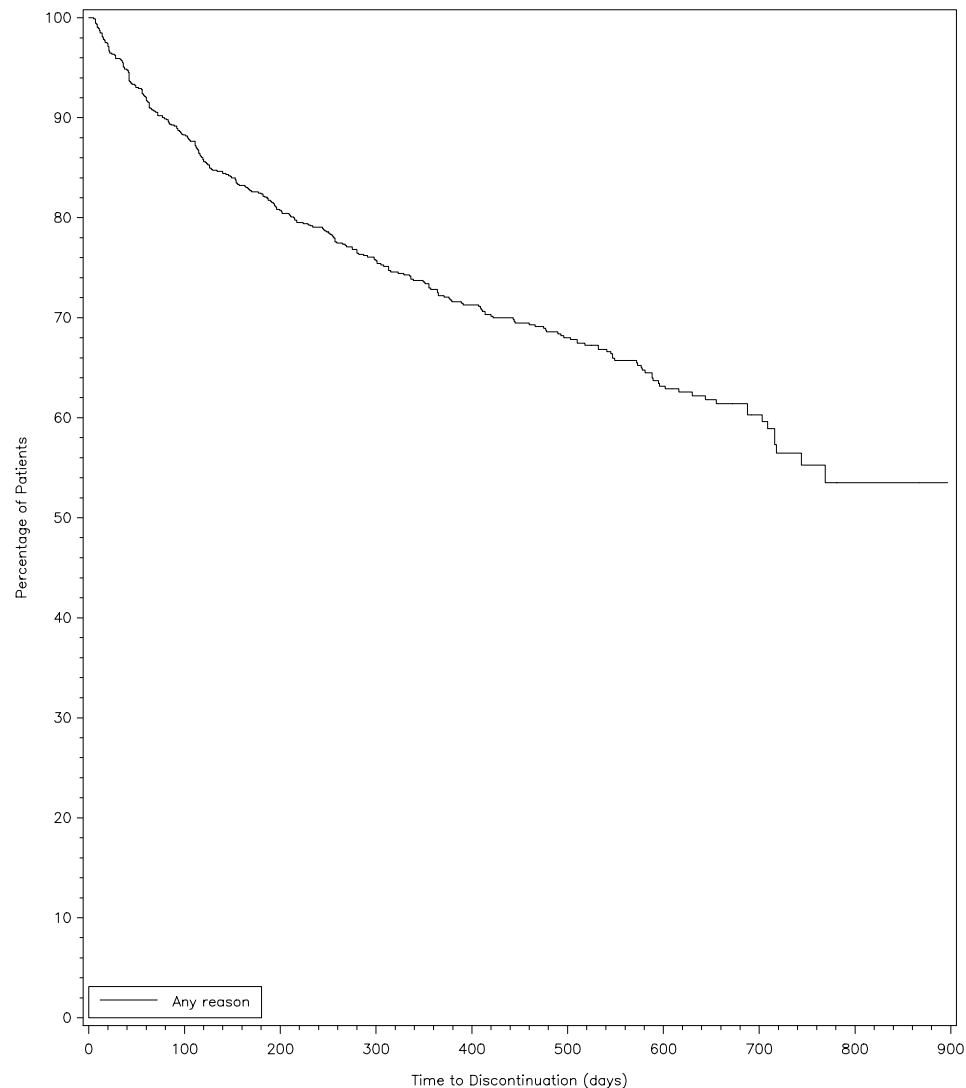
Program Name: RMP.F1DSHGKB.SASPGM(KMDISW22)
Output Location: RMP.F1DSHGKB.GRAPH(KMDISW22)

Figure 3.7.   Time to discontinuation, Study HGKB.

Patient Satisfaction. The Patient Satisfaction with Medication Questionnaire–Modified (PSMQ) was administered in Study HGKB. Although there are many limitations associated with measures of patient satisfaction, the PSMQ was administered in this study because patient satisfaction with treatment may affect treatment adherence and, thus, long-term outcome. The PSMQ was specifically designed to assess level of patient satisfaction with antipsychotic medications (Kalali 1999). Despite the practitioner belief that patients do not like receiving depot medications (Heres et al. 2006), the majority of patients (70.6%) in HGKB reported satisfaction with OP Depot; 69% reported that they preferred OP Depot over previous oral medications; and 71.6% reported experiencing

less impact from side effects on OP Depot compared with previous oral medications
(Figure 3.8).
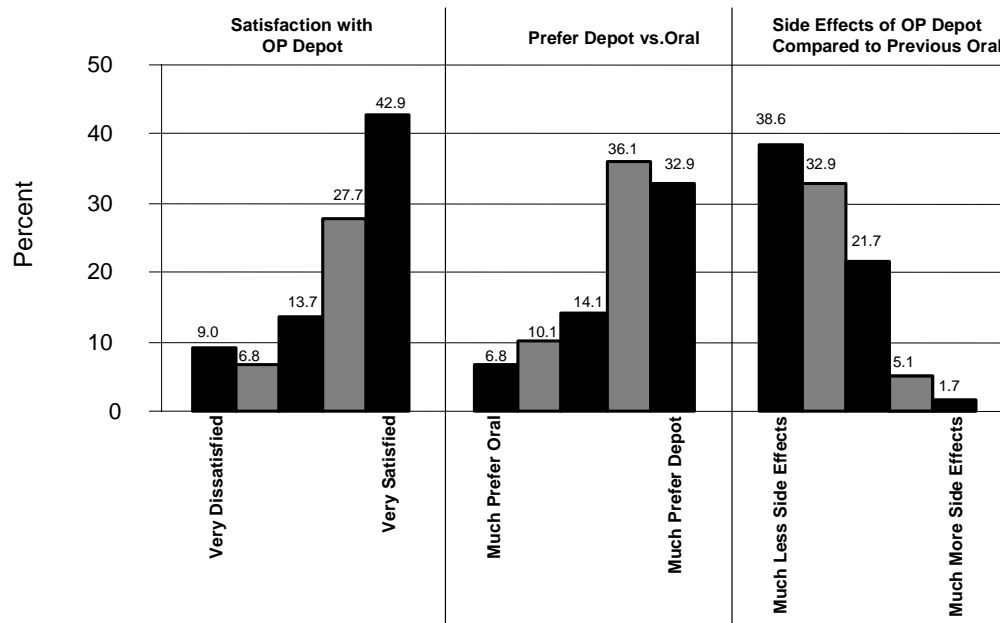
Figure 3.8.   **Patient-reported satisfaction with OP Depot, Study HGKB.**

Conclusions. Patients in Study HGKB showed maintenance of effect from baseline to
endpoint in PANSS and CGI scores, demonstrating maintenance of treatment effect
achieved in previous OP Depot studies. The rate of discontinuation from any cause was
low, at approximately 34% at 18 months. To put this in perspective, in the CATIE study,
64% of oral olanzapine-treated patients discontinued for any reason at 18 months, yet this
was the lowest discontinuation rate for all antipsychotics evaluated in the study (rates
ranged from 64% to 82%; Lieberman et al. 2005). Further, the majority of HGKB
patients reported satisfaction with OP Depot treatment, a preference for OP Depot
compared with previous oral medication, and fewer side effects with OP Depot treatment
compared with oral medications. Finally, flexible dosing was achieved within a range of
150 mg to 405 mg per injection and at dosing intervals of every 2 or 4 weeks, consistent
with determinations about treatment regimens in clinical practice.

3.4. Dosing Recommendations

The dose correspondence table (Table 3.1) presented previously in this efficacy section referred only to corresponding doses at steady state. That dose correspondence is supported by plasma olanzapine concentrations and is also consistent with mean daily dose as calculated by dividing the dose in milligrams by the number of days in the dosing interval. Clinical data also supported this correspondence based on examination of the statistically significant hazard ratios from the Study HGKA analyses, which compared risk of exacerbation relative to remaining on one's stabilized oral olanzapine dose after 24 weeks of treatment.

Examination of hazard ratios during the early period of depot treatment may represent a better clinical guide for determining the appropriate OP Depot dose at which to initiate treatment to ensure minimal risk of exacerbation. Based on analyses of Study HGKA at 2-months, an additional column was added to the dose correspondence table (Table 3.6) to provide guidance on an appropriate starting dose for patients.

Table 3.6.   **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

3.5. Efficacy Conclusions

OP Depot is an effective option for the treatment of schizophrenia and provides the following clinical benefits:

- Efficacy in acutely ill and stabilized patients, representing different phases in the longitudinal course of schizophrenia

- Robust acute efficacy, as early as 3 days post injection

- Long-term maintenance of treatment effect

- Efficacy for both the positive and negative symptoms of schizophrenia

- Low discontinuation rate over the long term. In Study HGKB, the all-cause discontinuation rate at 18 months was low (34%). The rate reported for oral olanzapine in the CATIE study (64%) was the lowest rate reported in all of the antipsychotics that were studied.

- Supplementation with oral antipsychotics was not needed to achieve or maintain efficacy.

- 4-week dosing with the option of shorter intervals

- OP Depot doses that provide olanzapine exposure similar to the full range of approved oral olanzapine doses

- The majority of patients reported satisfaction with OP Depot treatment, a preference for OP Depot compared to their previous oral treatment, and fewer side effects with OP Depot treatment compared with previous oral medications.

4.   Safety

Oral olanzapine is a well studied and widely used first-line therapy in the treatment of schizophrenia. The olanzapine clinical trial safety database is extensive and includes more than 12,000 patient exposures. The potential safety risks observed during treatment with oral olanzapine are well characterized and include hyperglycemia, hyperlipidemia, hemodynamic effects (orthostatic hypotension and syncope), hyperprolactinemia, elevations in transaminases, and weight gain. Sedation/somnolence is a common AE reported in patients during treatment with olanzapine. These potential safety risks were preselected for additional analyses as special safety topics in the OP Depot application in agreement with the FDA.

As previously noted (Section 2.1), the safety of OP Depot was evaluated in the context of oral olanzapine. Additionally, an oral olanzapine treatment arm was included in the maintenance-of-effect trial (HGKA), permitting comparisons between oral olanzapine and OP Depot.

This safety review will briefly summarize the results of the analyses performed for *general safety* parameters (AEs, laboratory tests, vital signs, electrocardiograms [ECGs], and extrapyramidal symptoms [EPS]) and for *special safety topics,* which included injection-site−related AEs. Overall, these analyses, which are summarized in Section 4.1, have shown that the safety profiles of OP Depot and oral olanzapine are generally comparable, with the exception of a new potential safety risk that emerged during clinical trials in OP Depot. The new potential safety risk, termed inadvertent intravascular (IAIV) injection events, is discussed extensively in Section 4.2, as the primary focus of this section on safety, and was analyzed as a *special safety topic* for the submission.

4.1.   Overview of OP Depot Safety

The safety of OP Depot has been evaluated in a total of 1918 patients with schizophrenia or schizoaffective disorder. Safety analyses were conducted in 3 databases: the Placebo-Controlled Database (N=404), the Olanzapine-Controlled Database (N=921), and the OP Depot Integrated Database (N=1918). The OP Depot Integrated Database included safety data from 2 controlled and 6 open-label studies as of 31 January 2007. Appendix 3 includes detailed information about each of the databases and a high-level discussion of key safety findings for general safety and special safety topic analyses. (Although the total number of patients in the OP Depot Integrated Database is 1918, 3 patients discontinued before receiving an injection; thus, 1915 patients received at least 1 injection of OP Depot.)

Safety analyses included mean changes from baseline to endpoint and the proportions of patients experiencing treatment-emergent potentially clinically significant (PCS) changes. The overall findings follow.

General Safety

- *Exposure.* The OP Depot Integrated Database includes 1915 patients who received at least 1 injection of OP Depot. The total number of injections is 27,210, and the total patient years of exposure are 1460.91. The longest exposure for a single patient is 951 days (approximately 2.6 years).

- *Discontinuations due to Adverse Events.* Discontinuations due to AEs were less than 6% in all databases, suggesting that OP Depot was generally well tolerated. In the controlled databases, no statistically significant differences were observed between OP Depot and oral olanzapine or between OP Depot and placebo in the overall incidence of discontinuations due to AEs or in the incidence of any specific AE as a reason for study discontinuation.

- *Deaths.* Three deaths (3/1918; 0.2%) were reported in patients receiving OP Depot. Causes of death (cardiomyopathy, leptospirosis, and essential hypertension) were determined by the investigators to be unrelated to study drug or study procedures.

- *Serious Adverse Events (SAEs) and Treatment-Emergent Adverse Events (TEAEs).* No statistically significant differences were observed between the OP Depot and oral olanzapine treatment groups or between the OP Depot and placebo treatment groups in the incidence of SAEs in the controlled databases. In the OP Depot Integrated Database, SAEs reported by 5 or more patients were related to symptoms of the underlying disease. Sedation was the only TEAE reported statistically significantly more often by OP Depot-treated patients than by placebo-treated patients.

- *Laboratory Analyses.* In the controlled databases, statistically significant differences in mean changes at endpoint were observed between treatment groups for several laboratory analytes, although absolute changes were small. As with oral olanzapine, increases in prolactin and fasting triglycerides were observed in patients during treatment with OP Depot. No statistically significant differences were observed between OP Depot- and oral olanzapine-treated patients for mean changes in prolactin or the incidence of treatment-emergent abnormal prolactin levels. A dose relationship was seen in the incidence of patients who experienced increased prolactin and elevated fasting triglycerides in Study HGKA. Patients treated with 300 mg/2 weeks OP Depot had statistically significantly higher mean changes in prolactin and a greater incidence of high fasting triglycerides postbaseline compared with the 405 mg/4 weeks and the 150 mg/2 weeks OP Depot dose groups; thus, as dose increased, mean changes in prolactin were greater and the percent of patients who met the criteria for high fasting triglycerides increased.

- *Vital Signs.* Vital sign findings for blood pressure and heart rate for patients treated with OP Depot were consistent with those seen for oral olanzapine in the Olanzapine-Controlled Database. No statistically significant differences between OP Depot and oral olanzapine were seen in the incidence of treatment-emergent orthostatic hypotension. In the Placebo-Controlled Database there were statistically significant differences between the OP Depot treatment group and placebo treatment group for supine pulse and weight; increases in weight have been reported in patients during treatment with oral olanzapine.

- *Weight.* Mean change in weight was not statistically significantly different for OP Depot-treated patients compared with oral olanzapine-treated patients in the Olanzapine-Controlled Database. A dose relationship was detected in the incidence of patients who gained at least 7% of their baseline weight in Study HGKA. Patients treated with 300 mg/2 weeks OP Depot had a statistically significantly higher mean increase in weight than did patients treated with 150 mg/2 weeks OP Depot.

- *ECG Measures.* No statistically significant differences were observed in the Olanzapine-Controlled Database between OP Depot- and oral olanzapine-treated patients in the incidence of potentially clinically significant changes from baseline in ECG intervals or heart rate.

- *EPS Measures.* No statistically significant differences were observed between OP Depot- and oral olanzapine-treated patients in mean change from baseline or incidence of patients with treatment-emergent parkinsonism, akathisia, or dyskinesia in the Olanzapine-Controlled Database. OP Depot-treated patients had a small but statistically significantly greater mean improvement on both the Barnes Akathisia Global and Abnormal Involuntary Movement Scale (AIMS) scales compared with placebo-treated patients in the Placebo-Controlled Database.

Special Safety Topic Analyses

- The incidence (8.4%) of injection-site–related AEs in the OP Depot Integrated Database was consistent with the incidence (8%) of injection-site–related AEs reported in the literature (Hamann et al. 1990). Injection-site pain was the most frequently reported (5.3%); all other injection-site–related AEs were reported in <1% of OP Depot-treated patients. Most events were reported to be of mild severity. The rate of discontinuations due to an injection-site–related AE in the OP Depot Integrated Database was low (4/1915; 0.2%).

- The special safety topic analyses for cardiovascular, metabolic, and hepatic measures did not reveal any new safety findings for any of these parameters during treatment with OP Depot that have not been previously reported during treatment with oral olanzapine. Dose relationships for weight, prolactin, and fasting triglycerides were addressed in the general safety findings (see above).

4.2. IAIV Injection Events

Sedation is a very commonly observed AE in patients treated with oral olanzapine. In OP Depot clinical trials, an unanticipated degree of sedation was reported in a small number of patients close in time following an injection. Given the unexpected degree of sedation, these events were further evaluated. The following sections provide an accounting of the events (IAIV injection events) and the evaluations that have been conducted.

- Section 4.2.1 provides a sampling of the events and evaluations of patient data.

- Section 4.2.2 summarizes the investigations that have been performed to identify the root cause of these events.

- Section 4.2.3 provides a brief overview of similar events in the literature, which provides a context for determining background rates for these events.

- Section 4.2.4 summarizes Lilly's belief about the mechanistic basis for these events.

- Section 4.2.5 summarizes the overall findings for IAIV injection events.

- Section 4.3 describes Lilly's risk management plan for these events.

The name "IAIV" was chosen for this event because this term is commonly used in product labeling for other drug products that carry this risk. Importantly, this term conveys the necessary public health message that OP Depot should not be injected intravascularly because it could result in this AE.

4.2.1. Patient Data

4.2.1.1. Sampling of Cases

Lilly physicians routinely monitor and evaluate safety information for all patients participating in clinical trials. Two SAEs of profound sedation occurred a few days apart in December 2004. In both cases, the events of sedation were observed in the first hour after the patient received an OP Depot injection. Lilly physicians therefore reviewed case records surrounding these events and *all* SAEs and TEAEs reported in OP Depot clinical trials. Similar events were identified, and ongoing surveillance ensued to quickly understand and characterize the clinical manifestations of these events.

As of 30 November 2007, a total of 25 of these events have been reported in 24 patients. These events are believed to be secondary to IAIV injection, a known complication of intramuscularly delivered medications. The clinical presentation, the proximity in time to injection, and the olanzapine concentrations in the 7 cases in which plasma concentrations were measured further support this etiology, which is discussed in more detail in Section 4.2.4.

