CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-253

MEDICAL REVIEW

Review and Evaluation of Clinical Data
NDA #21-253

Sponsor:	Eli Lilly and Company
Drug:	Zyprexa IntraMuscular
Proposed Indication:	Acute Agitation
Material Submitted:	Update to 4-19-01 Approvable Response
Correspondence Date:	March 27, 2003
Date Received:	March 28, 2003

I. Background

On 6-15-00, the sponsor submitted this NDA for the approval of an intramuscular formulation of olanzapine in the treatment of acute agitation.

After filing the application, holding a Psychiatric Drugs Advisory Committee meeting on 2-14-01 to discuss the indication and safety issues, and completion of the NDA review process, the Division issued an approvable letter on 3-29-01. In summary, this letter indicated that approval would be contingent on acceptable responses to chemistry deficiencies discovered in the sponsor's ——— drug manufacturing operations during an inspection performed from 1-29-01 to 2-23-01. These deficiencies were conveyed to the sponsor in an FD 483. In addition, the following were requested:

1) foreign regulatory update.
2) world literature update.
3) submission of final printed labeling identical to that attached to the approvable letter.

On 4-19-01, Lilly submitted a response which addressed the latter three items. This response was reviewed by the undersigned on 5-18-01 and, by 8-27-01, we had reached agreement on labeling issues. However, final approval action could not be taken until the above mentioned chemistry deficiencies were resolved.

In anticipation of impending resolution of these deficiencies, Lilly submitted an update to their 4-19-01

approvable response on 3-27-03. The review clock for this response was not started until reinspection of the manufacturing facilities confirmed resolution of the chemistry deficiencies on 11-3-03. In addition, the sponsor submitted an updated labeling proposal on 2-13-04.

The 3-27-03 updated approvable response and 2-13-04 updated labeling proposal are reviewed below.

II. Updated Approvable Response

A. Foreign Regulatory Update

Zyprexa — has been approved by the European Union (EU) and 31 other countries, including Australia and Canada.

[ ]

Lilly reports no negative actions by foreign regulatory agencies with respect to Zyprexa —

B. Foreign Labeling

Lilly states that no foreign labeling text for Zyprexa — is contradictory to the agreed upon U.S. labeling text.

Attachment 1 of the submission contains a copy of the EU labeling (Summary of Product Characteristics or SPC) as well as currently approved labeling for Australia and Canada. This material was reviewed by the undersigned. Two important discrepancies between the SPC and the currently proposed labeling were noted:

1) the SPC (section 4.2) recommends a maximum total daily dose of intramuscular olanzapine of 20mg whereas the proposed U.S. labeling indicates a maximum of 30mg. I previously noted this discrepancy and discussed this difference in a review dated 8-2-01. Lilly explained at that time that the EU had requested the lower daily dose of IM olanzapine for the following reasons: 1) lack of conclusive evidence that doses beyond the first dose had efficacy, 2) concerns about the high incidence of orthostatic hypotension after maximal dosing in study HGJA, and 3) limited safety experience with maximal dosing in the pivotal trials due to the design of those studies. After

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[1] These countries are listed in Attachment 1 of the submission.

extensive discussion between Lilly and the EU, Lilly agreed to limit the total daily dose to 20mg in European labeling. Nonetheless, the sponsor felt that data from the controlled clinical trials with olanzapine IM and study HGJA support a regimen of up to three 10mg injections per day. I agree..

2) The SPC (section 4.3) contraindicates the use of intramuscular olanzapine in patients with a "known risk of narrow angle glaucoma." The proposed U.S. labeling addresses this concern under PRECAUTIONS/Use in Patients with Concomitant Illness, which states that olanzapine should be used with caution in patients with narrow angle glaucoma (due to the cholinergic receptor antagonism associated with olanzapine). This is similar to the U.S. labeling of this issue for other antipsychotics with anticholinergic properties (e.g., Clozaril). The reason that this concern is labeled as a CONTRAINDICATION in EU labeling is not clear to me. Nonetheless, this issue is worthy of further consideration and Lilly should be requested to provide an explanation for this discrepancy.

Otherwise, no new safety concerns which would warrant a change to the proposed labeling were identified.

C. World Literature Update

Lilly has performed an update to their previous literature search, which had a cut-off date of 4-9-01. The methodology of the search and results were addressed in my 5-18-01 clinical review. The updated search encompasses the period from 4-10-01 to 3-10-03, inclusive. A total of 64 new articles were identified and systematically reviewed by the sponsor. Lilly states that this search did not reveal new data regarding the safety or efficacy of intramuscular olanzapine that has not been submitted to the NDA previously.

D. New Phase 1 Studies

This submission includes the study reports for three clinical pharmacology studies which were conducted as part of the Japanese registration program. These studies comprised the only new clinical trial experience with Zyprexa — as of the date of the submission.

From a clinical perspective, I examined all serious adverse experiences and adverse events that led to premature discontinuation in these three trials. Findings are summarized below.

Study F1D-JE-HGJM

This was a randomized, double-blind, placebo-controlled, sequential-dosing study of 3 single doses of intramuscular olanzapine (1, 2, and 4mg) in a total of 18 healthy Japanese males to determine safety and pharmacokinetics in this population.

There were no deaths, no serious adverse experiences, and no adverse events that led to dropout.