Thirteen (13) of the 25 cases are briefly discussed below to provide the reader with a clear sense of the clinical presentation of these events. The initial 3 cases are presented first, followed by additional cases that were selected for discussion because of the severity of symptoms or the time to onset. Finally, the sampling of cases is followed by a tabular overview of all 25 cases, organized by case number (Table 4.2).

The First Three Cases. Although a prominent symptom of these early cases included an unanticipated degree of sedation, other signs and symptoms were noted and included dizziness, confusion (delirium), altered or involuntary movements (primarily of the legs and arms), and general feelings of malaise. All 3 of these patients recovered within 60 hours of the start of the event. Two of the cases (Cases 2 and 3) are among the more severe of the 25 events that have been identified in 24 patients as of 30 November 2007.

- Case 1: A 31-year-old male experienced an AE of severe sedation approximately 45 minutes after receiving his second injection of 300 mg/4 weeks OP Depot. The same day (relative onset was not specified), the patient also experienced moderate akathisia and mild dizziness. According to the case report form comments, the patient experienced weakness, sleepiness, and tension in his legs; he was slightly disoriented, spoke briefly, and immediately fell asleep. Six hours after the injection, he felt better but was still experiencing sleepiness. The patient was given biperiden. Vital signs recorded before the injection, approximately 6 hours post injection, and the day after the injection were within clinically acceptable ranges. The study included olanzapine plasma sampling. The olanzapine plasma concentration measured at 6 hours post injection was unexpectedly elevated. The next day, sedation had decreased in severity to mild, and the akathisia and dizziness had both resolved. The olanzapine plasma concentration measured 24 hours post injection was decreased. Sedation was fully resolved 48 hours after the injection. The patient's dosage was subsequently lowered to 200 mg/4 weeks. He completed the 6-month study.

- Case 2: A 32-year-old male experienced an SAE of profound sedation 10 minutes after receiving his first injection of 405 mg/4 weeks OP Depot. The patient experienced dizziness and "a bad general state". His speech progressively altered, and somnolence appeared. After 1.5 hours, he stopped responding to verbal stimuli. Examination after 2 hours showed profound sedation, bilateral miosis with no photomotor reflex, automatic movements, Babinski on the left side, no response to verbal or painful stimuli, and heart rate of 110 beats per minute (bpm). The patient was admitted to the hospital, where the report mentions diminished reflexes, walk possible only with external assistance, positive Babinski, uncooperative, and somnolent. The patient was managed with intravenous fluids and was administered mannitol, piracetamum, infesol, and cerebrolysin. The following morning, the patient was able to speak, but with difficulty. Approximately 48 hours after the injection, the sedation had resolved, and only somnolence remained. Approximately 60 hours after the injection, the patient was fully recovered and was discharged from the hospital with a diagnosis of confusional syndrome post drug. Blood pressure, heart rate, CT Scan, urinary output, and temperature were all normal during hospitalization. The patient was discontinued from the study.

- Case 3: A 63-year-old male experienced the SAEs of severe confusional state and moderate seizures in the hands and legs after his second OP Depot injection. Approximately 15 to 20 minutes after a 405 mg/4 weeks OP Depot injection, the patient appeared pale and yellowish, had an unsteady gait, and was slightly confused. According to the investigator, approximately 30 minutes post injection, the patient experienced seizures in hands and legs, "the patient's movements were difficult to describe but appeared as clonic movements of the limbs without loss of consciousness, accompanied by disorientation and psychomotor agitation". The patient wanted to sleep but answered questions. These symptoms continued for approximately 40 minutes before the patient was transferred to the hospital. His vital signs before hospitalization were reported to be within normal ranges. The patient was administered intravenous benzodiazepines, haloperidol, and promethazine and was ventilated as a preventive measure. There was no report of the patient having experienced respiratory depression at any time. The patient was extubated shortly after being intubated. An EEG, an ECG, a CT Scan, and a lumbar puncture were reported to be normal. At 2 unspecified times during hospitalization, the patient's blood pressure was slightly elevated (140/100 mm Hg and 160/90 mm Hg). General laboratory and a drug urine screen showed no abnormalities. The patient was discharged from the hospital approximately 48 hours after the OP Depot injection, and the event was resolved within 60 hours post injection. The hospital discharge summary stated that the patient suffered from tonic clonic convulsions with partial consciousness. The patient was discontinued from the depot-treatment phase of the study.

Cases Involving Intubation. Like Case 3 above, another of the 25 cases (Case 14) involved intubation and was among the more severe of the cases. There was no report of this patient having experienced respiratory depression at any time.

- Case 14: A 56-year-old female experienced the SAEs of malaise, loss of consciousness, agitation, and somnolence after receiving a 210 mg/4 weeks OP Depot injection (25th injection). The patient left the site approximately 20 to 25 minutes after the injection. Approximately 75 minutes after the injection, she "experienced malaise in the street" and was admitted to the hospital with loss of consciousness. The patient experienced agitation, somnolence, dysarthria, and sweating. She was noted to have good response to stimuli, and no fever, neurological deficit, hemodynamic changes (except for a heart rate of 120 bpm), or respiratory depression. An ECG revealed tachycardia (114 bpm). A CT brain scan, lumbar puncture, EEG, and blood toxicology screen were negative. Because of persistence of agitation, the patient was given intravenous midazolam and was then intubated and ventilated for investigations to be performed. "Chemical sedation" was continued until the following day. During the night, bradycardia and hypotension were recorded and managed with intravenous fluid restitution. The following day, the patient was extubated. She was discharged within 60 hours after the injection, fully recovered, and continued in the study.

Cases of Interest due to Longer Time to Onset. The reported time of onset in 4 of the 25 cases was later than 60 minutes after the injection of OP Depot was received. These 4 cases include the case described above (Case 14), where the exact time of onset is unknown, but onset could have been as early as 25 minutes after injection. The 3 remaining cases are briefly summarized below. The onset of symptoms in 2 of these cases (Case 12, Case 17) was significantly later than in any of the other cases, occurring almost 3 hours after injection.

- Case 12: A 57-year-old male experienced an SAE of profound sedation after his second injection of 210 mg/2 weeks OP Depot. As reported to the investigative site by the patient's wife, approximately 3 hours after the injection, the patient experienced profound sedation (reported as "difficult to contact"), weakness, difficulty talking, and difficulty with communication but was not unconscious. The patient was at home. The event resolved after 3 hours with no hospitalization or corrective treatment. He continued in the study.

- Case 16: A 36-year-old male patient received his 17th injection of 405 mg/4 weeks OP Depot. Approximately 75 to 105 minutes post injection, he experienced somnolence, followed 60 to 90 minutes later by fatigue, inconsistent speech, mumbling, and "automatisms" such as picking up invisible things on the floor (pseudo-delirium). The event occurred during the 3-hour observation period. All vital signs recorded during this time were in the normal range. The investigator diagnosed a confusional state requiring overnight hospitalization. The neurological examination was unremarkable. The patient fell asleep at 4 hours post injection. Monitoring of vital organ function continued throughout the night; all was within normal limits except for one blood pressure determination performed at 5.52 a.m. the following morning (157/109 mm Hg). No other remarkable findings were reported. No corrective treatment was taken. Patient fully recovered within 24 hours. The patient was discharged from the hospital. At the next study visit, the patient stated that he had drunk 1 liter of beer on the same day that he had experienced the IAIV injection event. He continued in the study.

- Case 17: A 59-year-old female experienced the SAE of "profound sedation" of moderate severity after her 27th injection of OP Depot. At approximately 2 hours and 45 minutes following a 300 mg/2 weeks OP Depot injection, the patient, while still at the investigative site, experienced significant somnolence. After presenting with initial somnolence, she reported that she had taken 4 mg of unprescribed clonazepam 8 hours before the OP Depot injection. She was not reported to be sleepy or drowsy prior to the injection. At approximately 3 hours post injection, the patient experienced difficulty in speech but continued to be alert and oriented and displayed motor restlessness. Approximately 6 to 7 hours post injection, she presented with profound sedation and was unarousable for a period of 8 hours, although she did respond to painful stimuli. This event was considered serious because of the profound sedation. Vital signs were normal during the event, and laboratory tests taken at the visit were also normal. No corrective treatments were reported. The sedation lasted approximately 15 hours, and the patient was hospitalized in the observation area. She continued in the study.

Patients Who Left the Site before 60 Minutes. A sampling of cases in which the patient left the site before 60 minutes had elapsed post injection are summarized below.

- Case 6: A 51-year-old male experienced the SAE of coma. The patient received a 300 mg/2 weeks OP Depot injection (24th injection), left the site after 10 minutes, and approximately 50 minutes later, was found "in coma". According to the investigator, the patient was riding on a bus when he started to feel unwell. He got off the bus and was later found on a bench in a public plaza. The patient was hospitalized and remained unconscious and unresponsive to verbal stimuli for approximately 12 hours. Vital signs, laboratory tests, and ECG measurements were reported to be normal. Approximately 22 hours after the injection, the patient recovered and was discharged from the hospital. Upon questioning later, the patient described feeling unwell prior to losing consciousness. He continued in the study.

- Case 10: A 43-year-old male experienced an SAE of sedation. He received an injection of 405 mg/4 weeks OP Depot (20th injection), then returned immediately to work. Within 30 minutes of the injection, he became irritable and reported feeling badly. Approximately 60 minutes after receiving the injection, the patient was noted to have somnolence, dysarthria, and irritability. His coworkers contacted the site and were told to return him to the site. He was returned to the site and had difficulty walking and was sedated. Approximately 2 hours and 30 minutes after the injection, the patient was transferred to the emergency room for observation. Vital signs, laboratory tests, urine toxicology screen, ECG, and neurological exploration were normal. No treatment was performed. Olanzapine plasma concentrations were elevated. Approximately 24 hours after the injection, the patient was fully recovered and discharged from the hospital. He continued in the study.

- Case 13: A 23-year-old male experienced the SAEs of severe confusion and severe dizziness. Immediately after an injection of 270 mg/4 weeks OP Depot (12th injection), the patient complained of feeling weak and dizzy and that he had a headache. The patient stated that he had been working outside in the heat and had not eaten or drunk anything all day. The investigator instructed him to go get something to eat and come back to the site. The patient left the site 45 minutes post injection and purchased a sandwich and was starting to eat when he felt unwell. He began staggering and entered a bar but was turned away because he appeared to be drunk. A shopkeeper then contacted emergency services. The patient was admitted to the emergency room in a state of confusion and dizziness approximately 3 hours after the injection. Vital signs and oxygen saturation were reported to be normal. The Glasgow coma score was assessed as between 13 and 14, and neurological examination revealed confusion and disorientation. Electrocardiogram, cardiopulmonary examination, chest x-ray, laboratory tests, and CT brain scan were all normal, and blood ethanol was negative. Approximately 21 hours after the injection, the patient had fully recovered. He continued in the study.

Patient Who Experienced Two Events. One patient experienced two IAIV injection events. He is the only patient to have experienced the event more than once, and these events occurred approximately 6 months apart. Both episodes in this patient (Cases 5 and 8) are described together below.

- Case 5 and Case 8: A 49-year-old male experienced an SAE of severe change in mental status (Case 5) after receiving an injection of 250 mg/2 weeks OP Depot (22nd injection). Approximately 1 hour after the injection, the patient returned to the unit in what appeared to be a "drunken state", with unsteadiness and slurred speech. The patient was hospitalized, was having difficulty ambulating, and was incontinent of urine while in the hospital. Laboratory tests, urine drug screen, alcohol screen, and head CT scan were all reported to be negative. The only vital signs reported for this patient were taken at the hospital 2 days after the event; all measurements were normal. Olanzapine plasma concentrations were elevated on the day of the event. Approximately 48 hours after the injection, the patient appeared normal, and the changes in mental status had resolved. The patient later reported that he had drunk 3/4 pint of whiskey the evening before the injection. The patient continued in the study and experienced a second SAE reported as change in mental status approximately 6 months later (Case 8). Within 15 minutes of receiving 250 mg/2 weeks OP Depot (35th injection), the patient began to have slurred speech and an unsteady gait. His symptoms progressed to the point that he could not speak clearly and could not ambulate without assistance. The patient was hospitalized; all vital signs that were reported were within normal limits during this period, and no corrective treatment was noted. Olanzapine plasma concentrations were measured and judged to be elevated during the event. The patient recovered and was discharged from the hospital approximately 72 hours after the injection. The patient discontinued the study at the discretion of the investigator because of this second SAE.

Case of Sustained High Blood Pressure Determinations. One patient experienced sustained high blood pressure determinations during an IAIV injection event.

- Case 24: A 53-year-old male experienced confusion after receiving his 40th OP Depot injection, which was 330 mg/4 weeks. His medical history revealed untreated hypertension for the year prior to the event. The day of the event, the patient's blood pressure was elevated at 140/90 mm Hg prior to the injection. Thirty minutes postinjection, his blood pressure increased to 180/90 mm Hg, with a heart rate of 96 bpm. Forty-five minutes post injection, he complained of headache and stomachache; paracetamol (acetaminophen) was administered. His blood pressure was 160/100 mm Hg. He became restless, and dysarthria was observed. Sixty minutes post injection, the patient was confused, ataxic, with continued restlessness. Blood pressure was 190/110 mm Hg, and the patient's heart rate was 100 bpm. At 1.75 hours post injection, the patient's blood pressure was 210/110 mm Hg and his heart rate was 112 bpm. Enalapril and captopril were administered, and within 20 minutes, the patient's blood pressure and heart rate decreased to 170/90 mm Hg and 96 bpm, respectively. The patient was transferred to the emergency room and was admitted to the hospital for events that were later termed "confusion" and "arterial hypertension". Because of restlessness, the patient was administered intravenous diazepam and slept, which made it difficult for the investigator to assess the exact time of event resolution. The patient was also diagnosed with a urinary tract infection. No pharmacological long-term management for hypertension was given. This patient had experienced slight elevations in blood pressure at 15 and/or 30 minutes post injection on at least 5 previous occasions before experiencing the IAIV injection event. The patient recovered within 60 hours of the injection. He did not receive any other OP Depot injections and was later discontinued from the study because of this event.

4.2.1.2. Summary of IAIV Injection Events

A total of 34,825 injections have been given to 2006 patients in OP Depot clinical trials as of 30 September 2007. The incidence of IAIV injection events is therefore 0.07% of injections, or 1.2% of patients. On average, these events occurred after the patient had received several months of injections (median number of injections was 17) 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. Characteristics of patients experiencing IAIV injection events are summarized below (Table 4.1).

Table 4.1.   **Summary of Patient Characteristics**
IAIV Patients and All OP Depot Patients

Characteristic	IAIV Patients (N=24)	All OP Depot Patients (N=1918)
Gender		
Male	18 (75.0)	1306 (68.1)
Female	6 (25.0)	612 (31.9)
Origin		
Caucasian	20 (83.3)	1260 (65.7)
African	2 (8.3)	291 (15.2)
Hispanic	2 (8.3)	247 (12.9)
Other	0 (0.0)	120 (6.2)
Age in Years		
Mean	43.13	39.41
Maximum	63.49	74.12
Minimum	23.84	18.10
Standard Deviation	11.21	11.02

Abbreviations: IAIV = inadvertent intravascular; OP = Olanzapine Pamoate.

The AEs that have been reported by 5 or more patients during an IAIV injection event are sedation, confusion/confused state, dizziness, altered speech/dysarthria, and somnolence. All of these symptoms are consistent with AEs reported in patients experiencing oral olanzapine overdose; however, not all of the symptoms reported with oral olanzapine overdose have been seen in patients during an IAIV injection event. For example, in none of the IAIV injection events to date have orthostatic hypotension, arrhythmias, cardiac arrest, or decreased respiration been reported. Oral olanzapine overdose is discussed in more detail below (Section 4.2.2.5).

Several observations about these IAIV injection events are listed below.

- Typically, these events have occurred within 1 hour of the injection (21/25; 84%).

- The median time to onset is 20 minutes and has ranged from immediately post injection to within 3 hours of the injection.

- Twenty (20) of the 24 patients who have experienced an event were hospitalized or seen in the emergency room.

- To date, all patients have fully recovered from an IAIV injection event within 3 to 72 hours and without permanent sequelae.

- The majority of patients (16/24; 67%) who have experienced an event have continued to receive OP Depot injections.

Table 4.2 summarizes all 25 IAIV injection event cases. New cases and updated information on existing cases are reported to the FDA on an ongoing basis. All of the cases that have been identified as of 30 November 2007 are presented in the tabular

display below, by case number. (Note that the case numbers for the sampling of cases in Section 4.2.1.1 are the same as those in the table.)

Table 4.2.   **Summary of IAIV Injection Events Occurring through 30 November 2007**

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 1	31-year-old male	Inj #2 Apr 2001	300 mg/4 weeks 45 min	No	45 min after inj, patient experienced AEs of severe sedation, moderate akathisia (described as tension in legs), and mild dizziness. Patient also described feeling weakness. Patient was disoriented, spoke briefly, and immediately fell asleep. 6 hours after inj, patient still sleepy but felt better. Patient given biperiden. **Recovered approx 48 hr; Continued in study**
Case 2	32-year-old male	Inj #1 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 IV fluids, given mannitol, piracetamum, infesol, and cerebrolysin. Able to speak next morning, but with difficulty. **Recovered approx 60 hr; Discontinued study**
Case 3	63-year-old male	Inj #2 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. According to the investigator, patient experienced seizures in hands and legs, "the patient's movements were difficult to describe but appeared as clonic movements of the limbs without loss of consciousness, accompanied by disorientation and psychomotor agitation". Sent to hospital. Treated with IV benzodiazepines, haloperidol, and promethazine. Hospital diagnosed as tonic clonic convulsions with partial consciousness. Ventilated as preventive measure. Extubated shortly thereafter. **Recovered approx 60 hr; Discontinued depot; Completed study**

(continued)

Table 4.2.   **Summary of IAIV Injection Events Occurring through 30 November 2007 (Continued)**

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 4	30-year-old male	Inj #4 Mar 2005	405 mg/4 weeks Approx 60 min	Yes	Patient appears to have presented himself at hospital. Approx. 1 hr post inj, patient experienced sedation. Became drowsy and irritable, disoriented times 3. Also felt stiff and weak in legs. Stated that he passed out for a while, was very confused, slightly febrile (100.6°F). **Recovered approx 24 hr; Continued in study**
Case 5	49-year-old male	Inj #22 Oct 2005	250 mg/2 weeks Within 60 min	Yes	Patient 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. Patient reported drinking ¾ pint whiskey the evening before the inj. **Recovered approx 48 hr; Continued in study**
Case 6	51-year-old male	Inj #24 Dec 2005	300 mg/2 weeks Within 50 min	Yes	Patient left the site after 10 minutes, and approximately 50 minutes later, was found "in coma". According to the investigator, the patient was riding on a bus when he started to feel unwell. He got off the bus and was later found on a bench in a public plaza. Patient was hospitalized and remained unconscious and unresponsive to verbal stimuli for approximately 12 hours **Recovered approx 22 hr; Continued in study**
Case 7	31-year-old female	Inj #11 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**
Case 8	49-year-old male	Inj #35 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. Vitals normal; no treatment. **Recovered approx 72 hr; Discontinued study**

(continued)

Table 4.2.   Summary of IAIV Injection Events Occurring through 30 November 2007 (Continued)

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 9	34-year-old male	Inj #29 May 2006	300 mg/4 weeks 5 min	Yes	Patient 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 patient Coke to drink. Patient confused, disoriented, ataxic (as if drunk). 30 min post inj, glucose was 275 mg/dL. Site laid patient 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**
Case 10	43-year-old male	Inj #20 Jun 2006	405 mg/4 weeks 30 min	Yes	Patient returned to work soon after injection. Within 30 min post inj, felt bad. Approx 60 min post inj, patient noted to have somnolence, dysarthria, and irritability. Coworkers contacted and returned patient to the site. Patient had difficulty walking and became sedated. Sent to hospital for observation. **Recovered approx 24 hr; Continued in study**
Case 11	43-year-old female	Inj #27 Jun 2006	100 mg/2 weeks 10 min	Yes	10 min post inj, patient experienced weakness, dizziness, slurred speech, and profound sedation (described as slightly decreased level of consciousness). **Recovered approx 48 hr; Continued in study**
Case 12	57-year-old male	Inj #2 Jun 2006	210 mg/2 weeks Unspecified. Within 3 hr	No	3 hr post inj, felt weak. Wife contacted site, reported that patient experiencing profound sedation, weakness, slurred speech. Not unconscious. Patient remained at home. **Recovered approx 3 hr; Continued in study**

(continued)

Page 51

Table 4.2.　　　　　Summary of IAIV Injection Events Occurring through 30 November 2007 (Continued)

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 13	23-year-old male	Inj #12 June 2006	270 mg/4 weeks Immediately post injection	Yes	Immediately post inj, patient 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. Patient got sandwich on street and as started to eat, felt unwell. Began staggering; attempted to go into bar but was turned away, as appeared drunk. Shopkeeper called emergency medical services. 3 hours post inj, admitted to hospital confused and dizzy. Tests neg. **Recovered approx 21 hr; Continued in study**
Case 14	56-year-old female	Inj #25 Jul 2006	210 mg/4 weeks Unspecified. Within 75 min	Yes	Patient refused to stay at site. Left 20–25 min post inj. Experienced malaise 75 min post inj and admitted to hospital with loss of consciousness. There experienced agitation, somnolence, dysarthria, and sweating. Mild tachycardia (114 bpm). Due to persistence of agitation, given IV midazolam and intubated and ventilated to perform tests. Patient extubated and released. **Recovered approx 60 hr; Continued in study**
Case 15	40-year-old male	Inj #7 Jul 2006	300 mg/3 weeks 15 min	Yes	15 min post inj, became confused and weak. 1 hr 30 min post inj, condition worsened; patient was stunned, had deep sedation, with loss of consciousness. Recovered after 3 hours. (Seen by anesthetist.) **Recovered approx 3 hr; Discontinued from study**
Case 16	36-year-old male	Inj #17 Dec 2006	405 mg/4 weeks 75 to 105 min	Yes	75 to 105 min post inj, patient experienced somnolence (during 3-hr observation period). 60 to 90 min later, patient experienced fatigue, inconsistent speech, mumbling, and automatism (picking up invisible things on floor [pseudo-delirium]). Hospitalized overnight for confusional state. Patient later reported drinking 1 liter of beer prior to injection. **Recovered approx 24 hr; Continued in study**

(continued)

Page 52

Table 4.2.   **Summary of IAIV Injection Events Occurring through 30 November 2007 (Continued)**

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 17	59-year-old female	Inj #27 Jan 2007	300 mg/2 weeks 2 hours and 45 min	Yes	2 hr 45 min post inj, patient experienced significant somnolence. Patient took 4 mg unprescribed clonazepam 8 hr prior to injection (but did not appear drowsy when arrived at site). Approximately 3 hours post inj, patient experienced difficulty in speech, but continued to be alert and oriented, and displayed motor restlessness. 6 to 7 hrs post inj, presented with profound sedation; unarousable for 8 hours. Responsive to pain. Awoke next morning. **Recovered approx 15 hr; Continued in study**
Case 18	26-year-old male	Inj #17 Mar 2007	345 mg/4 weeks 30 min	Yes	30 min post inj, patient experienced dizziness, gummy legs, and insecurity while standing. Symptoms slowly increased, progressing to deep sedation, reported to be like deep sleep but patient could always be aroused by speaking to him loudly. Hospitalized for monitoring and hydration. **Recovered approx 24 hr; Discontinued from study**
Case 19	38-year-old female	Inj #16 Jan 2007	390 mg/4 weeks 5 min	No	5 min post inj, experienced somnolence that worsened gradually, but patient 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, patient was sent home with a friend in an improved but still slightly somnolent state. **Recovered approx 72 hr; Discontinued from study**
Case 20	48-year-old female	Inj #15 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 patient was able to be observed by staff there until recovered. **Recovered approx 16 hr; Continued in study**

(continued)

Table 4.2.   **Summary of IAIV Injection Events Occurring through 30 November 2007 (Continued)**

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 21	50-year-old male	Inj #35 May 2007	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**
Case 22	50-year-old male	Inj #20 Jun 2007	360 mg/4 weeks 10 min	Yes	10 min post inj, became somnolent, confused, and cramps developed. Patient 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 4 hrs of observation. Patient did not urinate despite attempts, so was catheterized. Cramps of moderate severity localized in arms & legs. **Recovered approx 24 hr; Discontinued from study**
Case 23	45-year-old male	Inj #17 Jun 2007	405 mg/4 weeks Within 30 min	Yes	Patient complained of dizziness prior to injection, probably due to fasting. Symptoms reportedly worsened. Patient ate 15 to 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. Patient 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**

(continued)

Page 54

Table 4.2.   **Summary of IAIV Injection Events Occurring through 30 November 2007 (Concluded)**

Event Number	Age, sex	Injection #/ Date of Event	Dose/ Postinjection Onset	Patient Hospitalized?	Description of Event/Duration/ Disposition
Case 24	53-year-old male	Inj #40 Jul 2007	330 mg/4 weeks 30 min	Yes	His medical history revealed untreated hypertension for the year prior to the event. Prior to injection BP of 140/90 mm Hg. Thirty minutes postinjection, his blood pressure increased to 180/90 mm Hg. Forty-five minutes post injection he complained of headache and stomachache. Sixty minutes post injection patient was confused, ataxic, with continued restless. Highest blood pressure was 210/110 mm Hg managed and resolved with enalapril and captopril. Because of restlessness, the patient was administered IV diazepam and slept. Diagnosed with UTI. **Recovered approx 60 hr; No further inj; later disc for this event**
Case 25	34-year-old male	Inj #36 Aug 2007	405 mg/4 weeks 15 min	Yes	Patient 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 patient 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**

Abbreviations: # = number; AE = adverse event; approx = approximately; BP = blood pressure; bpm = beats per minute; cont'd = continued; CRA = clinical research associate; hr = hour; HR = heart rate; IAIV = inadvertent intravascular; inj = injection; IV = intravenous; min = minutes; neg = negative; PI = primary investigator; psych = psychiatric; SAE = serious adverse event; UTI = urinary tract infection.

4.2.1.3. Sedation- and Delirium-Related Adverse Events

Incidences of sedation- and delirium-related AEs were evaluated to determine whether these events were more common in OP Depot-treated patients than in oral olanzapine-treated patients. The therapeutic OP Depot dose groups in Study HGKA were pooled for this analysis.

As shown in Table 4.3, no statistically significant difference was observed between OP Depot- and oral olanzapine-treated patients in the overall incidence of these AEs (total) or by individual event. In addition, the severity and timing of these events (time to onset within the injection cycle) were analyzed separately (not shown in the table), and similar results were seen in both treatment groups. Data regarding the timing of these events were included in the IAIV injection event special safety topics report that was submitted with the application to the FDA.

The findings demonstrated no differences in the incidence or timing of sedation- and delirium-related TEAEs between the OP Depot and oral olanzapine treatment groups. Thus, with the exception of the 25 cases of IAIV injection events, the overall patterns of sedation and delirium observed during OP Depot treatment do not differ from those seen during oral olanzapine treatment.

Table 4.3.   **Treatment-Emergent Sedation- and Delirium-Related Adverse Events Olanzapine-Controlled Database**

Event Term	OP Depot N	n (%)	Oral Olz N	n (%)	Total N	n (%)	p-Value
Patients with >= 1 TEAE	599	51 (8.5)	322	23 (7.1)	921	74 (8.0)	.526
Somnolence	599	23 (3.8)	322	9 (2.8)	921	32 (3.5)	.456
Fatigue	599	12 (2.0)	322	7 (2.2)	921	19 (2.1)	.814
Sedation	599	7 (1.2)	322	2 (0.6)	921	9 (1.0)	.507
Asthenia	599	5 (0.8)	322	1 (0.3)	921	6 (0.7)	.671
Hypersomnia	599	3 (0.5)	322	2 (0.6)	921	5 (0.5)	1.00
Disorientation	599	2 (0.3)	322	1 (0.3)	921	3 (0.3)	1.00
Apathy	599	2 (0.3)	322	0 (0.0)	921	2 (0.2)	.545
Disturbance in attention	599	2 (0.3)	322	0 (0.0)	921	2 (0.2)	.545
Malaise	599	0 (0.0)	322	2 (0.6)	921	2 (0.2)	.122
Confusional state	599	1 (0.2)	322	0 (0.0)	921	1 (0.1)	1.00
Prostration	599	1 (0.2)	322	0 (0.0)	921	1 (0.1)	1.00

Abbreviations: n = number of patients with TEAE; N = number of patients adjusted for gender-specific events; OP Depot = Olanzapine Pamoate Depot (pooled from 210mg/2weeks, 300mg/2weeks, 405mg/4weeks); TEAE = treatment-emergent adverse event.
Frequencies are analyzed using Fisher's Exact Test.

4.2.1.4.   Analysis of Patient Data from the 3-Hour Observation Period

In 2006, protocols for ongoing OP Depot studies were amended to include a 3-hour on-site observation period following each injection that included recording of AEs and assessment of mental status and vital signs at specified intervals. The purpose of these amendments was to collect additional patient data in the hours following injection to help characterize the clinical presentation and progression of the IAIV injection events as they occurred.

In 2007, an analysis of data collected during the 3-hour observation period was performed for a safety update that was submitted to the FDA. These data demonstrated that assessment of mental status ("Is patient alert, oriented, and absent of symptoms of olanzapine overdose?") prior to a patient's release from the site was an effective method for identifying potential IAIV injection events. Patients identified as experiencing an IAIV injection event after the protocol amendments had been instituted and up to the datalock for this analysis (31 January 2007) were appropriately identified by the postinjection mental status assessment.

Findings from this review indicated no notable changes in postinjection vital signs, with the exception of 1 patient who had a single incidence of low diastolic blood pressure 45 minutes post injection (Case 20; Table 4.2). No pattern could be identified to suggest a relationship between the administration of OP Depot and any clinically meaningful changes in vital signs (blood pressure, pulse, and respiratory rate). To date, 1 patient who experienced an IAIV injection event also had sustained increases in blood pressure during an event, although this case occurred after the database was locked for this analysis (Case 24; Table 4.2).

Relatively few AEs of any kind were reported during the observation period and the majority were reported as mild or moderate in severity. Over the course of observation of 5647 injections, 28 AEs were observed in 14 patients (28/5647, 0.5%) during the 3-hour observation period. Four (4) of these 14 patients also experienced an IAIV injection event.

4.2.1.5.   Incidence of IAIV Injection Events in OP Depot Clinical Trials

Based on an estimated 34,825 OP Depot injections and 25 events as of 30 September 2007, IAIV injection events have occurred in 0.07% of injections. Based on a total of 2006 patients in OP Depot trials and 24 patients with events as of 30 September 2007, 1.2% of patients (24/2006) have experienced an IAIV injection event.

Figure 4.1 provides a summary of the estimated cumulative risk of an IAIV injection event over time. The probability of experiencing at least one IAIV injection after a given number of injections follows a binomial distribution. A generalization of the binomial model, the beta binomial model, allows for the probability of an event occurring at any given injection (p) not to be constant between patients. The further assumption of the beta binomial model is that p follows a distribution. Because the data to date includes 1

patient with 2 events, the beta binomial model fits the IAIV data better than the binomial model and is used for calculating the risk of experiencing at least one IAIV event for a given number of injections (see Appendix 5 for details).
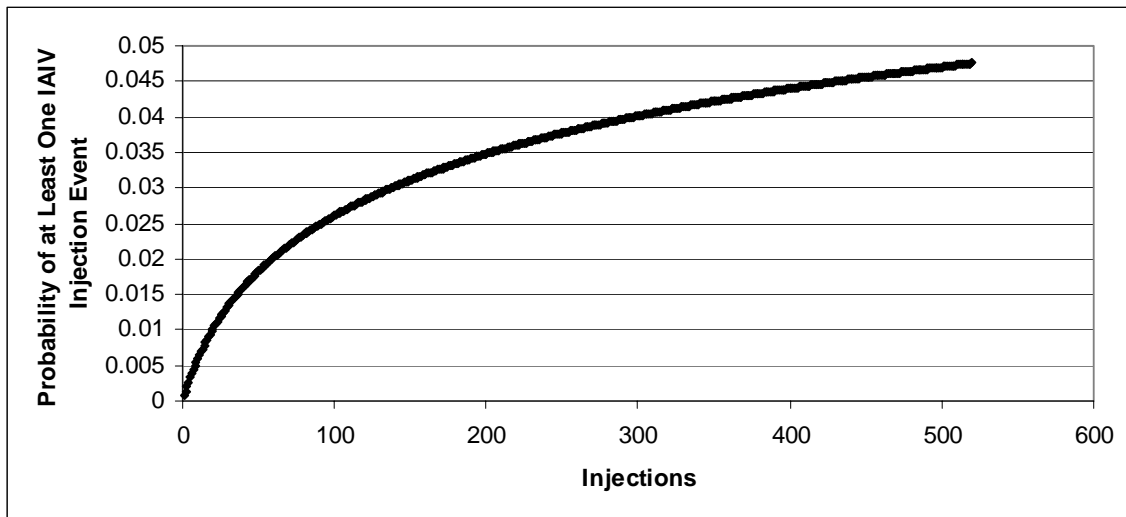
Figure 4.1.   Cumulative estimated risk of an IAIV injection event over time.

The cumulative estimated risk of an IAIV injection event occurring in an individual patient during various time points is described below (Table 4.4).

Table 4.4.   Cumulative Risk of an IAIV Injection Event at Different Time Points

Years of Treatment	Risk of Experiencing IAIV Event
1	0.7–1.2%
2	1.2–1.9%
3	1.6–2.3%
5	2.1–2.9%
10	2.9–3.8%
20	3.8–4.8%

Calculations are based on the 34,825 injections and 25 IAIV events from the locked database through 30 September 2007.

These risks are expressed as ranges because the length of the injection intervals (4 weeks or 2 weeks) affects the number of injections received in a given year of treatment.

4.2.1.6. Logistic Regression for Identification of Factors in IAIV Injection Events

Lilly periodically analyzes IAIV injection event data for factors that might be associated with a greater risk of an event. An analysis of data for the 25 IAIV injection events was performed. The logistic regression model identified high dose (p=0.037), greater age (p=0.055), and low body mass index (BMI; [p=0.052]) as potential risk factors for an IAIV injection event. The most robust finding was of a statistically significantly increased potential risk of an IAIV injection event at higher dose. Patients who are 20 years older than other patients are at a 1.95-times (1.034^20) higher risk of an IAIV injection event; patients with a BMI 5 units lower than other patients are at a 1.48-times (1/0.924)^5 higher risk. Similarly, patients receiving a 405-mg injection are at a 2.64-times (1.005^195) higher risk compared to a patient receiving a 210-mg injection.

It is important to note that 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. The larger volume of IM injection (for example, 2.7 mL for a 405 mg OP Depot dose) might be a mechanistic factor by which higher doses are associated with a greater risk. (Appendix 4 includes additional details on the methods and results of the statistical analysis used to assess these potential risk factors.)

Although these increases in risks are statistically significant, the overall risk of experiencing an IAIV injection event is still low, even for patients exhibiting all 3 risk factors simultaneously. For example, the logistic regression model predicts that a 50-year-old patient with a BMI of 22 who received a 405-mg injection would have a probability of 0.0032 for experiencing an IAIV injection event.

As new injection information becomes available, risk factor analyses will be updated. Further discussions with the FDA will determine whether these factors should be incorporated into product labeling.

4.2.2. Investigations to Determine the Root Cause of IAIV Injection Events

The available evidence supports accidental intravascular injection, a known risk with IM injections, as the mechanism for the events Lilly has termed "IAIV injection events". This evidence includes temporal relationship to injection, substantially elevated olanzapine plasma concentrations during events in which blood samples were obtained, and an incidence rate similar to that of another IM-administered drug product. To be more comprehensive in the evaluation of these events, however, Lilly conducted further investigations, including in vitro solubility experiments in biological fluids, an examination of olanzapine plasma concentrations after a normal OP Depot injection versus those during an IAIV injection event, the examination of clinical trial materials (drug product vials and the batch release and stability records for drug product lots), and

a review of information about overdose with oral olanzapine. The key findings from these investigations are summarized below.