Study F1D-FW-LOBI

This was a randomized, double-blind, three-period crossover study which involved two groups of 12 healthy subjects of different ethnic origin (Chinese and Caucasian). The study objectives were to assess the pharmacokinetics and pharmacodynamics of intramuscular olanzapine at single doses of 1, 2, and 4mg in these two populations.

There were no deaths and no serious adverse events. No subjects were discontinued due to adverse experiences.

Study F1D-JE-LOBJ

This was a double-blind, three-period crossover study in which 12 healthy Japanese subjects received a sequence of three single doses of intramuscular olanzapine (1, 2, and 4mg) in randomized fashion to assess pharmacokinetics and pharmacodynamic responses.

No subjects died or experienced serious adverse events. No adverse experiences led to discontinuation from the study.

III. Updated Labeling Proposal

On 2-13-04, Lilly provided updated proposed labeling in electronic format, with text and tables relevant to Zyprexa IM highlighted.[2]

[2] Information for all three Zyprexa formulations (Zyprexa Tablets, Zyprexa Zydis, and Zyprexa IntraMuscular) is conveyed in single, unified labeling.

[redacted] this labeling supplement provides for the addition of safety data regarding the use of olanzapine in treating psychosis in elderly, demented patients.

I compared the highlighted text and tables to the labeling agreed-upon on 8-27-01. These are acceptable with one possible exception: although the sponsor has deleted [redacted] it appears that some of the information in the Clinical Efficacy Data section has not been modified to reflect this deletion. Specifically, in the first paragraph under Agitation Associated with Schizophrenia and Bipolar I Mania, the mean baseline PANSS Excited Component score ([redacted] and score range [redacted] are identical to those for the pool of all four studies (i.e., including the agitation in [redacted] trial). The sponsor should either verify that these figures remain correct or recompute them as appropriate.

IV. Conclusions and Recommendations

This approvable response update raises only two minor issues which should be resolved prior to final approval:

1) the sponsor should provide an explanation for the contraindicated use of olanzapine in patients with narrow angle glaucoma in the EU SPC so that a decision can be reached regarding a corresponding contraindication in Zyprexa labeling.

2) the sponsor should verify that the baseline PANSS Excited Component information (mean and range) is accurate under the Clinical Efficacy Data subsection of proposed labeling, as discussed above.

From a clinical perspective, once these issues have been resolved, this NDA may be approved.

/S/

Gregory M. Dubitsky, M.D.
February 26, 2004

cc: NDA #21-253
HFD-120 (Div. File)
HFD-120/GDubitsky
/PAndreason
/TLaughren
/SHardeman

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	21-253
Sponsor:	Eli Lilly and Company
Due Date:	April 16, 2001

Drug Name:

Generic Name:	Olanzapine for injection
Trade Name:	Zyprexa IntraMuscular

Drug Categorization:

Pharmacological Class:	Dopamine/Serotonin Receptor Antagonist
Proposed Indication:	Rapid control of agitation
Dosage Forms:	10mg Vials
Route:	Intramuscular

Review Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Completion Date:	March 10, 2001

NDA 21-253
ZYPREXA —
Table of Contents

1.0 Materials Utilized in the NDA Review

1.1 Materials from NDA/IND

This NDA review utilized the following materials:

NDA VOLUMES	SUBMISSION DATE	MATERIAL
1.1	6/15/00	Table of contents Financial disclosure data Draft labeling
1.2	"	Foreign marketing information Application summary
1.33-1.35	"	LOAC Study Report
1.36-1.37	"	LOAW Study Report
1.38-1.40	"	LOAV Study Report
1.41-1.44	"	LOAR Study Report
1.45-1.48	"	LOAT Study Report
1.49-1.54	"	HGHB Study Report
1.55-1.59	"	HGHV Study Report
1.60-1.64	"	HGHW Study Report
1.65-1.72	"	— Study Report
1.83	"	Integrated Summary of Efficacy
1.84-1.86	"	Integrated Summary of Safety
2.1	9/1/00	Errors in original submission
3.1	10/11/00	HGIO Study Report
3.2-3.3	"	HGJA Study Report
4.1	12/1/00	—— Amended Study Report
7.1-7.2	12/20/00	Amended ISS and Draft Labeling
T32405	1/26/01	Telemetry Tracings

Additionally, Case Report Tabulations (as SAS transport (.XPT) files) and Case Report Forms were provided in electronic format with the original submission and were accessed via the CDER Electronic Document Room (EDR) at Y:\\CDSESUB1\N21253\N_000\2000-06-15.

Since much individual patient data were derived from Narrative Summaries, summaries were audited to check the accuracy and completeness of safety information compared to

the information in the corresponding Case Report Forms (see section 8.3). This audit entailed a review of Case Report Forms for the following four patients:

Study HGHB, Patients 0272 and 3051
Study LOAV, Subject 2843
Study ——, Patient 3602

1.2 Related Reviews and Consultations

This NDA was the subject of a meeting of the Psychopharmacological Drugs Advisory Committee (PDAC) on February 14, 2001.

A statistical review of the key efficacy studies was performed by Ohidul Siddiqui, Ph.D., of the Division of Biometrics I.

A review of the pharmacokinetic studies was performed by Hong Zhao, Ph.D., of the Office of Clinical Pharmacology and Biopharmaceutics.