4.2.2.1. Solubility of the Olanzapine Pamoate Monohydrate Salt

Direct entrance of the suspension of olanzapine pamoate into the vasculature could occur if the needle has punctured a vessel, nicked a vessel, or entered a rich capillary bed or a bleed around the vasculature. In vitro experiments that evaluated the solubility of olanzapine pamoate in plasma or blood were performed. These solubility experiments provide evidence that when OP Depot is injected into the muscle as intended, the dissolution of olanzapine pamoate salt is very gradual, leading to the desired slow release of olanzapine into the bloodstream. However, when the olanzapine pamoate monohydrate salt comes into contact with a substantial amount of blood or plasma, the salt dissolves more quickly. When the olanzapine pamoate salt dissolves, it dissociates into olanzapine and pamoic acid, which are readily absorbed into the systemic circulation; therefore, when the OP Depot injection comes into contact with enough blood, the dissolution of that portion of the OP Depot dose may occur over a period of minutes to hours rather than at the rate that normally occurs in muscle tissue, where the dissolution of the salt requires a period of days to weeks.

Various physical factors such as the amount of olanzapine pamoate suspension entering the blood stream, the volume and rate of blood flow, and the degree of vascular injury may all have an impact on the increase in the rate at which the pamoate salt dissolves.

4.2.2.2. Expected Olanzapine Plasma Concentration Profile Immediately after an OP Depot Injection

An extensive pharmacokinetic characterization of single and multiple doses of the OP Depot formulation across a range of doses and for periods of treatment for more than 2 years shows that olanzapine is slowly absorbed and plasma concentrations are sustained for a prolonged interval of weeks. Although several studies intensively evaluated the plasma concentration profile and showed a very slow and sustained absorption of olanzapine, almost no samples in these evaluations had been collected in the time period of 0 and 2 hours immediately after the injection. Because the pharmacokinetic information and effects associated with an IAIV injection event suggest that a patient experiencing an event may have received an OP Depot injection in which an initial portion of that dose was released too quickly, a key question was whether a small initial release of olanzapine occurred after each injection (including injections that had *not* resulted in an IAIV injection event) of OP Depot. This question prompted a specific pharmacokinetic investigation, which became an addendum to Study HGKB. In each of 10 patients, a series of blood samples was collected immediately before and then at 5, 10, 15, 30, and 45 minutes, and at 1, 2, 4, 6, and 8 hours after a 300 mg OP Depot injection. The results showed that the olanzapine concentration after the injection remained essentially unchanged compared to the pre-injection concentration. These data

confirmed both the slow in vivo release of olanzapine immediately after injection and the lack of initial burst release of olanzapine following a typical IM injection of OP Depot.

4.2.2.3. Olanzapine Plasma Concentrations Collected during IAIV Injection Events

Olanzapine plasma concentrations were measured in 7 of the 25 IAIV injection events. In each of these events, a much higher olanzapine plasma concentration was observed than would have been expected. Although Lilly identified IAIV injection events as a phenomenon and recommended to investigators that they collect blood samples in any patient they believed to be experiencing an IAIV injection event, the investigators were not always able to collect blood samples. Not only were investigators understandably focused on the status of the patient and providing appropriate medical care, but many of the patients were transferred to emergency rooms or hospitals for continued care. The staff in those facilities did not obtain blood samples for measurement of olanzapine concentration.

Figure 4.2 illustrates the olanzapine plasma concentration profiles after 6 different OP Depot injections in one patient who experienced an IAIV event (after the second injection). Higher-than-expected olanzapine plasma concentrations occurred after the second 300 mg OP Depot injection. An arrow in the figure shows the point at which the IAIV injection event was experienced. The other five injections received by this patient exhibited a typical plasma concentration profile associated with the OP Depot regimen. It is important to note that the time scale in Figure 4.2 is in weeks. Therefore, the time scale during the period when olanzapine concentrations are elevated is very compressed and is actually a period of about 2 days. The substantial increase in the olanzapine concentration occurred over a period of hours. The graph clearly shows that the concentrations during the IAIV injection event were substantially higher than other concentration data for the same patient.
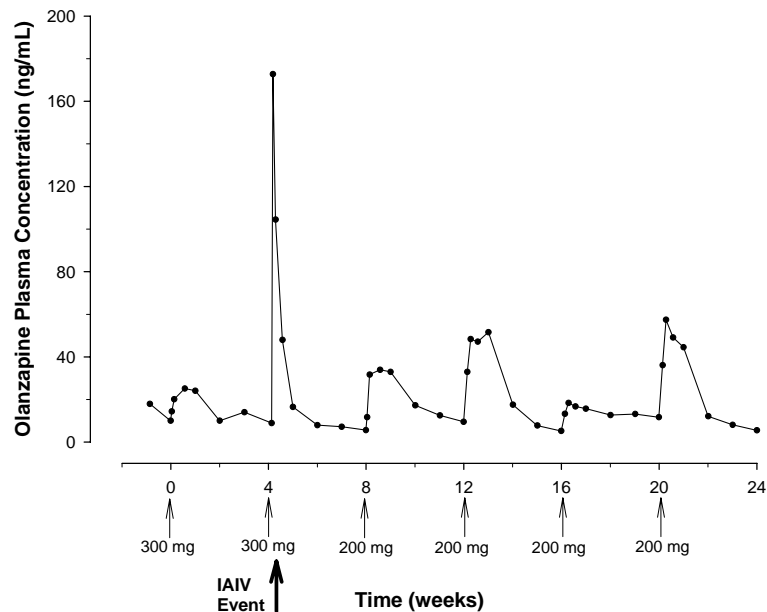
Figure 4.2.   **Olanzapine plasma concentration-versus-time profile during an IAIV injection event.**

A similar finding of higher olanzapine plasma concentrations during IAIV injection events was observed in each of the 7 events. In 2 of the events, the patients did not have blood samples drawn for the measurement of olanzapine other than those drawn after the IAIV injection event itself, so a comparison to their own data prior to the event was not possible. Nonetheless, the concentrations measured during the events in these patients were also clearly higher than expected based on typical olanzapine exposure for OP Depot.

Based on extensive pharmacokinetic sampling during the clinical development program, Lilly learned that olanzapine plasma concentrations in all OP Depot-treated patients must be interpreted in the context of a wide range of interpatient variability regardless of which olanzapine formulation is administered.

Although the olanzapine concentrations observed during the IAIV injection events have been clearly above the range of concentration typically seen during OP Depot treatment, the clinical effects of the events may be related to the relatively quick change in concentration over a period of hours rather than to concentrations exceeding a specific concentration or threshold value. Many examples exist of a given patient's olanzapine concentration over the course of treatment being substantially and consistently lower or higher from those for another patient receiving the same treatment, yet each patient may exhibit a similar degree of tolerability and response to olanzapine. Any patient would be

very likely to experience clinically notable symptoms if the olanzapine concentrations rise over a period of minutes to hours to a level that is substantially above prior concentrations. It is therefore Lilly's belief that the clinical symptoms associated with IAIV injection events not only reflect high concentration but also are affected by the rate at which concentrations increase during the events.

4.2.2.4. Clinical Trial Material Involved in IAIV Injection Events

Throughout the development process for OP Depot, manufacturing controls were used to ensure that the drug product had consistent extended-release characteristics. Because of the IAIV injection events, a review of the manufacturing data was conducted for the clinical trial lots associated with drug product used by patients who experienced an IAIV injection event. The results of the review demonstrated homogeneity of the drug product.

Lilly requests that investigative sites return vials of clinical trial material involved in IAIV injection events to Lilly. The used vials from several IAIV injection events have been analyzed, and the analysis of the residual suspension remaining in the drug product vials has demonstrated the expected physicochemical properties (potency, related substances, pH, particle size, morphology). The results of this investigation indicate that no data exist to suggest that the manufacturing of OP Depot (vehicle or drug product) has led to the IAIV injection events.

4.2.2.5. Description of Signs and Symptoms Observed in Oral Olanzapine Overdose

Because the signs and symptoms seen in the IAIV injection events are consistent with many of the signs and symptoms of oral olanzapine overdose, information about oral olanzapine overdose was carefully reviewed. This review included a search of the relevant literature, clinical trial data, and postmarketing data pertaining to oral olanzapine overdose. The key findings from this review are summarized briefly below.

Notably, the spectrum of toxicity following overdose with olanzapine is highly variable and shows little correlation between dose/blood concentration and severity of clinical outcomes. It is likely that these depend largely on the presence of coingestants and on the patient's age, habituation to olanzapine or other drugs used, and the elapsed time between the overdose and medical intervention.

- *Clinical Manifestations Reported in Clinical Trials and Postmarketing Data for Oral Olanzapine.* In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with an incidence of 10% or greater included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias, delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Based on the estimated patient exposure to olanzapine as of 30 September 2007, death following an acute ingestion of an oral olanzapine-alone overdose was very rarely reported (<0.01%; data on file at Eli Lilly and Company).

- *Dose and Olanzapine Concentrations.* Dose ingested and concentration data are often not available in cases of overdose. The review of these data focused on well-documented cases and revealed that fatal outcomes have been reported for acute overdoses as low as 450 mg of oral olanzapine but that survival has also been reported following acute overdose of approximately 2000 mg of oral olanzapine (data on file at Eli Lilly and Company). There is significant variability in blood concentrations of olanzapine at therapeutic doses as well as significant redistribution of drug after death, which makes it difficult to interpret postmortem concentration findings.

- *Case Series in the Published Literature.* Findings from two published case series (N=63 patients) are somewhat more useful than spontaneous reports for assessing expected typical outcomes, as they imply systematic reporting of all olanzapine overdose cases observed at a specific center (Palenzona et al. 2004; Morgan et al. 2007). Notably, no deaths were observed in these series, supporting the assessment that death is a very rare outcome of olanzapine overdose. The commonly observed symptoms, notably sedation and agitation/delirium, in these series are similar, overall, to those seen with IAIV injection events and as with the IAIV injection cases observed in OP Depot clinical trials, patients appeared to recover fully. Tachycardia appeared to be more common in the overdose cases than in IAIV injection events. Miosis was also more common in these overdose cases. The relative absence of cardiovascular compromise observed in IAIV injection events is consistent with the habituation effect observed by Morgan et al. (2007).

  Chue and Singer (2003) reported plasma concentration data in 27 deaths for which olanzapine overdose was either the principal cause of toxicity or a significant contributor to combined toxicity. In 11 of the cases in which olanzapine was the only drug detected, postmortem olanzapine levels in blood ranged from 237 ng/mL to 4900 ng/mL. The cause of death for all but 2 of these cases was described as "olanzapine toxicity" (Chue and Singer 2003).

- *Overall Conclusion.* The symptoms associated with elevated olanzapine concentrations observed with IAIV injection events are generally consistent with clinical observations of oral olanzapine overdose. Because death has been observed with oral olanzapine overdose, it is potentially a risk with IAIV injection; however, death should be considered an exceptional outcome, as the oral overdose review suggests a typical course of full resolution that is likely dependent on associated patient-specific predispositions. The nature of circumstances surrounding intentional overdoses that result in fatalities also need to be considered. For example, intentional overdoses tend to be taken at high overdoses, with concomitant overdoses of other medications, and when the patient is in isolation. In contrast, OP Depot will be administered as a specific dose as directed by healthcare professionals in a clinical setting, and patients will be monitored for at least one hour after injection for signs and symptoms of overdose.

4.2.2.6. Discussion of the Adverse Events Reported in OP Depot IAIV Injection Events and in RAIM Olanzapine

Signs and symptoms in OP Depot-treated patients experiencing IAIV injection events differ from the AEs reported during clinical trials with the RAIM formulation of olanzapine. The formulations are differentiated by their intended patient populations and physical characteristics. As noted previously (Section 1.4), RAIM is intended for the immediate management of an agitated patient, whereas OP Depot is intended for long-term treatment.

Regarding physical characteristics, RAIM is a solution, whereas OP Depot is a crystalline suspension, and the two produce substantial differences in the rate of absorption of olanzapine. RAIM olanzapine is immediately, rapidly, and completely absorbed within hours, whereas the olanzapine pamoate of OP Depot dissolves slowly so olanzapine is absorbed over a period of weeks (Section 1.4). Even during an IAIV injection event, olanzapine pamoate must dissolve before a substantial increase in olanzapine plasma concentrations occurs. Although the rate of dissolution of the olanzapine pamoate is faster in plasma than in muscle, the rate of rise in olanzapine plasma concentration will be substantially slower than the concentration increase associated with a normal administration of RAIM.

Thus, the AEs associated with an IAIV injection event (sedation, confusion/confused state, dizziness, altered speech/dysarthria, somnolence) are distinct from those for RAIM (sedation, bradycardia, tachycardia, hypotension) and are similar to the AEs observed during an overdose of oral olanzapine (Zyprexa PI).

4.2.3. Intravascular Injection of Products Intended for Intramuscular Administration

A review of the literature found that the risk of accidental intravascular injection is a known risk for all IM products and is typically reflected in label warnings for such medications as penicillin G procaine (Bicillin®; Downham et al. 1978; Cummings et al. 1987; ISMP 1997, 1999, 2004; do Carmo de Castro Miranda et al. 2004), methylprednisolone acetate (Depo-Medrone® [Sen et al. 2005] and Depo-Medrol® [ISMP 2003]), and promethazine hydrochloride injection (Sen et al. 2005). Although this risk is well known, incidence rates are not well documented (Sen et al. 2005). The challenge in determining background rates of these events comes from the fact that most inadvertent intravascular occurrences are not readily identified or reported.

- *Penicillin G procaine.* When injected intravascularly, the procaine release results in rapid onset of symptoms that can be directly related to procaine toxicity allowing for estimation of incidence. In a study published by Downham et al. (1978), systemic toxic reactions were observed in 8 of 10,469 patients during or immediately after IM injection of penicillin G procaine. The estimated incidence per injection was 0.08%, or approximately 1 in 1300 injections. In these events, the salt dissolved rapidly into penicillin and procaine, causing symptoms consistent with the toxic reaction. The rapid release of penicillin alone does not appear to be associated with any notable symptoms, but presentation of symptoms from rapid penicillin G procaine release may range from fear of imminent death, visual and auditory disturbances, violent combativeness, confusion, disorientation and restlessness, and cardiovascular changes to more severe symptoms such as grand mal seizures and death (Downham et al. 1978; Cummings et al. 1987; ISMP 1999, 2004; do Carmo de Castro Miranda et al. 2004). When procaine penicillin is injected into the muscle tissue as expected, these adverse effects do not occur, as the procaine is metabolized in the muscle before reaching the systemic circulation.

- *Septocaine.* Accidental intravascular injection of SEPTOCAINE®, a dental anesthesia, is reported as a warning in product labeling. The warning reads, "Accidental intravascular injection may be associated with convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest." Incidence rates have not been reported for these events (Septocaine PI).

- *Phenergan.* Risk of intravascular injection has been reported with PHENERGAN® injection. Deep IM injection into a large muscle is the preferred route of administration for this antihistamine. Clinical manifestations of an IAIV injection range from burning, pain, swelling, nerve damage, and, in the extreme case, gangrene. No incidence rates for these occurrences have been reported (ISMP 2006).

- *Risperidone.* In November 2007, risperidone added the following text to the Precaution section of the US Package Insert (Risperdal PI) prescribing recommendations: "RISPERDAL® CONSTA® should be injected into the gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel. Retinal artery occlusion after injection of RISPERDAL CONSTA has been reported during postmarketing surveillance." Retinal artery occlusion in this long-acting atypical antipsychotic has also been reported in the literature. Tang and Weiter (2007) noted that inadvertent injection of the microspheres into the blood stream resulted in retinal artery occlusion in the presence of an asymptomatic, persistent foramen ovale in the heart. They estimate that as many as 20% of the population may have an undiagnosed, asymptomatic form of this condition.

- *Other Antipsychotics.* The risk of intravascular injection is reflected in sections of product labeling for other long-acting antipsychotics such as flupenthixol decanoate (Flupenthixol PI), zuclopenthixol acetate (Zuclopenthixol PI), and haloperidol decanoate (Haloperidol PI).

As shown in the examples above, the risk of accidental intravascular injection is well known. There are also documented steps to reduce the occurrence, and these steps have been included in product labeling for some IM-administered drugs (Beyea and Nicoll 1996). This guidance recommends the ventrogluteal site of IM injection as a safer option to access the gluteus medius muscle and to avoid all major nerves and blood vessels. A procedure of "aspiration" prior to injection of the drug has also been incorporated into product labeling for some of these drugs. These guidances were incorporated into the label and/or the educational materials for prescribers as described further in Section 4.3.

4.2.4. *Hypothetical Mechanistic Basis for IAIV Injection Events*

The weight of evidence obtained by reviewing IAIV injection event data and from additional investigations into the cause of these events suggests that accidental contact between the olanzapine pamoate suspension and blood is the proximate cause for IAIV injection events. It is important to recognize that the potential mechanisms by which the suspension comes into contact with blood could be various. For instance, direct injection into a blood vessel may be one method, but the nicking of a blood vessel during the injection procedure or development of a hematoma could also be methods by which blood comes into contact with the suspension. An undisputable aspect, however, is that

the olanzapine pamoate must dissolve and an excessive amount of olanzapine must reach the bloodstream to produce symptoms.

Although the initial delay between injection and the onset of symptoms is likely due to the time it takes for olanzapine pamoate to dissolve in blood (see Section 4.2.2.1), it would also be expected that the continuing dissolution of the olanzapine pamoate would be reflected by a progression of clinical symptoms over time, which is consistent with the clinical presentation of these events. Although proper injection technique is absolutely essential to minimize the risk of an IAIV injection event, such events can still occur, even when proper technique is used.

4.2.5. *Conclusions Regarding IAIV Injection Events*

The key findings regarding IAIV injection events are summarized briefly below.

- As of 30 November 2007, a total of 25 IAIV injection events have been identified in 24 patients during OP Depot clinical trials.

- Twenty (20) of the 24 patients experiencing IAIV injection events were hospitalized or seen in the emergency room.

- Based on the 34,825 OP Depot injections as of 30 September 2007, the cumulative risk of an IAIV injection event occurring in the first year of treatment is 0.7% to 1.2%; the risk during 2 years of treatment is 1.2% to 1.9%; and the risk during 3 years of treatment is 1.6% to 2.3%.

- Higher dose (also corresponding to an increased injection volume), greater age, and low BMI have been identified as potential risk factors of an IAIV injection event, but the risk is still low, even for patients with these specific risk factors.

- Signs and symptoms reported with IAIV injection events are consistent with many of the AEs reported with an oral olanzapine overdose.

- The time to onset for 21 of the 25 IAIV injection events was within 1 hour after the injection; for the other 4 events, time to onset was within 3 hours after the injection. An IAIV injection event with an onset later than 60 minutes post injection therefore occurred in 0.011% (4/34,825) of injections.

- None of the IAIV injection events were considered to have involved sudden onset of incapacitation; instead, they were reported to have begun with milder symptoms and usually progressed in severity.

- All patients who experienced an IAIV injection event fully recovered from the event, and the majority (16/24) continued to receive OP Depot injections.

Accidental intravascular injections have been reported in the literature for other IM-administered medications. Lilly believes that the risk of an IAIV injection event with OP Depot can be safely managed in clinical practice by following the precautions in the proposed label and through activities outlined in the Risk Management Plan.

4.3. Risk Management Plan for OP Depot

Lilly carefully evaluated the literature and the labeling and other risk management activities used to manage other drug products with identified safety risks before developing the Risk Management Plan (RMP) for OP Depot. The OP Depot RMP includes strategies related to product labeling, education and training, routine postmarketing surveillance, and an observational study to mitigate the potential risks associated with IAIV injection events. Each of these areas is further discussed below.

4.3.1. Risk Management Plan for IAIV Injection Events

4.3.1.1. Product Labeling

Part of Lilly's strategy to mitigate the potential risk associated with IAIV injection events involves providing clear and adequate instructions to health care providers (HCPs) in the product label for OP Depot. Specific information and instructions will include

- Description of this risk and provisions for safe use, proposed as a bolded warning

- Description of proper injection technique

- Recommendation for a 3-hour precautionary period: After a 1-hour, on-site postinjection observation period, healthcare professionals will consider each patient's individual circumstance when determining whether it is appropriate for the patient to leave the site or to remain on site for a longer observation period.

- Recommendation for informing patients that, for a period of 3 hours after the injection, they should (1) not drive or operate heavy machinery, (2) be vigilant for signs and symptoms of potential IAIV injection events and (3) be able to obtain assistance if needed

- Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in IAIV injection events

- Recommended management if an IAIV injection event occurs

4.3.1.2. Training and Advice to Healthcare Providers

To provide an additional level of precaution, Lilly proposed that HCPs take the following steps:

- Inform patients and their caregivers that they should be vigilant for signs and

symptoms of potential IAIV injection events for an additional 2 hours after the initial 1-hour on-site precautionary period and that they should be able to obtain assistance if needed (consistent with product labeling above)

- Advise patients and caregivers of the types of symptoms that may be associated with a potential IAIV injection event so they can notify their HCPs if they become aware of any of these symptoms

- Advise patients not to drive or operate heavy machinery for a total of 3 hours post injection (consistent with product labeling above)

In addition, Lilly will provide a patient package insert (PPI) and a takeaway card for patients to keep with them that would include their HCP's phone numbers and instructions to follow in the event of certain symptoms. The PPI will include information about the 3-hour precautionary period and will assist patients in identifying symptoms of these events should they occur. Lilly will also conduct a healthcare awareness program that will include training activities targeted for HCPs. This program will include detailed descriptions of observed events, recommendations for management of such events when they occur, training in proper injection techniques, and education on where to go to learn more or to have questions answered.

4.3.1.3. Management of Risk

Table 4.5 presents a high-level summary of the RMP for OP Depot, which includes IAIV injection events as an identified risk. As noted above, specific actions will target increasing awareness of patients, caregivers, and HCPs about IAIV injection events through labeling, product inserts, and training. Additionally, although the risk of such events cannot be totally eliminated, these recommendations are intended to safely manage events if they should occur.

The potential risk for medication error was also included in the RMP. This risk identifies the possibility that RAIM olanzapine might accidentally be administered in the place of the long-acting OP Depot formulation, and vice versa. To minimize this risk, Lilly used distinctly different label covers in packaging (for example, different package sizes and different vial cap and label coloring) as well as different dosage strengths to differentiate between the two formulations.

Table 4.5.   Summary of Risk Management Plan

Safety Concern	Actions Proposed for Pharmacovigilance	Actions Proposed for Risk Minimization[a]
IAIV injection event	• Monitor AEs and SAEs: routine clinical trial and spontaneous postmarketing surveillance (routine pharmacovigilance[b]); targeted surveillance for specific AEs preidentified for targeted follow-up (targeted surveillance[c]) • Undertake a postmarketing observational study to further characterize, evaluate possible risk factors, and estimate the incidence rate of IAIV injection events in clinical practice	• Provide adequate labeling to prescribers and patients about clinically relevant safety observations, including those related to IAIV injection events. Labeling will include a Patient Package Insert. Specific information and instructions to be included in the label will address the following topics: • Description of this risk, proposed as a bolded warning • Description of proper injection technique • Recommendation for a 1-hour on-site observation period post injection • Recommendation for informing patients that, for a period of 3 hours after the injection, they should (1) not drive or operate heavy machinery, (2) be vigilant for signs and symptoms of IAIV injection events, and (3) be able to obtain assistance if needed • Description of IAIV injection events and the proposed mechanism for the event • Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in IAIV injection events • Recommended management if the IAIV injection event occurs • Provide administrator-of-treatment–, pharmacist-, and physician-targeted education about the risk and clinical presentation of IAIV injection events and proper injection techniques to minimize IAIV injection event risk • Provide administrator-of-treatment–, pharmacist-, and physician-targeted education about labeling and product differences between RAIM and OP Depot to minimize medication error risk • Provide patient counseling kits with tools (eg, take-away card) to support the 1-hour observation period and provide key product and event management information (eg, medical center contact information)
Medication error	• Routine and targeted pharmacovigilance[b]	• Prescriber education about the 2 intramuscular formulations of olanzapine, including packaging differences • Distinct packaging differences between OP Depot and RAIM

Abbreviations: AE = adverse event; eg = for example; IAIV = inadvertent intravascular; OP = olanzapine pamoate; RAIM = rapid-acting intramuscular; SAE = serious adverse event.

[a] Routine risk minimization includes product information, labeling, and packaging.

[b] Standard pharmacovigilance includes monitoring AE data to be in compliance with regulatory responsibilities for expedited and periodic reporting. Data are collected in a global safety database, from which signal detection and safety evaluation are performed.

[c] Targeted surveillance is based on pharmacovigilance of specific AEs preidentified for targeted follow-up.

Page 72

4.3.2. Pharmacovigilance Plan for IAIV Injection Events

4.3.2.1. Routine Pharmacovigilance and Targeted Surveillance

Lilly has a robust quality system for routine pharmacovigilance of all marketed products. As part of this system, AE data are routinely monitored for potential public health issues, in compliance with regulatory responsibilities for expedited and periodic reporting. Data are collected in a global safety database, from which signal detection and safety evaluations are performed. Routine pharmacovigilance of spontaneously reported cases, including potential IAIV injection events, will therefore be conducted.

In addition, active follow-up of targeted signs and symptoms will enable collection of additional scientific or medical data for evaluation. Targeted surveillance terms for the OP Depot formulation have been preliminarily identified based on the signs and symptoms reported in association with IAIV injection events, including sedation and delirium, and terms in olanzapine overdose. The list of terms is also derived from the FDA list of Designated Medical Events. All of these terms were included in the RMP that was previously submitted to the FDA.

4.3.2.2. Observational Study

In addition to the standard risk minimization activities of product labeling and active postmarketing surveillance, Lilly will conduct a multinational Phase IV, noninterventional, prospective cohort study, F1D-MC-B034 (Inadvertent Intravascular Injection Events among Patients with Schizophrenia Receiving Olanzapine Pamoate Depot) in approximately 5000 patients. This sample size will have at least 80% power to observe 27 IAIV injection events, assuming a beta binomial distribution with $\alpha=0.004256$ and $\beta=5.09198$ and assuming a 50% two-year completion rate and 75% one-year completion rate. These estimates for the beta binomial come from probability analyses that were included in a special safety topic report for IAIV injection events that was included in the application to the FDA. The completion rate assumptions are based on interim results of Study HGKB.

The study will be initiated soon after OP Depot is approved for marketing; it is designed to

- Estimate the crude incidence of IAIV injection events over a 2-year period in patients treated with OP Depot in clinical practice

- Identify potential risk factors associated with the occurrence of IAIV injection events and further characterize the clinical presentation (signs and symptoms) of these events in a naturalistic setting

- Compare the incidence, severity, and outcomes of IAIV injection events in clinical trials with normal clinical practice to determine if there are any clinically meaningful differences

4.4. Safety Summary and Conclusions

The evaluation of OP Depot demonstrated that its safety profile is similar to that of oral olanzapine for most parameters that were measured. Common AEs (sedation, somnolence) and other safety-related changes (weight gain, increases in prolactin, elevated triglycerides, orthostatic hypotension) observed during treatment with OP Depot have also been observed during treatment with olanzapine. These potential safety risks have been incorporated into the proposed labeling for OP Depot.

Although injection-site–related AEs and the risk of intravascular injection are potential risks for all drugs injected intramuscularly, the clinical manifestations of IAIV injection events are unique to OP Depot. With respect to the potential risk of an IAIV injection event, the key findings were summarized in Section 4.2.5 and are not repeated here.

The incidence of injection-site–related AEs in the OP Depot Integrated Database was consistent with the incidence reported in the literature for another IM antipsychotic medication. Injection-site pain was the most frequently reported AE, while all other injection-site–related AEs were reported in <1% of OP Depot-treated patients. Most events were reported to be of mild severity.

Overall, this safety review suggests that the safety profile of OP Depot is generally comparable to oral olanzapine, with the additional potential risks of IAIV injection events and injection-site–related AEs. Lilly believes that the potential risk of an IAIV injection event can be safely managed in clinical practice through labeling and the activities described in the RMP.

5.   Benefit-to-Risk Profile Summary

5.1. Risk of Schizophrenia

Relative to the general population, people with schizophrenia suffer disproportionately from medical illnesses and other psychiatric disorders (Kaplan and Sadock 1998). Nearly 50% of patients with schizophrenia have co-occurring substance use disorders (Green et al. 2007), and over a 20-year period, an estimated 10% to 15% will die by suicide (Kaplan and Sadock 1998). Treatment with oral antipsychotic medications is the first line of care for most patients; however, many treatment options are needed in this chronically ill patient population because no single medication will be effective or well tolerated by all patients. Further, nonadherence to treatment is common in patients with schizophrenia and is associated with poorer outcomes.

5.2. Benefits of Long-Acting Antipsychotics and OP Depot in Treatment of Schizophrenia

Benefits of Long-Acting Antipsychotics. As discussed in Section 1.2, long-acting antipsychotics may offer many benefits over oral antipsychotics in the treatment of schizophrenia:

- Prevention or delay of relapse

- Clear attribution of the cause of relapse

- Early identification of nonadherence

- Regular interaction between patient and HCP

- Controlled administration

- Improved global functioning

- Stable plasma levels of the drug

- Patient convenience

Benefits of OP Depot in Treatment of Schizophrenia. The robust benefits of the long-acting formulation of olanzapine have been demonstrated in 2 large, controlled clinical trials (HGJZ and HGKA) and 1 long-term open-label study (HGKB), which have been previously described in detail (Section 3). The clinical benefits of OP Depot are summarized below.

- Efficacy in acutely ill patients and patients during maintenance treatment

- Efficacy for both the positive and negative symptoms of schizophrenia

- Separation from placebo within 3 days of treatment in acutely ill patients without oral supplementation

- Low study discontinuation rates in the acute and long-term studies. In Study HGKB, the all-cause discontinuation rate at 18 months was 34%. To put this into context, the rate reported for oral olanzapine in the CATIE study was 64%, which was the lowest rate reported in all of the antipsychotics studied (rates ranged from 68% to 82%).

- Successful switching from oral antipsychotics to OP Depot without oral supplementation in 2 large clinical trials

- Option for 2- or 4-week dosing intervals compared with only 2-week dosing intervals, which is the option for the only currently approved long-acting atypical antipsychotic

- Flexible dosing, with a range of 150 mg to 405 mg per injection, allowing clinicians to select from a variety of doses for individual patients

- The OP Depot drug product does not need to be refrigerated, which is a requirement for the only currently approved long-acting atypical antipsychotic.

- Patient-reported treatment satisfaction with OP Depot, preference for OP Depot over previous oral medications, and fewer side effects with OP Depot compared with previous oral antipsychotic medications were reported in Study HGKB. Patient perception of mediation benefit has been shown to be a strong predictor of treatment duration (Liu-Seifert et al. 2007).

- Low risk of tardive dyskinesia, which is a significant concern with older long-acting antipsychotics

- OP Depot would provide an additional long-acting atypical antipsychotic for clinicians and patients who currently have only one approved long-acting atypical antipsychotic option.

5.3. Risks of OP Depot in the Treatment of Schizophrenia

The safety of OP Depot was examined in the context of the well-known safety profile of oral olanzapine. As previously discussed, potential risks with OP Depot treatment include the potential risks that have been observed during treatment with oral olanzapine, with the additional risks associated with the route of administration (injection-site–related AEs and IAIV injection events). Lilly has included the potential risks of oral olanzapine in the proposed label for OP Depot, including weight gain, hyperglycemia, hyperlipidemia, elevated prolactin, elevations of liver enzymes (transient, asymptomatic), sedation, drug-drug interactions, and other information such as neuroleptic malignant syndrome, tardive dyskinesia, seizures, and anticholinergic activity related to its status as an antipsychotic medication.

Additionally, the potential risks of IAIV injection events (summarized in detail in Section 4.2.5) and injection-site–related AEs have also been incorporated into labeling. With respect to IAIV injections, the following are of note:

- As described previously, the potential risk of an IAIV injection is critically important. The greatest potential risk is that a patient might experience the event in an unsafe situation such as while driving a car or operating machinery. Lilly has developed label language and RMP activities to ensure that HCPs, patients, and families are thoroughly aware of this risk and can take the necessary precautions to minimize negative outcomes.

- The symptoms associated with high olanzapine levels observed with IAIV injections are generally consistent with clinical observations of oral olanzapine overdose. Because death has been observed with olanzapine overdose, it must be considered as a potential risk with IAIV injection, likely dependent on associated patient-specific predisposition. Death should be considered an exception to the usual outcome, however, based on findings from the oral overdose review that suggested a typical course of full resolution, and because of the innate differences in the setting and circumstances between intentional overdoses and IAIV injections.

- Intentional overdoses generally occur with a plan of self harm, tend to include higher than prescribed doses and/or concomitant overdoses with other medications. Individuals ingesting the overdose do so without the knowledge of others and in settings where symptoms of overdose or distress might go undetected and unaddressed for extended periods of time. Because OP Depot will be administered under medical supervision where patients will be observed for a minimum of 1 hour after injection (with the option for longer observation if warranted, based on the patient's circumstances), the majority of IAIV events that occur will be readily identified by healthcare professionals and will be addressed appropriately.

- The RMP for OP Depot, which includes detailed product labeling about IAIV injection events, has been developed with the intention of addressing everything known about these events and of minimizing the risk of negative outcomes when events do occur. The symptoms of an IAIV injection are readily identifiable, and all patients have fully recovered from these events.

- Higher OP Depot dose, low BMI, and greater age have been identified as risk factors for IAIV injection events. Clinicians should be vigilant with all patients because events have occurred at low doses, high BMIs, and in a patient who was only 23 years of age.

- The majority of patients who experienced an injection-site–related AE reported it to be mild; incidence of injection-site–related AE was consistent with the rate (8%) reported in the literature for haloperidol decanoate.

5.4. Benefit-to-Risk Profile

Despite the availability of effective antipsychotic treatments, schizrenia remains a serious public health concern. As noted previously, the risks associated with the disease are markedly greater in patients who fail to achieve adequate symptom response and in patients who are nonadherent to medication. Apart from the obvious negative effects on all aspects of life for an individual who is experiencing unrelenting symptoms of schizophrenia, many patients will find it difficult to maintain an oral treatment regimen or may experience intolerable side effects requiring a medication change. These patients will need many treatment options, including long-acting formulations. This is particularly important, as most patients who are treated with depot formulations are among the most severely ill.

The APA (2004) recommends use of long-acting injectable antipsychotics in nonadherent patients with schizophrenia, but only three depot antipsychotics (one atypical and 2 typicals) are available to patients in the US. Further, given the variability in patients' responsiveness to and tolerability of different antipsychotics, multiple long-acting antipsychotic medications are needed. Currently, a patient with schizophrenia who requires a depot formulation because of a significant history of nonadherence to oral medications and who cannot tolerate or does not respond to the only approved atypical depot antipsychotic has no other option for treatment than the older long-acting antipsychotic medications. Approval of a long-acting formulation of olanzapine would increase the number of available atypical depot options. The strong performance of oral olanzapine, in terms of its effectiveness reported in the CATIE trial, suggests that a depot formulation of oral olanzapine would potentially benefit many patients.