Consultation was obtained from the Division of Cardiorenal Drug Products (HFD-110) for an assessment of sinus pauses documented on telemetry in clinical pharmacology studies (see sections 8.1.2, 8.1.3.2, and 8.4.3).

2.0 Background

2.1 Indication

This NDA is intended to obtain approval of intramuscular olanzapine (Zyprexa—— for the treatment of acute agitation.

At present, acutely agitated patients in the clinical setting who require parenteral medication generally receive a benzodiazepine or a older, typical antipsychotic. Benzodiazepines have some potential disadvantages, such as sedation and ataxia. Among the typical antipsychotics, the low potency agents, such as chlorpromazine, tend to produce excessive sedation and orthostatic hypotension; the higher potency agents, such as haloperidol, are associated with acute dystonic reactions and other extrapyramidal symptoms.

Although olanzapine and other atypical antipsychotics also possess some disadvantages, such as postural hypotension, they are thought by many to have less propensity to cause extrapyramidal effects which may negatively impact on future compliance with antipsychotic medication. Since there are no other atypical antipsychotics available in the U.S. for parenteral administration, intramuscular olanzapine may be a useful addition to the armamentarium for treating acute agitation.

Agitation has not generally been viewed as a specific diagnostic entity but instead as a non-specific behavior that commonly occurs across a number of disorders. The Agency is willing to recognize such non-specific signs and symptoms (e.g., pain and fever) as an indication for drug treatment under certain circumstances, the following of which are considered ideal: 1) if they can be universally defined, 2) if they can be assessed using a commonly accepted method, 3) if they have a well understood pathophysiologic basis, 4) if they are equally responsive to treatment regardless of context, and 5) if the claim is supported across several disease models.[1]

While our understanding of the pathophysiologic basis for agitation (condition 3 above) is incomplete, the sponsor does presume that agitation can be universally defined and can be assessed by generally accepted methods.

Furthermore, in this application, they purport to demonstrate that agitation is equally and rapidly responsive to treatment with intramuscular olanzapine across —— diagnostic groups (patients with schizophrenic illness, bipolar disorder, ——— . Hence, Lilly contends that agitation is a legitimate indication for treatment with intramuscular olanzapine.

2.2 Important Information from Related IND's and NDA's

Olanzapine is structurally related to the approved atypical antipsychotic clozapine and shares many features of the safety profile of that drug, such as orthostatic hypotension, weight gain, and constipation. However, at

oral doses to 20 mg/day, olanzapine is not known to be associated with agranulocytosis, a major toxic effect of clozapine.

2.3 Administrative History[2]

IND 55,342 for intramuscular olanzapine was received by the Agency on March 4, 1998. The review team met on April 1, 1998, and it was decided to allow the sponsor to proceed.

The sponsor met with the Division on May 14, 1998, to discuss several options for developing intramuscular olanzapine, including a potential plan for the treatment of acute agitation. The sponsor was informed that pursuing an agitation indication would require clinical trials in a variety of patient populations, analogous to development programs for the indication [ ]

A teleconference was held on November 12, 1998, between Lilly and the Agency regarding a plan to study IM olanzapine for agitation in [ ] patient populations (schizophrenia, bipolar mania, [ ]. We indicated general agreement with this plan.

On January 15, 1999, the sponsor submitted a written summary of their proposed development program for the use of intramuscular olanzapine in the treatment of acute agitation. This plan was reviewed by Paul Andreason, M.D., and was deemed to be adequate; however, a biometrics consultation was requested to evaluate the impact of an interim analysis in study HGHB.

A pre-NDA meeting was held with the sponsor on January 6, 2000. We acknowledged that the program conducted to support an agitation indication was consistent with our previous recommendations and stated that input from the Psychopharmacological Drugs Advisory Committee would be sought regarding the new agitation indication. [ ]

[ ] It would also be necessary to conduct a trial to study the

[2] Most of the information in this section was derived from the sponsor's submission (volume 1.1, Tab 0.C) since many items (e.g., meeting minutes) were missing from the Division file.

pharmacokinetics of dosing under the conditions of maximum dose and frequency of administration to be recommended in labeling. Finally, we agreed that submission of pediatric data could be deferred until after approval of IM olanzapine for adult use.

On March 6 and April 13, 2000, the sponsor submitted protocol summaries for two clinical pharmacology studies (HGJA and HGIO) intended to address concerns raised at the pre-NDA meeting, [redacted]. Lilly also requested permission to submit the reports from these studies within 4 months of the initial NDA submission. We responded by E-Mail that the study designs were acceptable as was their plan to submit the reports within 4 months of the initial submission.

This NDA was submitted on June 15, 2000. A Refuse-to-File meeting was convened on August 1, 2000, and the submission was judged to be fileable.

Representatives of the sponsor and the Division met on January 18, 2001, to discuss the Agenda for the February 2001 PDAC meeting.

The PDAC convened on February 14, 2001, to discuss this NDA, in particular the "agitation" indication for Zyprexa IntraMuscular.