Weighing the Benefits and Risks

Ultimately, the clinician will determine which medication is right for any given patient. In making this determination, the clinician must weigh benefits and risks of specific treatment options and consider the following factors:

- Characteristics and disease symptoms of the patient (age, age of onset, overall severity, specific positive and/or negative symptoms, number of relapses)

- Previous antipsychotic history (tolerability issues, response to treatment, suspected or identified nonadherence)

- Comorbidities (obesity, hypertension, substance abuse)

- Social support (level of family and/or caregiver support, employment status, independent living)

- Current functioning of the patient relative to the known progression of the disease (early stage, chronic stage)

The benefit-to-risk ratio for OP Depot may be particularly favorable to those patients who are at risk for relapse due to nonadherence or for whom other medications are not effective. In these patients, the negative sequelae of relapse may outweigh the known risks of oral olanzapine and the added risk of IAIV injection events. This is supported by the clinical trial data: Concern about the potential risk of an IAIV injection event has not led to increased rates of discontinuation in ongoing OP Depot studies; instead, discontinuations due to AEs and all-cause discontinuations during OP Depot studies have remained low. Furthermore, patient perception of the benefits of OP Depot is favorable, as reported in Study HGKB, in which the majority of patients reported treatment satisfaction, a preference for OP Depot over previous oral medication, and fewer side effects with OP Depot. These findings are important because patients who perceive treatment benefits have a greater likelihood of adhering to treatment (Perkins et al. 2006; Liu-Seifert 2007). Finally, 16 of the 24 patients experiencing an IAIV injection event weighed the benefits against the risks of OP Depot treatment and continued to receive OP Depot injections.

The body of evidence presented in the OP Depot submission and summarized in this briefing document is thought to be sufficient to conclude that, with appropriate labeling and risk minimization activities, OP Depot would provide an important addition to the cache of available therapies in the treatment of patients with schizophrenia.

6. References

Adams CE, Fentin MK, Quraishi S, David AS. 2001. Systemic meta-review of depot antipsychotic drugs for people with schizophrenia. British Journal of Psychiatry 179:290-299.

[APA] American Psychiatric Association. 2000. Diagnostic and Statistical Manual of Mental Disorders. 4th ed, Text Revision. Washington, DC.

[APA] American Psychiatric Association. 2004. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Washington, DC.

Almond S, Knapp M, Farancois C, Toumi M, Brugha T. 2004. Relapse in schizophrenia: costs, clinical outcomes and quality of life. British J of Psychiatry 184:346-351.

Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. 2006. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry 67:453-460.

Ayd FJ. 1975. The depot fluphenazines: a reappraisal after 10 years' clinical experience. Am J Psychiatry 132:491-500.

Beasley CM Jr, Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S, Olanzapine HGAP Study Group. 1996a. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacol 124:159-167.

Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S, Olanzapine HGAD Study Group. 1996b. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacol 14(2):111-123.

Beasley CM Jr, Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, Blin O, Beuzen JN. 1997. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 7(2):125-137.

Beasley CM Jr, Sutton VK, Hamilton SH, Walker DJ, Dossenbach M, Taylor CC, Alaka KJ, Bykowski D, Tollefson GD. 2003. Olanzapine Relapse Prevention Study Group. A double-blind, randomized, placebo-controlled trial of olanzapine in the prevention of psychotic relapse. J Clin Psychopharmacol 23(6):582-594.

Beasley CM Jr, Stauffer VL, Liu-Seifert H, Taylor CC, Dunayevich E, Davis JM. 2007. All-cause treatment discontinuation in schizophrenia during treatment with olanzapine relative to other antipsychotics. J Clin Psychopharmacol 27(3):252-258.

Belanger-Annable MC. 1985. Long acting neuroleptics: technique for intramuscular injection. Can Nurse 81(8):1-3.

Beyea SC, Nicoll LH. 1996. Back to basics. Administering IM. injections the right way. Am J Nurs 96(1):34-35.

Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, Magouirk B, Rush AJ. 2005. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Res 133:129-133.

Carlson CD, Cavazzoni PA, Berg PH, Wei H, Beasley CM, Kane JM. 2003. An integrated analysis of acute treatment-emergent extrapyramidal syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidol, risperidone, or clozapine. J Clin Psychiatry 64(8):898-906.

Chue P, Singer P. 2003. A review of olanzapine-associated toxicity and fatality in overdose. J Psychiatry Neurosci 28(4):253-261.

Conley RR, Kelly DL. 2001. Management of treatment resistance in schizophrenia. Biol Psychiatry 50:898-911.

[CPMP] Committee for Proprietary Medicinal Products. 1999. Concept paper on the development of a Committee for Proprietary Medicinal Products (CPMP) points to consider on biostatistical/methodological issues arising from recent CPMP discussions on licensing applications: choice of delta. London: The European Agency for the Evaluation of Medicinal Products (EMEA). CPMP/EWP/2158/99.

Cummings JL, Barritt CF, Horan M. 1987. Delusions induced by procaine penicillin: case report and review of the syndrome. Int J Psychiatry Med 16(2):163-168.

Davis JM, Metalon L, Watanabe M, Blake L. 1994. Depot antipsychotic drugs. Drugs 47(5):741-773.

Dellva MA, Tran P, Tollefson GD, Wentley AL, Beasley CM Jr. 1997. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. Psychiatr Serv 48(12):1571-1577.

do Carmo de Castro Miranda M, Rozenfeld S, Pacheco de Oliveira S. 2004. A systemic review of the non-allergic adverse reactions following benzathine benzylpenicillin injection. J Vasc Br XX(3):253–260.

Downham TF 2nd, Cawley RA, Salley SO, Dal Santo G. 1978. Systemic toxic reactions to Procaine Penicillin G. Sex Transm Dis 5(1):4-9.

Dursun S. 2005. An atypical long-acting injectable antipsychotic: implications for pharmacotherapy of schizophrenia. J Psychopharmacol 19(5 Suppl 1):3-4.

[EMEA] European Agency for the Evaluation of Medicinal Products. 2003. Methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia (appendix to the note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia). CPMP/EWP/49/01, February 2003. Available at: http://www.emea.europa.eu/pdfs/human/ewp/004901en.pdf. Accessed 20 February 2007.

Fleischhacker WW, Eerdekens M, Karcher K, Remington G, Llorca PM, Chrzanowski W, Martin S, Gefvert O. 2003. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. J Clin Psychiatry 64:1250-1257.

Flupenthixol decanoate [package insert (PI)]. 2007. Canada.

Funck-Brentano C, Jaillon P. 1993. Rate-corrected QT interval: techniques and limitations. Am J Cardiology 72:17B-22B.

Glazer WM. 2007. Who receives long-acting antipsychotic medications? Psychiatric Services 58(4):437.

Green AI, Drake RE, Brunette MF, Noordsy DL. 2007. Schizophrenia and co-occurring substance use disorder. Am J Psychiatry 164(3):402-408.

Haloperidol Decanoate Injection [package insert (PI)]. 2005. Irvine, CA: Sicor Pharmaceutical.

Hamann GL, Egan TM, Wells BG, Grimmig JE. 1990. Injection site reactions after intramuscular administration of haloperidol decanoate 100 mg/mL. J Clin Psychiatry 51(12):502-504.

Haro JM, Novick D, Suarez D, Alonso J, Lepine JP, Ratcliffe M; SOHO Study Group. 2006a. Remission and relapse in the outpatient care of schizophrenia: three-year results from the Schizophrenia Outpatient Health Outcomes study. J Clin Psychopharmacol 26(6):571-578.

Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D; the SOHO Study Group. 2006b. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. Eur Neuropsychopharmacol 17(4):235-244.

Harvey PD, Jacobsen H, Mancini D, Parrella M, White L, Haroutunian V, Davis KL. 2000. Clinical, cognitive and functional characteristics of long-stay patients with schizophrenia: a comparison of VA and state hospital patients. Schizophr Res 43:3-9.

Hawton K, Sutton L, Haw CC, Sinclair J, Deeks J. 2005. Schizophrenia and suicide: systemic review of risk factors. British J of Psychiatry 187:9-20.

Hay J. 1995. Complications at site of injection of depot neuroleptics. British Medical Journal 311:421-425.

Heres S, Hamann J, Kissling W, Leucht S. 2006. Attitudes of psychiatrists toward antipsychotic depot medication. J Clin Psychiatry 67:1948-1953.

Herings RM, Erkens JA. 2003. Increased suicide attempt rate among patients interrupting use of atypical antipsychotics. Pharmacoepidemiology and Drug Safety 12:423–424.

Hosalli P, Davis JM. 2007. Depot risperidone for schizophrenia. Cochrane Collaboration Volume (3).

[ISMP] Institute for Safe Medication Practices. 1997. ISMP medication safety alert. Sep 10, 1997. Available at: http://www.ismp.org/Newsletters/acutecare/archives/Sep97.asp. Accessed 20 March 2007.

[ISMP] Institute for Safe Medication Practices. 1999. ISMP medication safety alert. June 30, 1999. Available at: http://www.ismp.org/Newsletters/acutecare/archives/Jun99.asp#June30,1999. Accessed 20 March 2007.

[ISMP] Institute for Safe Medication Practices. 2003. ISMP medication safety alert. May 29, 2003. Available at: http://www.ismp.org/Newsletters/acutecare/archives/May03.asp#May29. Accessed 20 March 2007.

[ISMP] Institute for Safe Medication Practices. 2004. ISMP medication safety alert. May 6, 2004. Available at: http://www.ismp.org/Newsletters/acutecare/archives/May04.asp. Accessed 20 March 2007.

[ISMP] Institute for Safe Medication Practices. 2006. ISMP medication safety alert. August 10, 2006. Available at http://www.ismp.org/Newsletters/acutecare/articles/20060810.asp. Accessed 20 December 2007.

Johnson DAW. 1977. Practical considerations in the use of depot neuroleptics for the treatment of schizophrenia. Br J Hosp Med 17:546-558.

Kalali A. 1999. Patient satisfaction with, and acceptability of, atypical antipsychotics. Curr Med Res Opin 15(2):135-137.

Kane J, Aguglia E, Altamura A, Gutierrez JL, Brunello N, Fleischhacker W, Gaebel W, Gerlach J, Guelfi D, Kissling W, Lapierre Y, Lindstom E, Mendlewicz J, Racagni G, Carulla L, Schooler N. 1998. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology 8:55-66.

Kane JM. 2003. Strategies for improving compliance in treatment of schizophrenia by using a long-acting formulation of an antipsychotic: clinical studies. J Clin Psychiatry 64(S16):34-40.

Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. 2003. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 160(6):1125-1132.

Kane JM. 2006. Reducing nonadherence: new formulations of antipsychotic medications. Psychiatric Times (XXV):2.

Kaplan H, Sadock B. 1998. Chapter 13 Schizophrenia. Synopsis of Psychiatry. 8th ed. Baltimore: Lippincott Williams & Wilkins. 456-491 p.

Keith SJ, Kane JM, Turner M, Conley RR, Nasrallah HA. 2004. Guidelines for the use of long-acting injectable atypical antipsychotics. J Clin Psychiatry 65(1):120-131.

Keks NA, Ingham M, Khan A, Karcher K. 2007. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. British J Psychiatry 191:131-139.

Lambert T. 2006. Selecting patients for long-acting novel antipsychotic therapy. Australasian Psychiatry 14(1):38-42.

Leucht S, Pitschel-Walz G, Abraham D, Kissling W. 1999. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophrenia Res 79:231-238.

Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. 2005. What does the PANSS mean? Schizophrenia Res 79:231-238.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353(12):1209-1223.

Lindenmayer JP, Khan A, Eerdekens M, Van Hove I, Kushner S. 2007. Long-term safety and tolerability of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder. European Neuropsychopharmacology 17:138-144.

Liu-Seifert H, Houston JP, Adams DH, Kinon BJ. 2007. Association of acute symptoms and compliance attitude in noncompliant patients with schizophrenia. Journal of Clinical Psychopharmacology 27(4):392-394.

Love RC, Conley RJ. 2004. Long-acting risperidone injection. Am J Health-Syst Pharm 61:1792-1800.

Mahmoud RA, Engelhart LM, Janagap CC, Oster G, Ollendorf D. 1997. Risperidone versus conventional antipsychotics: a prospective randomized, naturalistic effectiveness trial of outcomes in chronic schizophrenia [poster]. Presented at the 36th annual meeting of the American College of Neuropsychopharmacology; Dec 8-12, 1997; Waikoloa, Hawaii.

McEvoy JP. 2006. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry 67(5 Suppl):15S-18S.

Meltzer HY. 1999. Outcome in schizophrenia: beyond symptom reduction. J Clin Psychiatry 60(3 Suppl):3-7.

Meyer JM. 2007. Strategies for the long-term treatment of schizophrenia: real-world lessons from the CATIE trial. J Clin Psychiatry 68(1):28-33.

Morgan M, Hackett L, Isbister G. 2007. Olanzapine overdose: a series of analytically confirmed cases. International Clinical Psychopharmacology. 22:183-186.

[NIMH] National Institutes of Mental Health. Mental Disorders in America-Schizophrenia. Accessed on 31 August 2007 at http://www.nimh.nih.gov/publicat/numbers.cfm.

Palenzona S, Meier P, Kupferschmidt, Rauber-Luethy C. 2004. The clinical picture of olanzapine poisoning with special reference to fluctuating mental status. Journal of Toxicology 42(1):27-32.

Patel MX, David AS. 2005. Why aren't depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment 11:203-213.

Perkins DO. 2002. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 63:1121-1128.

Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrhino F, Green AI, Glick IB, Kahn RS, Sharma T, Tohen M, McEvoy JP, Weiden PJ, Lieberman JA. 2006. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophrenia Research 83:53-63.

Risperdal Consta [package insert (PI)]. 2007. Titusville, New Jersey: Janssen Pharmaceutical.

Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Lieberman JA. 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 56:241-247.

Septocaine with epinephrine [package insert (PI)]. 2005. Canada: Novocol Pharmaceuticals of Canada, Inc.

Schooler NR. 2003. Relapse and rehospitalization: comparing oral and depot antipsychotics. J Clin Psychiatry 64(16 Suppl):14S-17S.

Schooler NR. 2006. Relapse prevention and recovery in the treatment of schizophrenia. J Clin Psychiatry 67(5 Suppl):19S-23S.

Sen S, Chini EN, Brown MJ. 2005. Complications after unintentional intra-arterial injection of drugs: risks, outcomes and management strategies. Mayo Clin Proc 80(6):783–795.

Shi L, Ascher-Svanum H, Zhu B, Faries D, Montgomery W, Marder S. 2007. Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. Psychiatric Serv 58(4):482-488.

Tang J, Weiter JJ. 2007. Branch retinal artery occlusion after injection of a long-acting risperidone preparation. Ann Intern Med 147(4):283-284.

Tiihonen J, Walhbeck K, Lonnqvist J, Klaukka T, Ioannidis JP, Volavka J, Haukka J. 2006. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 333:224-229.

Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, Graffeo KA, Thieme ME. 1997. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 154(4):457-465.

Tran PV, Dellva MA, Tollefson GD, Wentley AL, Beasley CM Jr. 1998. Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. Br J Psychiatry 172:499-505.

Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, Bingham CR, Stavenger T. 2002. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care 40(8):630-639.

Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. 2006. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry 67(10):1542-1550.

Weiden PJ, Kozma C, Grogg A, Locklear J. 2004. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatric Serv 55: 886-891.

Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, Aggarwal J. 2005. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry 66(9):1122-1129.

Zuclopenthixol decanoate [package insert (PI)]. 2007. Lundbeck Ltd.

Zyprexa IM [package insert (PI)]. 2007. Indianapolis: Eli Lilly.

Appendix 1.
Summary of Nonclinical Studies

A.1.1.   Overview of Toxicological Evaluation for OP Depot

In animals, the pharmacology, pharmacokinetics, and toxicology of olanzapine were well characterized in conjunction with the development of the oral and RAIM formulations. The nonclinical studies performed to support the sustained release IM formulation (OP Depot) therefore focused on considerations relevant to this parenteral route of administration. Areas of study involved the likely differences in systemic exposure that might occur following administration of OP Depot via the IM route, potential reactions at the site of injection, and any identified safety issues with pamoic acid, which is a component of olanzapine pamoate monohydrate and acts as a counter ion. All toxicity studies included a pamoic acid control group, the dose for which corresponded to that contained in the high-dose OP Depot group, as well as a vehicle-only control group. High doses of OP Depot were chosen to approximate a maximum feasible administered dose, while the low and mid doses were selected to provide a range of doses for evaluation. Because of limitations on the volume of test article that could be humanely administered, systemic toxicity was not elicited with OP Depot in most instances; hence, the oral safety data remains the cornerstone to understanding the potential toxicity of olanzapine pamoate monohydrate. The nonclinical studies conducted with OP Depot did not identify any new toxicity due to systemic exposure to olanzapine.

In consultation with FDA reviewers, the nonclinical toxicology studies designed and conducted to supplement the oral data package included single-dose rat and dog studies, a 3-month repeat-dose rat study, a 6-month repeat-dose dog study, embryo-fetal studies in rats and rabbits, a perinatal study in rats, and a 2-year carcinogenicity study in rats. Because of volume limitations that can be accommodated by the much smaller muscle mass in laboratory animals and the maximum suspension capabilities of the formulation, doses were administered once monthly to rats and twice monthly to dogs. Unlike humans, all laboratory species developed significant injection-site lesions. Histologically, the injection-site reactions from OP Depot were characterized by focally extensive areas of myocyte loss with replacement by fibroblasts, collagen, and variable numbers of inflammatory cells, consistent with chronic inflammation in response to tissue injury and injection of foreign material. The reactions were most severe in the dog and least severe in rat and rabbit. Reactions subsided within a few days and did not worsen with repeat injection. Little, if any, systemic toxicity was elicited because of the lower plasma concentrations that could be achieved as compared to daily oral dosing of olanzapine base. Nevertheless, at no time during the conduct of any of the nonclinical safety studies for OP Depot was there an observation of sudden profound sedation. (Sedation can be elicited in laboratory animals by high doses of oral or RAIM olanzapine, and sedation has been frequently documented in several acute and short-term repeat dose studies conducted in support of the oral olanzapine drug product.)

A.1.2.   Overview of Nonclinical ADME Evaluation for OP Depot

Prior preclinical studies have established the disposition and metabolism of oral olanzapine in mice, rats, dogs, and monkeys. Although these studies were conducted with olanzapine (free base), the results provide relevance for OP Depot because olanzapine is absorbed after an injection of olanzapine pamoate monohydrate. Radiocarbon drug ($[^{14}C]$olanzapine) was utilized to evaluate single-oral-dose pharmacokinetics in rats, to characterize single- and multiple-oral-dose tissue distribution in rats, and to investigate the role of biliary and other routes of excretion in different species of animals. Furthermore, $[^{14}C]$olanzapine was used to evaluate placental transfer and the secretion of olanzapine into the milk of lactating rats. The plasma concentrations and excretion profiles for radioactivity were compared with those obtained from humans dosed orally with $[^{14}C]$olanzapine. In other studies, mice, rats, and dogs were dosed orally for periods of at least 1 year, and the plasma assayed for the presence of olanzapine. Metabolites of olanzapine detected in plasma, urine, and bile were identified by LC/MS/MS techniques. Olanzapine was extensively metabolized, yielding multiple metabolites in all species investigated. In vitro studies in human liver microsomes and human liver slices were performed to further investigate the involvement of CYP450 in the metabolism of olanzapine. In summary, a full ADME evaluation of oral olanzapine was conducted in laboratory animals and in vitro systems.

The ADME characteristics for OP Depot were examined in the context of the full evaluation of oral olanzapine. Once absorbed, the disposition of OP Depot would be expected to be the same as that of oral olanzapine; thus, the evaluation of OP Depot focused on the absorption characteristics of OP Depot in the relevant animal species. The pharmacokinetics of OP Depot were evaluated in both rats and dogs following multiple doses. For both genders in all dosage groups in the 3-month rat study, peak plasma concentrations for olanzapine and pamoic acid generally occurred within the first day after the first and third injections. For both olanzapine and pamoic acid, the area under the concentration-time curve over the dosing interval (AUC_{0-t}) increased both for a larger dose and after consecutive injections of the same dose. Maximum observed plasma concentration (C_{max}) values increased with a larger dose but did not increase between the first and third injections of the same dose.

In animals receiving OP Depot, plasma concentrations of olanzapine and pamoic acid were observed to gradually decrease during the first 2 to 3 weeks after each injection and then to remain near or below the quantifiable limit for an additional 1 to 2 weeks. Pamoic acid administered alone at a dosage comparable to that for the highest OP Depot dose produced much higher peak plasma pamoic acid concentrations that declined more rapidly than pamoic acid concentrations observed in the high-dose OP Depot group.

In beagle dogs, mean pamoic acid T_{max} values for OP Depot were 104 to 145 hours after the first dose and 15 to 120 hours after the 13th dose in the 6-month study. Mean pamoic acid T_{max} values for doses of pamoic acid occurred within the 1st hour after the first dose and within 3 hours after the dose on Day 168 for both genders. Olanzapine AUC_{0-t}

increased proportionally with increasing dose, whereas the increase in pamoic acid AUC_{0-t} was less than proportional. Olanzapine exposure on Day 84 was greater than the exposure after the first dose or on Day 168. Pamoic acid exposure was less on Day 168 than after the first dose.

In summary, in animals receiving OP Depot, plasma concentrations of olanzapine and pamoic acid were observed to gradually decrease following C_{max} and were measurable in almost all dosage groups for at least 14 days after an OP Depot injection, demonstrating a prolonged exposure consistent with the IM administration of a suspension of OP Depot. Fluctuations in exposure over the study were attributed to a high degree of interanimal variability. No consistent gender differences were observed for olanzapine or pamoic acid exposure.

Appendix 2.
Definitions of Exacerbation and
Justification of Noninferiority Criteria in Study HGKA

A2.1.   **Definition of Exacerbation**

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

1. 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 ≥2 on that specific item since randomization at Visit 10 or

2. 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 ≥4 on the BPRS Positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization at Visit 10 or

3. Hospitalization due to worsening of positive psychotic symptoms.

This definition of exacerbation, by including only part of the BPRS and excluding other psychopathology, was a more sensitive approach, selected to avoid false positives. The increased sensitivity was considered to be ethically and clinically necessary in this patient population to detect early exacerbation before hospitalization was necessary, allowing rapid intervention.

A2.2.   **Justification of Noninferiority Criteria**

The estimated cumulative exacerbation rates at 6 months by Kaplan–Meier estimates were the basis of noninferiority. Noninferiority was defined as no worse than 0.20 difference (Δ0.20) in 6-month exacerbation rates as estimated by the Kaplan-Meier curves at Day 168.

The choice of Δ=0.20 was made based on results seen in the olanzapine Study HGGI (Olanzapine Relapse Prevention versus Placebo in the Treatment of Schizophrenia) and on comments received from the Committee for Proprietary Medicinal Products (CPMP). The CPMP suggested that the true placebo-versus-oral olanzapine difference in exacerbation rates should be conservatively estimated by the lower limit of an 80% confidence limit on the difference observed in Study HGGI. In this study, the Kaplan–Meier-estimated exacerbation rate at Day 168 for placebo was 0.552 and for oral olanzapine was 0.055. The associated standard errors for these estimated exacerbation rates were 0.106 and 0.019, respectively, for placebo and oral olanzapine. The assumption that the difference between estimated exacerbation rates was approximately normally distributed led to a one-sided 80% lower confidence limit of 0.406 for the difference in exacerbation rates at Day 168. A one-sided confidence limit was

appropriate because only the lower limit was of interest; there was no interest in how large the difference could be.

In a CPMP concept paper (CPMP 1999) on the choice of Δ for noninferiority trials, it was suggested that it was acceptable to use a Δ of one-half of the established superiority of the comparator to placebo, especially if the new agent has a compliance advantage. Given the compliance advantage of a depot formulation, and using the conservative estimate of 0.406 in the 6-month exacerbation rates therefore results in a choice of Δ equal to 0.20.

Appendix 3.
General Safety Analyses

A3.1.   **Overview**

General safety parameters (exposure, demographics, disposition, AEs, laboratory values, vital signs and weight measurements, ECGs, EPS) and special safety topic analyses were 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) assigned to 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. The data cut-off date for data from locked databases that have been included in this database was 31 January 2007.

Presentation of Information

This safety review will begin by presenting general safety information followed by special safety analyses, which were chosen for analysis based on the well established safety profile of oral olanzapine or on the route of administration for OP Depot. For many of these measures, analyses will be presented for both mean changes in the parameters from baseline to endpoint and the proportions of patients experiencing treatment-emergent changes beyond certain thresholds characterized as potentially clinically significant.

Throughout this section, the Placebo-Controlled and Olanzapine-Controlled Databases are also referred to as the controlled databases.

A3.2.   **Extent of Exposure**

Table A3.1 summarizes exposure information for all patients who have received at least one injection of OP Depot. Cumulative exposure represents a maximum length of 951 days (approximately 2.6 years).

Table A3.1.   **Summary of Patient Exposure to All OP Depot Doses**
All Patients with OP Depot Exposure
OP Depot Integrated Database

	Min	Med	Mean	Max	Total
			N=1915a		
Number of injectionsb	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 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.

A3.3.   **Demographics and Patient Disposition**

Demographics. Although a few statistically significant differences were seen (age and gender) in the Placebo-Controlled Database, 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 OP Depot Integrated Database had a mean age of 39.4 years; 66% were Caucasian, and 68% were male.

As a whole, baseline PANSS scores indicated that patients in the Placebo-Controlled Database were clinically more acutely ill (baseline PANSS Total score = 101), while patients in the Olanzapine-Controlled Database were clinically stable (baseline PANSS Total score = 56). A subset of patients in both controlled databases (71% in the Placebo-Controlled Database and 36.9% in the Olanzapine-Controlled Database) reported at least 2 previous episodes or exacerbations of schizophrenia in the past 24 months. In patients with schizophrenia, 2 or more exacerbations of the disease in a defined period are generally indicative of poor adherence to medication and suggestive of patients who may benefit from a depot formulation (Lambert 2006).

Overall, these study population demographics are consistent with the general population of patients with schizophrenia who are likely to benefit from a long-acting formulation of olanzapine.

Discontinuations due to Adverse Events. Discontinuations due to AEs were less than 6% 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. The most common AEs reported by 5 or more patients as the reason for study discontinuation in the OP Depot Integrated Database were psychotic disorder (n=14; 0.73%), schizophrenia

(n=10; 0.52%), increased weight (n=7; 0.36%), diabetes mellitus (n=5; 0.26%), and somnolence (n=5; 0.26%).

A3.4. Adverse Events

A3.4.1. Serious Adverse Events Including Deaths

No statistically significant between-group differences in the incidence of SAEs were observed in the controlled databases. In the OP Depot Integrated Database, SAEs reported by 5 or more patients were associated primarily with symptoms of the underlying disease (Table A3.2) as described in the literature (Kaplan and Sadock 1998; APA 2000).

Table A3.2. **SAEs in at Least 5 Patients**
All Patients with OP Depot Exposure
OP Depot Integrated Database

Event Term	OP Depot Integrated Database (N=1918) n (%)
Patients with ≥1 SAE	193 (10.06)
Schizophrenia	42 (2.19)
Psychotic disorder	37 (1.93)
Agitation	9 (0.47)
Paranoia	7 (0.36)
Sedation	7 (0.36)
Suicidal ideation	7 (0.36)
Anxiety	6 (0.31)
Hallucination, auditory	6 (0.31)
Suicide attempt	6 (0.31)
Aggression	5 (0.26)
Schizophrenia, paranoid type	5 (0.26)

Abbreviations: n = number of patients; OP = olanzapine pamoate; SAE = serious adverse event.

Three deaths (3/1918; 0.2%) have been reported in patients assigned to OP Depot. None of these deaths were reported to be related to study medication or study procedures.

- A 33-year-old Caucasian female with a history of chronic alcoholism died of acute heart failure with associated toxic/alcoholic heart damage (cardiomyopathy).

- A 30-year-old male of African descent died of a severe case of leptospirosis.

- A 52-year-old Caucasian male died of essential hypertension that the investigator reported was probably hypertension stroke.

One additional death, due to sepsis, occurred in a patient who was receiving oral olanzapine in Study HGLQ.

Narrative descriptions and other safety findings for each patient were included in the NDA or in additional safety reports that have been provided to the FDA.

A3.4.2.   Treatment-Emergent Adverse Events

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 statistically significant overall difference between groups was observed in the incidence of patients with 1 or more TEAE (p=.147). Statistically significant differences were observed between treatment groups in the incidence of chest pain, menstrual disorder, parkinsonism, and rhinitis, although all of these events were reported only by patients in the oral olanzapine treatment group.

Table A3.3 summarizes TEAEs that were reported in at least 5% of patients in the OP Depot Integrated Database. All of these events, except injection-site pain (expected with an injectable product) and headache and nasopharyngitis (common in clinical trials of all drugs), are consistent with symptoms of the disease state or with events observed historically in patients treated with oral olanzapine. There were no patterns in TEAEs suggestive of new safety concerns.

Table A3.3.   TEAEs with an Incidence of at Least 5%
All Patients with OP Depot Exposure
OP Depot Integrated Database

Event Term	OP Depot Integrated Database (N=1918) n (%)
Patients with ≥1 TEAE	1252 (65.3)
Insomnia	216 (11.3)
Weight increased	168 (8.8)
Anxiety	150 (7.8)
Somnolence	145 (7.6)
Headache	140 (7.3)
Injection-site pain	102 (5.3)
Sedation	97 (5.1)
Nasopharyngitis	96 (5.0)

Abbreviations: n = number of patients; OP = olanzapine pamoate; TEAE = treatment-emergent adverse event.

Time to onset and time to resolution of TEAEs of special interest were evaluated in the controlled databases to assess tolerability over time. Extrapyramidal symptom-related events were selected for these analyses because these events are clinically important in this study population. Cardiovascular-, hepatic-, metabolic- (hyperglycemia and lipids), and weight gain-related events were selected because each topic was also assessed as a

special safety topic. These analyses revealed no clinically relevant differences between treatment with OP Depot and placebo or between treatment with OP Depot and oral olanzapine.

Although potential dose effects could not be assessed from pooled or integrated databases that included variable dose studies, dose effects were evaluated in specific TEAEs using fixed OP Depot doses in Study HGKA. The analysis revealed no pattern suggesting a trend by dose for any of the TEAEs evaluated (sedation-, delirium-, weight gain- lipids-, diabetes-, hepatic-, cardiovascular-, and syncope-related events). Potential dose effects were further evaluated for vital sign and laboratory data and are discussed below (Section A3.5.1).

A3.5. General Analyses of Laboratory Measures, Vital Signs and Weight, Electrocardiograms, and Extrapyramidal Symptoms

Assessments of laboratory measures, vital signs and weight, ECGs, and EPS were appropriately performed as part of routine safety monitoring in clinical trials with OP Depot. Overall, the results of these analyses were generally as expected, based on the known safety profile of olanzapine. No unique findings for patients treated with the depot formulation were apparent in any of these analyses. The findings are summarized below.

Laboratory Analyses. In the controlled databases, statistically significant differences in mean changes at endpoint were observed between treatment groups for several laboratory measures, although absolute changes were small. Statistically significant differences in the incidence of abnormal values at anytime for OP Depot-treated patients versus placebo-treated patients and OP Depot-treated patients versus oral olanzapine-treated patients are summarized (Table A3.4). Overall, the percentages of patients were very small, suggesting normal variance versus potentially drug-related changes. There were no patterns in laboratory analyses suggesting clinically relevant differences between OP Depot-treated patients 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 as discussed in Section A3.5.1. In the OP Depot Integrated Database, clinical laboratory findings were consistent with the known safety profile of oral olanzapine; incidence rates for abnormal values were low, representing small increases or decreases in analyte values.

Table A3.4. 　　　　　**Laboratory Evaluations**
　　　　　　　　　　　　Statistically Significant Treatment-Emergent
　　　　　　　　　　　　Abnormally High or Low Values at Anytime
　　　　　　　　　　　　Controlled Databases

Database	N	n	%	p-Value
Placebo-Controlled Database				
Low Leukocyte Count				
OP Depot	293	1	0.3	.013
Placebo	94	4	4.3	
High Urea Nitrogen				
OP Depot	297	0	0.0	.014
Placebo	95	3	3.2	
Olanzapine-Controlled Database				
High Lymphocytes				
OP Depot	539	3	0.6	.043
Oral Olanzapine	312	7	2.2	
Low Lymphocytes				
OP Depot	536	3	0.6	.044
Oral Olanzapine	312	7	2.2	
Low Cholesterol				
OP Depot	516	5	1.0	.016
Oral Olanzapine	305	11	3.6	

Abbreviation: N = number of patients; n = number of patients who met the criteria; OP = olanzapine pamoate.

Vital Signs and Weight Analyses. Mean change analyses for vital signs and weight in the Placebo-Controlled Database revealed statistically significant differences between OP Depot- and placebo-treated patients for supine pulse and weight. Weight gain has been reported in patients treated with oral olanzapine. In the Olanzapine-Controlled Database (Study HGKA), a statistically significant difference between the OP Depot (0.21 mean decrease) and oral olanzapine (1.43 mean increase) treatment groups was observed for orthostatic systolic blood pressure. Mean increases from baseline to endpoint in weight in this 24-week study were low and not statistically different between the OP Depot (1.03 kg) and oral olanzapine (1.30 kg) treatment groups. This finding may be driven by prior antipsychotic use, which included oral olanzapine; thus, weight may have stabilized prior to participation in Study HGKA. In the OP Depot Integrated Database, statistically significant within-treatment group increases were observed for standing diastolic and systolic blood pressure, supine systolic blood pressure, orthostatic diastolic blood pressure, standing pulse, supine pulse, and temperature (Table A3.5). A statistically significant within-treatment group mean weight gain (1.87 kg) was also observed.

Table A3.5. **Vital Signs and Weight**
Mean Change from Baseline to Endpoint
OP Depot Integrated Database

Vital Sign and Weight	Unit	Treatment	N	Baseline Mean	Baseline Std	Change to Endpoint Mean	Change to Endpoint Std	Change to Endpoint Median	Within P-Value
Systolic BP – Standing	mm Hg	OP Depot	1409	120.23	13.64	2.0660	14.72	0.00	<.001
Systolic BP – Sitting	mm Hg	OP Depot	531	122.16	13.89	0.8531	13.95	0.00	.159
Systolic BP – Supine	mm Hg	OP Depot	1411	120.40	13.45	1.5485	13.68	0.00	<.001
Systolic BP – Orthostatic	mm Hg	OP Depot	1407	0.21	8.50	-0.5430	11.20	0.00	.069
Diastolic BP – Standing	mm Hg	OP Depot	1409	78.21	10.16	1.0802	11.26	0.00	<.001
Diastolic BP – Sitting	mm Hg	OP Depot	531	77.78	10.63	0.3390	10.91	0.00	.474
Diastolic BP – Supine	mm Hg	OP Depot	1411	76.70	9.61	0.5159	10.27	0.00	.059
Diastolic BP – Orthostatic	mm Hg	OP Depot	1407	-1.51	7.28	-0.5586	9.08	0.00	.021
Pulse – Standing	bpm	OP Depot	1335	81.63	12.00	2.5243	13.75	2.00	<.001
Pulse – Sitting	bpm	OP Depot	533	80.12	12.54	0.4503	12.85	0.00	.419
Pulse – Supine	bpm	OP Depot	1338	76.26	10.67	2.5000	12.28	2.00	<.001
Pulse – Orthostatic	bpm	OP Depot	1333	5.34	7.68	0.0368	9.08	0.00	.882
Temperature	degree C	OP Depot	1572	36.41	0.45	0.0434	0.46	0.00	<.001
Weight	kg	OP Depot	1885	81.29	18.46	1.8684	5.56	1.20	<.001

Abbreviations: BP = blood pressure; bpm = beats per minute; N = number of patients with a baseline and at least one post-baseline measurement; OP Depot = Olanzapine Pamoate Depot; Std = standard deviation.

Range=3rd quartile-1st quartile.

*1- Within group p-values are from paired t-test on mean change.

Categorical assessment of PCS changes in vital signs or weight in the Placebo-Controlled Database revealed a significant difference between the OP Depot and placebo treatment groups for weight gain and weight loss; significantly more OP Depot-treated patients gained weight (28.5% versus 12.4%), while significantly more placebo-treated patients lost weight (12.4% versus 2.0%). In the Olanzapine-Controlled Database, no statistically significant differences were observed between the OP Depot and oral olanzapine treatment groups for any PCS change in vital signs or weight.