2.4 Financial Disclosure Information

There are four trials in this NDA submission that are considered "covered clinical studies" in accordance with 21 CFR 54.2(e): HGHB, HGHV, HGHW, and [redacted]

Among the clinical investigators in these trials, two were identified by the sponsor as having participated in financial arrangements with the sponsor that require disclosure:

1) [redacted] was the principal investigator for site [redacted] in study [redacted] and site [redacted] in study [redacted] speakers fees, [redacted] received $118,500 in [redacted] and $42,000 in [redacted] contributed 3% of the randomized patients in [redacted] and 3% of the randomized patients in study [redacted]

2) ——————————— principal investigator for ——————————— As speakers fees, [ ] received $118,000 in — and $48,000 in — — contributed 1% of the randomized patients in study———

Given the double-blind design of these studies and the relatively small numbers of patients contributed by these investigators, it is very unlikely that these financial interests have an appreciable impact on the reliability of these studies.

A number of sub-investigators in these trials were identified by Lilly as not having provided financial disclosure information: 9 sub-investigators in study HGHB, 5 in HGHV, 24 in HGHW, and 34 ——— The sponsor indicated that, despite due diligence, the required information could not be obtained because of lack of response to repeated requests or departure of the individual from the research site with no available forwarding address.

2.5 Directions for Use

The directions for the administration of Zyprexa — for the rapid control of agitation, as described in the sponsor's 12-20-00 proposed labeling, are as follows:

[ ]

[ ]

[ ]

[ ]

2.6 Foreign Marketing

The short-acting intramuscular [ ] formulation of olanzapine is not marketed in any country. The first marketing application was submitted during May 2000 in Europe.

3.0 Drug Substance and Product Information

3.1 Chemistry

According to the reviewer from the Office of New Drug Chemistry, Sherita McLamore, Ph.D., the Lilly manufacturing site failed an Agency inspection.

Unless the deficiencies can be resolved, this drug product may not be approved.

3.2 Microbiology

The Microbiology Review of this NDA was conducted by Bryan S. Riley, Ph.D., of HFD-805, and signed-off on 2-16-01. This review encompassed the manufacture of — the lyophilized drug product [ ]

Dr. Riley noted a number of deficiencies that must be resolved before this NDA may be approved.

4.0 Animal Pharmacology

Non-clinical pharmacology information is cross-referenced to NDA 20-592 for oral olanzapine.

At this time, the pharmacology/toxicology review has not yet been completed and the information below has been extracted from the Nonclinical Pharmacology, ADME, and Toxicology Summary in the NDA (volume 1.2, Tab 3.E).

A one-month study in beagle dogs administered IM olanzapine doses of 0, 0.5, 1.25, or 2.5 mg/kg/day in 1.5ml of solution revealed no compound-related systemic changes. The maximum solution concentration was about 8.4 mg/ml.[3] Injection site lesions were variable both between dogs and between sites on the same dog and were generally mild.

In an in vitro study using rat skeletal myoblast cell cultures, olanzapine concentrations ≥4.2 mg/ml were slightly to moderately irritating.

An in vivo study in rabbits demonstrated that olanzapine formulations of 1.7, 4.2, and 8.4 mg/ml were slightly irritating to skeletal muscle, with the high dose being associated with slightly more reaction.

ADME studies were conducted in beagle dogs and cynomolgus monkeys. After intramuscular injection, olanzapine was rapidly absorbed in both species.

The absolute bioavailability in dogs was about 100%. Intramuscular administration produced greater peak plasma levels and AUC's, shorter times to Cmax, and similar half-lives compared to oral administration.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Design and Patient Enumeration

As of October 11, 2000, the Lilly development program for intramuscular olanzapine consisted of 11 completed human studies involving a total of 848 patients/healthy volunteers who received at least one dose of IM olanzapine:

[3] This information was obtained from the Pharmacology/Toxicology reviewer, Lois Freed, Ph.D.

• 4 studies in healthy volunteers (F1D-EW-LOAC, F1D-EW-LOAW, F1D-LC-LOAV, and F1D-BD-HGIO).

• 2 open-label studies in patients with acute non-organic psychosis (F1D-EW-LOAR and F1D-EW-LOAT).

• 1 open-label tolerance and pharmacokinetic study in patients with chronic schizophrenia (F1D-MC-HGJA)

• 4 randomized, double-blind, placebo-controlled studies in schizophrenia/schizophreniform disorder/schizoaffective disorder (F1D-MC-HGHB and F1D-MC-HGHV), bipolar I disorder (F1D-MC-HGHW),

For sake of brevity, these studies will hereafter be referred to by the last four letters of the protocol number.

Table 5.1.1.1 in Appendix 5.0 summarizes the 11 completed studies. Table 5.1.1.2 in Appendix 5.0 provides an enumeration of these subjects by treatment group.

The safety review will focus on two subsets of the pool of the four placebo-controlled studies in patients:

• the pool of studies HGHB, HGHV, and HGHW; this is referred to as the placebo-controlled IM safety database.

•

5.1.2 Demographic Characteristics

Demographic characteristics for the placebo-controlled IM safety database are displayed in Appendix 5.0, Tables 5.1.2.1 and 5.1.2.2, respectively. For both datasets, treatment groups were comparable with respect to age, race, and gender.

5.1.3 Extent of Exposure

Appendix 5.0, Table 5.1.3, summarizes patient exposure to IM olanzapine based on total dose during the 24 hour IM period for the placebo-controlled IM safety database

Over half of the IM olanzapine patients in the placebo-controlled IM safety database received a total dose of 10.0mg of IM olanzapine over 24 hours (223/415 or 54%). The mean dose in this dataset was 10.8mg.

5.2 Secondary Sources of Clinical Data

5.2.1 Post-Marketing Experience

The short-acting intramuscular formulation of olanzapine had not been marketed in any country as of the time of this NDA submission (June 15, 2000). A marketing application was submitted in Europe during May 2000.

5.2.2 Literature Review

The sponsor conducted no search of the published literature for articles directly relevant to intramuscular olanzapine.

A literature search conducted by the undersigned on October 5, 2000, revealed no published articles with data relevant to intramuscular olanzapine.[4]

6.0 Human Pharmacokinetics

The pharmacokinetics of olanzapine after intramuscular administration in man is described by a two-compartment model. After intramuscular injection, there is a rapid rise in plasma olanzapine concentration to a peak value within several minutes secondary to rapid absorption. This is followed by a sharp drop in plasma concentration for a brief period, representing rapid redistribution from a central to a peripheral compartment. Finally, there is a monoexponential terminal elimination phase after the first 2 hours, with sustained concentrations for at least 96 hours post-injection. Please see Figure 6.0 below.

Pharmacokinetic attributes of olanzapine administered intramuscularly can be summarized as follows:

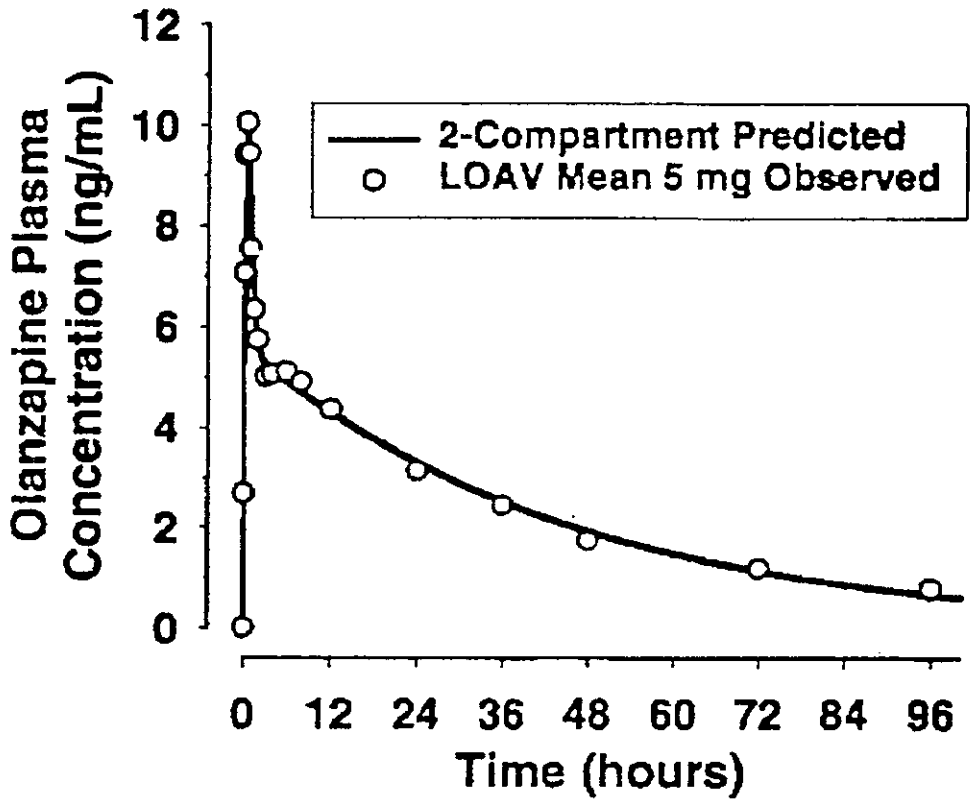
[4] This search utilized the search string "intramuscular olanzapine" in the PubMed database.

- IM administration of olanzapine produces a 4.5-fold higher Cmax than the same oral dose.
- Tmax after IM administration is 15-45 minutes versus 5-8 hours after oral administration.
- with both intramuscular and oral administration, Cmax and AUC are directly proportional to dose.
- administration of one or more IM doses daily produces a two-fold accumulation in plasma concentrations between days 1 and 3.
- metabolic profiles after intramuscular and oral administration are quantitatively similar and qualitatively identical.
- the administration of lorazepam one hour after an IM dose of olanzapine did not affect the pharmacokinetics of either drug but did produce additive sedation.

Additionally, a comparison of the range of values for Cmax under maximal dosing with IM olanzapine (10mg IM q4 hrs × 3 in study HGJA) with the range for Cmax at steady state under dosing with oral olanzapine 20 mg/day (from study HGAJ) revealed no substantial difference.[5]

[5] This is based on a separate analysis conducted by the OCPB reviewer.

FIGURE 6.0:
Time-Concentration Relationship
After Olanzapine 5mg IM In Healthy Volunteers



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7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The sponsor has conducted four multicenter, placebo-controlled trials to evaluate the efficacy of intramuscular olanzapine in the rapid control of agitation. These studies were performed in three different diagnostic groups:

- two trials (HGHB and HGHV) were done in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder.
- one trial (HGHW) was in patients with bipolar I disorder in an acute manic or mixed state.

In addition to the above four trials, the sponsor also conducted two open-label studies in South Africa in patients with acute, non-organic psychosis (LOAR and LOAT) and a third open-label study in patients with chronic stable schizophrenia (HGJA). In studies LOAR and LOAT, assessment of efficacy was a secondary objective. In study HGJA, efficacy was neither a primary nor secondary objective. By design, these trials are not capable of demonstrating the efficacy of IM olanzapine in the treatment of agitation and they will not be reviewed in detail here.