The incidence of patients with orthostatic hypotension defined as ≥30 mm Hg decrease in systolic blood pressure (when going from a supine to standing position) was 4.4% in the OP Depot Integrated Database. The incidence of patients with orthostatic hypotension defined as ≥20 mm Hg decrease in systolic blood pressure (when going from a supine to standing position) was 16.3% in the OP Depot Integrated Database.

In summary, findings with respect to vital signs and weight were consistent with the known safety profile of oral olanzapine. Weight gain and orthostatic hypotension are both consistent with the known historical profile of oral olanzapine. Differences among OP Depot dose groups were observed in the mean change analyses for weight using Study HGKA treatment groups; these findings are discussed in Section A3.5.1.

ECG Analyses. With respect to mean change in heart rate and ECG intervals, no statistically significant differences were observed between the OP Depot and placebo treatment groups. In the Olanzapine-Controlled Database, were statistically significant differences were observed between the OP Depot and oral olanzapine treatment groups for PR interval and Fridericia-corrected QT (QTcF) interval: In both comparisons, OP Depot-treated patients had small and clinically insignificant mean decreases, while oral olanzapine-treated patients had small mean increases. In the OP Depot Integrated Database, there were statistically significant within-group changes for heart rate, PR interval, QT interval, and Bazett's-corrected QT (QTcB) interval, although the changes were very small. Note that small differences can be statistically significant if the sample size is large.

Categorical assessment of PCS changes in ECG intervals and heart rate for the Placebo-Controlled Database revealed no statistically significant differences between the OP Depot and placebo treatment groups in the incidence of PCS changes on any measure. In the Olanzapine-Controlled Database, no statistically significant differences were observed between the OP Depot and oral olanzapine treatment groups.

Analysis of PCS changes in QTc interval for the Placebo-Controlled Database revealed that the incidence of QTcB interval ≥450 msec was statistically significantly higher in the OP Depot treatment group than in the placebo treatment group, an expected finding because olanzapine has been associated with a slight tendency to tachycardia. Although the Bazett is a common method of QT correction (Funck-Brentano and Jaillon 1993), it is known to underestimate QTc in drugs associated with a lowered heart rate and to overestimate in drugs associated with increased heart rate. Of note, this significance was

not repeated using the Fridericia correction, which is more appropriate for drugs associated with increased heart rate. In the Olanzapine-Controlled Database, no statistically significant difference was observed between the OP Depot and oral olanzapine treatment groups in the incidence of PCS changes in QTc interval. In the OP Depot Integrated Database, 1 patient had a QTcF interval ≥ 500 msec.

Overall, findings in the ECG analyses were as expected and were consistent with the known safety profile of oral olanzapine.

EPS Analyses. Mean change analyses in the Placebo-Controlled Database revealed that OP Depot-treated patients had statistically significant improvement on both the Barnes Akathisia Global and AIMS scales compared with placebo-treated patients. This improvement is likely related to the fact that a number of patients in the study had previously been taking antipsychotics or atypical antipsychotics that have demonstrated a less favorable EPS profile than olanzapine (Leucht et al. 1999; Carlson et al. 2003). In the Olanzapine-Controlled Database, no statistically significant differences were observed between the OP Depot and oral olanzapine treatment groups for mean change in any of the EPS measures. Statistically significant within-treatment group mean decreases were observed for each EPS measure in the OP Depot Integrated Database.

Categorical assessments of treatment-emergent dyskinesia, akathisia, and parkinsonism revealed no statistically significant differences between the OP Depot and placebo treatment groups or between the OP Depot and oral olanzapine treatment groups on any of the EPS measures. In the OP Depot Integrated Database, the incidence of patients with treatment-emergent parkinsonism, akathisia, or dyskinesia was low: 2.3% of OP Depot-treated patients met the definition for treatment-emergent dyskinesia, 4.0% met the definition for treatment-emergent akathisia, and 6.3% met the definition for treatment-emergent parkinsonism. These low incidence rates of treatment-emergent EPS for OP Depot-treated patients in all 3 databases were generally consistent with those of oral olanzapine studies (Beasley et al. 1997).

A3.5.1. Relationship to Dose

Additional analyses of changes in weight, prolactin, and fasting triglycerides were conducted based on the known safety profile of oral olanzapine, which has identified weight gain, elevated prolactin, and high triglycerides as occurring in some patients during treatment with oral olanzapine. Changes in weight, prolactin, and fasting triglyceride levels were reviewed by dose in the 24-week double-blind maintenance-of-effect Study HGKA. In this analysis (Table A3.6), patients treated with 300 mg/2 weeks OP Depot had statistically significantly higher mean change in prolactin and a higher incidence of high fasting triglycerides postbaseline compared with the 405 mg/4 weeks and 150 mg/2 weeks OP Depot doses. Similarly, patients treated with 300 mg/2 weeks OP Depot also had a statistically significantly higher mean increase in weight than did patients treated with 150 mg/2 weeks OP Depot.

Table A3.6.   **Weight, Prolactin, and Triglycerides**
                      Summary of Changes by Dose
                      Double-Blind Maintenance Period, Study HGKA

	OP Depot Dose		
	150 mg/2 weeks	405 mg/4 weeks	300 mg/2 weeks
Weight: mean change in kg (N)	0.67 (140)	0.89 (315)	1.70[a] (140)
Prolactin: mean change in µg/L (N)	-5.61 (109)	-2.76 (259)	3.57[a,b] (115)
Fasting triglycerides: patients who met criteria[c] for change from normal at baseline to high at anytime n/N (%)	4/62 (6.5)	13/133 (9.8)	13/53 (24.5)[a,b]

Abbreviations: n = number of patients with specific result at baseline; N = total number of patients with at
   least one postbaseline measure; OP = olanzapine pamoate.
[a]   p<0.05 versus 150 mg/2 weeks OP Depot; pairwise p-values.
[b]   p<0.05 versus 405 mg/4 weeks OP Depot; pairwise p-values.
[c]   Triglycerides normal to high limits are <150 mg/dL to 200 mg/dL ≤ X < 500 mg/dL.

Dose relationships were not analyzed for the safety update because patients in ongoing
Studies HGKB and HGLQ received flexible doses of OP Depot. There have been no new
data with regard to fixed doses or from controlled studies since the NDA was submitted.

A3.6.   **Analyses of Special Safety Topics (Cardiovascular,**
                        Metabolic Parameters and Weight Gain, Hepatic Measures,
                        and Injection-Site–Related Adverse Events)

Three of the 5 special safety topics (cardiovascular, metabolic parameters and weight,
and hepatic measures) that were evaluated for the NDA were selected based on the
known safety profile of oral olanzapine. These topics are further discussed in the
sections below. In these analyses, the primary comparison was between OP Depot-
treated patients and oral olanzapine-treated patients.

Additional analyses of injection-site–related adverse events were also conducted because
these events are known to occur in all medications intended for IM injection. This topic
is also summarized below. In these analyses, the primary comparison was to placebo
using the Placebo-Controlled Database. In the double-blind, controlled studies, patients
who were not randomized to OP Depot received placebo injections to maintain the blind.

A3.6.1.   **Cardiovascular Events**

Some potential cardiovascular and related risks are described in the Zyprexa product
label. Elderly patients appear to be at increased risk of cardiovascular events during
treatment with olanzapine, and orthostatic hypotension and other hemodynamic-related
AEs have been reported during treatment with RAIM olanzapine. Hypertension,
hypotension, cardiac arrhythmias, and cardiorespiratory arrest have been described with

acute olanzapine overdose in postmarketing spontaneous reports; thus, a careful review of data relevant to cardiovascular events reported in OP Depot clinical trials was warranted. A further analysis of cardiovascular-related data in the presence of benzodiazepines was conducted because of a number of postmarketing SAEs reported after the launch of RAIM in 2004. Specifically, a number of SAEs, including deaths, were reported in patients administered RAIM. In most cases, it was reported that patients were treated with RAIM in a manner that was not studied in clinical trials, including the use of concomitant administration of RAIM and parenteral benzodiazepines or other antipsychotics or with the presence of significant medical comorbidities or other clinical conditions associated with potentially fatal outcomes.

In historical oral olanzapine clinical trials, clinically relevant events were infrequent, and the majority of the few cardiac electrophysiological events that occurred were secondary to other primary pathology. The analyses of numeric ECG data have not suggested that olanzapine has any negative influence on ventricular repolarization.

Lilly carefully monitored and extensively analyzed reports of cardiovascular events during OP Depot clinical trials. These analyses did not reveal any safety findings that have not been previously reported during treatment with oral olanzapine. The key findings are summarized below.

- No statistically significant differences were observed between OP Depot-treated patients and oral olanzapine-treated patients 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 QTcF were observed between any dose in 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 that have been associated with hypotension, bradycardia, and respiratory or central nervous system depression.

- The incidence of cardiovascular- and syncope-related TEAEs; incidence of orthostatic hypotension; mean change from baseline to endpoint in blood pressure, pulse, heart rate, and QTcF interval by gender; and categorical analysis of PCS changes in blood pressure, pulse, heart rate, and QTcF interval by gender in the OP Depot Integrated Database indicate no new safety concerns with respect to cardiovascular measures.

A3.6.2. Metabolic Parameters and Weight Gain

Weight gain and elevations in glucose and lipids have been reported during olanzapine treatment. As a result, Lilly carefully monitored weight and metabolic parameters during

clinical trials. Additional analyses were conducted to assess changes in metabolic parameters and weight in OP Depot-treated patients compared with changes seen in oral olanzapine-treated patients. The findings showed 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 with patients treated with oral olanzapine. In addition, the types of weight gain-, diabetes- and dyslipidemia-related AEs in OP Depot-treated patients were similar to those seen in oral olanzapine-treated patients. The key findings are summarized below.

- The proportions of patients in the OP Depot Integrated Database with treatment-emergent diabetic- or dyslipidemia-related AEs were 2.5% and 3.2%, respectively. No statistically significant differences were observed between the OP Depot and oral olanzapine treatment groups in incidence of treatment-emergent glucose-, lipid-, or weight gain-related AEs. Increased weight was reported in 8.8% of patients in the OP Depot Integrated Database.

- No statistically significant differences in the incidence of treatment-emergent significant change in metabolic analytes, whether fasting or nonfasting, and whether at anytime or endpoint, were observed between patients treated with OP Depot and patients treated with oral olanzapine.

A3.6.3. Hepatic Measures

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. Postmarketing reports of hepatitis have been rare, and reports of cholestatic or mixed liver injury temporally associated with oral olanzapine treatment have been very rare. Reports of jaundice during oral olanzapine clinical trials and postmarketing experience have also been very rare.

OP Depot remains in the body for an extended period of time; therefore, in the case of hepatic changes, it is helpful to determine if patients, especially those with transaminemia, develop clinically relevant hepatic AEs. Hepatic changes in patients treated with OP Depot were therefore reviewed in detail to assess whether they were consistent with hepatic changes seen in patients treated with oral olanzapine.

Lilly carefully monitored hepatic analytes during OP Depot clinical trials using a progressive series of thresholds to clarify the clinical relevance of outcomes. Analyses did not reveal hepatic changes in patients treated with OP Depot that were different in nature from those seen in patients treated with oral olanzapine. Because the existing oral olanzapine USPI addresses hepatic-related changes generally seen during early treatment, the proposed OP Depot product labeling would also reflect the information already

included in oral olanzapine labeling. In some cases, statistically significant mean increases in hepatic analytes were detected in patients treated with OP Depot relative to patients treated with oral olanzapine. The key findings from the additional analyses of hepatic measures are summarized below.

- No patients treated with OP Depot met criteria for Hy's rule [ALT $\geq$3 times upper limit of normal (ULN) and total bilirubin (TBILI) $\geq$1.5 times ULN]. Two patients treated with oral olanzapine (0.6%) met the criteria; however, the between-group difference for OP Depot and oral olanzapine was not statistically significant.

- Categorical shifts in ALT, TBILI, and alkaline phosphatase were not statistically significantly different between patients treated with OP Depot and patients treated with oral olanzapine.

- The incidence of patients with at least 1 hepatic-related AE was not statistically significantly different between patients treated with OP Depot and patients treated with oral olanzapine. Furthermore, no hepatic-related AEs occurred in more than 0.7% of patients treated with OP Depot. Most hepatic-related AEs among patients treated with OP Depot were limited to elevations in hepatic enzymes.

A3.6.4. Injection-Site–Related Adverse Events

Safety analyses of injection-site–related AEs such as injection-site pain and injection-site reactions did not reveal any clinical findings or patterns that would preclude the use of OP Depot in the treatment of adult patients with schizophrenia. Moreover, the rate of one or more injection-site–related AEs reported in patients treated with OP Depot (161/1918; 8.4%) in the OP Depot Integrated Database was consistent with the rate (8%) that has been reported during treatment with other products administered intramuscularly (Belanger-Annable 1985; Hamann et al. 1990; Hay 1995). Injection-site pain was more common (5.3% in the OP Depot Integrated Database) than all other injection-site–related AEs and was reported for most patients as "mild" in severity. The incidence and severity of treatment-emergent injection-site–related AEs were not statistically significantly different between OP Depot- and placebo-treated patients.

Instructions on proper injection technique will be included in the proposed label for OP Depot.

Appendix 4.
Logistic Regression of IAIV Injection Events

Logistic regression was conducted to identify risk factors for IAIV injection events. The methods, results, and conclusions are presented below.

Methods. Data in the locked database up to 31 January 2007 contained 27,210 injections and 19 IAIV injection events. Six (6) additional IAIV injection events were reported between 01 February and 30 September 2007. These 6 injections were added to the locked database for further evaluation. A logistic regression analysis of these 27,216 injections (27,210 + 6 additional injections) was performed to identify potential risk factors for an IAIV injection event. Previous logistic regression analyses of fewer events and fewer injections had not yielded clinically meaningful risk factors.

The variables included dose, BMI, and PANSS Total score (illness severity) for each patient who experienced an IAIV injection event and for all non-IAIV injection event patients. Demographic variables included age, gender, race (dichotomized as Caucasian or non-Caucasian), and geographic region (dichotomized as United States [US] or outside the US [OUS]). A forward stepwise procedure was used to fit the model. The p-value criteria for explanatory variables entering the model and staying in the model were set to 0.10.

Results. The resulting model identified dose, age, and BMI as risk factors of IAIV injection events. Table A4.1 summarizes the results. Using a significance level of 0.10, dose (p=0.037), BMI (p=0.052), and age (p=0.055) were statistically significant.

Table A4.1.   **Analysis of Maximum Likelihood Estimates from Logistic Regression Model with 3 Explanatory Variables**

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-7.7818	1.5133	26.4419	<.0001
BMI	1	-0.0792	0.0409	3.7621	0.0524
DOSE	1	0.00519	0.00248	4.3735	0.0365
AGE (YRS)	1	0.0333	0.0174	3.6793	0.0551

Abbreviations: BMI = body mass index; ChiSq = chi square; DF = degrees of freedom; Pr = probability; YRS = years.
Wald test statistic calculated from the data to be compared with the chi-square distribution with 1 degree of freedom.

Odds ratios with 95% confidence intervals were calculated from the logistic regression model (Table A4.2). Odds ratios were used as an approximation of relative risk to indicate the magnitude of the association between each factor and an IAIV injection

event. The odds ratios identified 3 factors in association with the occurrence of an IAIV injection event: higher dose, greater age, and lower BMI.

Table A4.2. **Odds Ratio Estimates**
Logistic Regression Model
with 3 Explanatory Variables

```
-------------------------------------------------------------
                   Point         95% Wald
Effect             Estimate   Confidence Limits

BMI                 0.924       0.853       1.001
SDYDOSE             1.005       1.000       1.010
AGEYR               1.034       0.999       1.070
-------------------------------------------------------------
```
Abbreviations: AGEYR = age in years; BMI = body mass index; SDYDOSE = study dose.

The point estimates of the odds ratios reflect the increased odds for a one-unit increase in the variable. To convert the point estimates to a more-than–one-unit increase, the estimates are raised to the changes of interest. For example, patients who are 20 years older than other patients are at a 1.95-time (1.034^{20}) higher risk of an IAIV injection event, and patients with a BMI 5 units lower than other patients are at a 1.48-time $(1/0.924)^5$ higher risk. Similarly, patients receiving a 405 mg injection are at a 2.64-time (1.005^{195}) higher risk of an event compared to a patient receiving a 210 mg injection.

Conclusions. Although these increases in risks are statistically significant, it should be noted that the overall risk is still low even for patients exhibiting all three risk factors simultaneously. For example, the logistic regression model predicts the probability of a 50-year-old patient with a BMI of 22 receiving a 405 mg injection to experience an IAIV injection event to be 0.0032.

Thus, although these factors are predictive of risk, they do not ensure an event. In illustration of this point, although greater age, higher dose, and low BMI were found to be potential risk factors for an IAIV injection event, IAIV injection events have occurred in relatively young patients (in a 23-year-old- and a 27-year-old patient), in patients at lower OP Depot doses (in a patient receiving 100 mg/2 weeks), and in patients with high BMIs (three patients with BMIs defined as obese [BMI ≥30]).

Appendix 5.
Rationale for Using Beta-Binomial Model

The fact that 1 patient in the clinical trial database has experienced 2 IAIV injection events means that the binomial model is not accurate in calculating probabilities of patients experiencing an IAIV injection event; the binomial assumption of the probability (p) of a patient experiencing an IAIV injection event being constant for all patients and all injections does not hold.

One patient (Case 5) experienced a second IAIV injection event following his 35th injection (Case 8). If these IAIV injection events followed a binomial distribution, then p would be constant and could be estimated to be 25/34,825=0.000718. The probability that a patient would experience more than one event in 35 injections using the binomial model is 0.00030:

Pr{Patient has more than 1 event | 35 injections} =

   $= 1 - $ Pr{Pt has 0 events | 35 injections} $- $ Pr{Pt has 1 event | 35 injections}

   $= 1 - 0.975179 - 0.02452$

   $= 0.00030$

The binomial assumption of p being constant is therefore unlikely. The beta-binomial model is more appropriate for calculating probabilities of events occurring for a given number of injections.