The Excited Component of the Positive and Negative Symptom Scale (PANSS), consisting of the poor impulse control, tension, hostility, uncooperativeness, and excitement items of the PANSS, was selected as the primary efficacy variable for the key IM olanzapine studies.[6] This variable was selected for the following reasons: 1) it has high face validity in measuring agitation, 2) it has been validated by the sponsor (see next paragraph), 3) it based on clinician observation as opposed to a verbal report from the patient, making it useful in diverse patient populations, and 4) it can be generalized to the populations studied.

[6] This component was derived by factor analysis from the PANSS by its creators. Each item was analyzed on a scale from 0 to 6 by subtracting 1 from each score, yielding a range for total scores of 0 to 30.

The PANSS Excited Component met all criteria for internal consistency, construct and discriminant validity, responsiveness, and reliability that were established in the sponsor's validation plan using a large sample of agitated and non-agitated patients in a premarketing study of oral olanzapine (HGAJ, N=1995, including 742 agitated patients). Internal consistency was assessed by Cronbach's alpha ($.7<\alpha<.9$). Evaluation of construct validity entailed investigation of the correlation at baseline of the Excited Component with the CGI-severity score ($r>.3$, $p<.05$). Discriminant validity was evaluated by demonstrating greater changes from baseline in the Excited Component for patients with CGI-severity scores >3 vs. ≤3 in the total population and for patients with a CGI score >4 vs. ≤4 in the agitated subset. Responsiveness was assayed by showing that the Excited Component change over time was greater for patients showing improvement on the CGI vs. those showing no improvement. Measurement of reliability demonstrated an intraclass correlation coefficient >.70.

Other scales for assessing agitation have been designed for specific patient groups and were assessed in these trials. The Corrigan Agitated Behavior Scale is used in patients with mania, psychoactive substance abuse, schizophrenia, schizophreniform disorder, and psychosis not otherwise specified. This is a 14 item scale, each item being a specific behavior that is rated 1 to 4. Also, the Cohen-Mansfield Agitation Inventory is a 30 item checklist of behaviors reflecting agitation and aggression (e.g., hitting, biting, screaming) that has been validated in patients [ ]

Additionally, to help insure that improvement in agitation was not merely secondary to oversedation, the sponsor developed a scale to differentiate between agitated, calm, and sleep states, the Agitation-Calmness Evaluation Scale (ACES). This single item scale is rated as 1 (marked agitation) to 9 (unarousable).

Results with respect to these additional, secondary scales will also be reviewed below.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study HGHB

Investigators/Locations

The 51 principal investigators and study sites are identified in Appendix 7.0, Table 7.2.1.1.

Objectives

The primary objectives of this study were :

1) to compare the efficacy of IM olanzapine to IM placebo as measured by the change from baseline to 2 hours post-injection on the PANSS Excited Component.
2) to determine if IM olanzapine is "non-inferior" to IM haloperidol as measured by the change from baseline to 2 hours post-injection on the PANSS Excited Component.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 18 years old.
- inpatient status during the study.
- DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.
- considered clinically agitated and appropriate candidates for treatment with IM medication.
- prior to the first IM injection, a PANSS Excited Component total score ≥14 with at least one item score ≥4 on a 1-7 scale.

Important exclusion criteria were:

- previous participation in a Lilly olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness.
- benzodiazepine treatment within 4 hours of the first IM administration of study drug.

- treatment with an injectable depot neuroleptic or injectable zuclopenthixol acetate within one injection interval prior to study drug administration.
- treatment with psychostimulants or reserpine within one week of study drug.
- treatment with clozapine within 6 weeks of study drug.
- requiring concomitant ECT.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

For at least 2 hours prior to randomization, antipsychotic medication was stopped and patients were screened. Also, patients were not to receive any benzodiazepine treatment during the four hours prior to the first injection of study drug.

Eligible patients were then randomized in a 2:2:1 ratio to olanzapine, haloperidol, or placebo, respectively, and received an intramuscular injection of the assigned medication (i.e., 10mg of olanzapine, 7.5mg of haloperidol, or placebo), which marked the beginning of the 24 hour "injectable treatment phase" of the study. During this phase, the following dosing rules applied:

- minimum number of injections was one.
- maximum number of injections was three.
- if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
- if a third injection was clinically indicated, it would be given at least 4 hours after the second injection.
- all injections would be given within 20 hours of the first injection.
- the maximum cumulative dose of IM olanzapine was 30mg and of IM haloperidol was 22.5mg within 20 hours.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The study drug for the injectable treatment phase was supplied in unblinded form. Blinding of the patient and personnel involved in clinical assessments was preserved by

utilizing an unblinded third party to prepare and administer the injections.

Vials for IM injections and all ancillary supplies (e.g., needles and syringes) were provided in randomized patient kits. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

The concomitant use of benzodiazepines was discouraged but were allowed during the IM treatment phase according to the following rules:

- patients who received only one injection of study drug could not be given a benzodiazepine.
- patients who received two injections of study drug may have received a benzodiazepine once, at least one hour after the second injection.
- patients who received a third injection may have been given a benzodiazepine dose at least one hour after the third injection.
- if no benzodiazepine was administered after the second injection, either one or two benzodiazepine doses may have been given after the third injection.
- permitted benzodiazepines and maximum total doses during the injectable treatment phase were as follows:

Lorazepam (IM or oral)	4mg
Diazepam (IM, IV, or oral)	20mg
Oxazepam (oral)	30mg
Chlorazepate (IM or oral)	50mg

Anticholinergic medication (specifically benztropine, biperiden, or procyclidine) was allowed to control extrapyramidal symptoms. However, their use as prophylaxis was not permitted.

An oral treatment phase followed the injectable treatment phase. This part of the study will be discussed in section 7.3.5.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the

assigned medication was not taken, the correct treatment was not received, or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 15, 30, 45, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

Analysis was performed using an ANOVA model with terms for treatment, country, and treatment-by-country interaction. If the interaction was not significant ($p>0.10$), then it was removed from the model.

Comparisons of IM olanzapine with IM placebo were tested at a two-sided significance level of 0.05.

Investigator sites were pooled within country for analysis. If there were less than 10 patients in a country, those data were pooled with data from other countries enrolling a small number of patients.

For total scores derived from individual scale items, the total score was treated as missing if any of the individual items were missing.

A re-estimation of sample size was conducted under the auspices of a data monitoring board from the first 109 patients that completed the 24 hour injectable treatment phase. This was not considered a formal interim analysis. Based on data from both active therapy groups (n=89), it was calculated that the originally planned sample size was adequate.

Baseline Demographics

Demographic characteristics of patients entered into the injectable period are displayed in Appendix 7.0, Table 7.2.1.2. Treatment groups were comparable with respect to age, gender composition, and race.

Baseline Severity of Illness

Baseline mean scores on the PANSS Excited Component were comparable across treatment groups (13.35, 13.17, and 13.37 for the IM olanzapine, haloperidol, and placebo groups, respectively).

Patient Disposition

A total of 325 patients entered the screening period. Ten patients were excluded due to entry criteria not being met and 4 due to patient decision. The remaining 311 eligible patients were randomized and, of these, 285 patients completed the injectable phase of the study. Patient disposition is displayed in Table 7.2.1.3 below. The proportion of completers was lowest in the placebo group (87%); most of the dropouts in this group (5/7) were for lack of efficacy.

Protocol Violations

Over 350 protocol violations were noted in this trial. Table 7.2.1.4 below enumerates the types of violations that could confound the efficacy results of the study.

The impact of these violations on the efficacy results cannot be accurately gauged but, given the generally small number of violations, it is unlikely that the results were significantly biased.

TABLE 7.2.1.3:
STUDY HGHB
INJECTABLE PHASE
PATIENT DISPOSITION

Reason	IM Olanz	IM Hal	IM Placebo
Randomized	131	126	54
Dropouts (by reason)			
Adverse Event	2	3	0
Lack of Efficacy	2	0	5
Patient Decision	5	4	2
Criteria/Compliance	0	2	0
Physician Decision	0	1	0
Completed Phase	122	116	47

TABLE 7.2.1.4 STUDY HGHB INJECTABLE PHASE ENUMERATION OF POTENTIALLY SIGNIFICANT PROTOCOL VIOLATIONS			
Violation Category	IM Olanz	IM Hal	IM Plac
Use of excluded medication ≤2 hours before first injection	2[7]	4	0
Use of excluded medication during the entire study	3[8]	0	0
Prohibited use of benzodiazepines after the first injection	2	2	1
Inadequate study drug dose for first injection	5	6	0
Excessive study drug dose for first injection	1	1	0
Same person administered drug and performed ratings	3	1	2

Efficacy Results

The efficacy results for the first 2 hour period of the injectable treatment phase on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.1.5.

IM Olanzapine was superior to placebo to a highly significant degree ($p<0.001$) on the PANSS Excited Component at 30, 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis.

The Corrigan Agitated Behavior Scale and the Agitation-Calmness Evaluation Scale were examined as supportive secondary efficacy variables. Data for these variables are displayed in Appendix 7.0, Tables 7.2.1.6 and 7.2.1.7, respectively. Results were the same as for the primary variable.

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine occurred without

[7] Patient 102-1063 received a dose of clomipramine, sodium valproate, thioridazine, and maprotiline. Patient 013-0611 received temazepam.
[8] Patient 202-2081 received propranolol, patient 851-8556 received cyproterone (an antiandrogenic steroid), and patient 006-0254 received nifedipine intermittently.

excessive sedation on average. The mean change on this 9 point rating scale was +1.79 (range [redacted]): from a baseline mean of 2.59 (indicating mild-moderate agitation) to 4.37 (normal-mild calmness) at 120 minutes post-injection (LOCF).

There was no evidence to suggest a treatment-by-country interaction (p=0.843 in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted during the IM treatment phase but subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of the optional injections, and 3) benzodiazepine use. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Data from the oral treatment phase of this study will be presented in section 7.3.5.

Conclusions

Study HGHB provides strong evidence for the efficacy of IM olanzapine 10mg versus placebo in the acute treatment of agitation in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder.

7.2.2 Study HGHV

Investigators/Locations

The 14 investigators and study sites are listed in Appendix 7.0, Table 7.2.2.1.

Objectives

The primary study objective was to evaluate the efficacy of IM olanzapine 2.5, 5, 7.5, and 10mg relative to IM placebo for agitation as measured by changes from baseline to 2 hours post-injection on the PANSS Excited Component.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 18 years old.
- inpatient status.
- DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.
- considered clinically agitated and appropriate candidates for treatment with IM medication.
- prior to the first IM injection, a PANSS Excited Component total score ≥14 with at least one item score ≥4 on a 1-7 scale.

Important exclusion criteria were:

- previous participation in a Lilly intramuscular olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness.
- benzodiazepine treatment within 4 hours of the first IM administration of study drug.
- treatment with an injectable depot neuroleptic or injectable zuclopenthixol acetate within one injection interval prior to study drug administration.
- treatment with psychostimulants or reserpine within one week of study drug.
- treatment with clozapine within 6 weeks of study drug.
- requiring concomitant ECT.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

For at least 2 hours prior to randomization, antipsychotic medication was stopped and patients were screened. Also, patients were not to receive any benzodiazepine treatment during the four hours prior to the first injection of study drug.

Eligible patients were then randomized to one of four fixed doses of IM olanzapine (2.5, 5, 7.5, or 10mg), IM haloperidol 7.5mg, or IM placebo. The following rules for dosing applied:

- minimum number of injections was one.

- maximum number of injections was three.
- if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
- if a third injection was clinically indicated, it would be given at least 4 hours after the second injection.
- all injections would be given within 20 hours of the first injection.
- the maximum cumulative dose within 20 hours for IM olanzapine was 7.5, 15, 22.5, and 30mg for each of the above dose groups, respectively; the maximum dose of IM haloperidol was 22.5mg within this period.
- if a concomitant benzodiazepine was administered, at least one hour was to elapse between this administration and further injection of study drug.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The study drug was supplied in unblinded form. Blinding of the patient and personnel involved in clinical assessments was preserved by utilizing an unblinded third party to prepare and administer the injections.

Vials for IM injections and all ancillary supplies (e.g., needles and syringes) were provided in randomized patient kits. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

The concomitant use of benzodiazepines was discouraged but were allowed during the IM treatment phase according to the following rules:

- patients who received only one injection of study drug could not be given a benzodiazepine.
- patients who received two injections of study drug may have received a benzodiazepine once, at least one hour after the second injection.
- patients who received a third injection may have been given a benzodiazepine dose at least one hour after the third injection.

- if no benzodiazepine was administered after the second injection, either one or two benzodiazepine doses may have been given after the third injection.
- permitted benzodiazepines and maximum total doses during the injectable treatment phase were as follows:

Lorazepam (IM or oral)	4mg
Diazepam (IM, IV, or oral)	20mg
Oxazepam (oral)	30mg
Chlorazepate (IM or oral)	50mg

Anticholinergic medication (specifically benztropine, biperiden, or procyclidine) was allowed to control extrapyramidal symptoms. However, their use as prophylaxis was not permitted.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the assigned medication was not taken, the correct treatment was not received, or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 30, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

Analysis was performed using an ANOVA model with terms for treatment, country, and treatment-by-country interaction. If the interaction was not significant ($p>0.10$), then it was removed from the model.

Investigator sites were pooled within country for analysis. If there were less than 12 patients in a country, those data were pooled with data from other countries enrolling a small number of patients.

For total scores derived from individual scale items, the total score was treated as missing if any of the individual items were missing.

Baseline Demographics

Demographic characteristics of patients entered into the injectable period are displayed in Appendix 7.0, Table 7.2.2.2. Treatment groups were comparable with respect to age, gender composition, and race.

Baseline Severity of Illness

Baseline mean scores on the PANSS Excited Component were comparable across treatment groups: 13.25, 14.71, 13.85, 14.30, 14.28, 13.78 for the IM olanzapine 2.5, 5, 7.5, and 10mg groups; the haloperidol group, and the placebo group, respectively.

Patient Disposition

A total of 282 patients were screened. Twelve patients were not randomized, 2 due to physician decision, 9 due to not meeting entry criteria, and 1 due to patient decision.

The remaining 270 patients were randomized and, of these, 268 patients completed the study. There were only 2 dropouts, both from the IM olanzapine 5mg group: one due to lack of efficacy and one due to physician decision. Both dropped out after the 2 hour post-first injection period.

Protocol Violations

Over 100 protocol violations were noted in this trial. Table 7.2.2.3 below enumerates the types of violations that would seem to possess the most potential to confound the efficacy results of the study.

TABLE 7.2.2.3
STUDY HGHV
ENUMERATION OF POTENTIALLY SIGNIFICANT PROTOCOL VIOLATIONS

Violation Category	IM Olanz				IM Hal	IM Plac
	2.5	5	7.5	10		
Prohibited use of benzodiazepines	2	1	0	4	0	2
Use of excluded medication	0	1	0	2	2	1
Study drug not administered per protocol	1	1	1	1	1	3

The impact of these violations on the efficacy results cannot be accurately gauged but, given the relatively small number of violations, it is unlikely that the results were significantly biased.

Efficacy Results

The efficacy results at 2 hours after the first injection of study drug on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.2.4.

The sponsor did not specify a method of adjusting for multiplicity when comparing each dose of olanzapine to placebo in pairwise fashion. For purposes of interpreting these efficacy data, this reviewer used the conservative Bonferroni procedure, which yields an alpha level of 0.0125 (0.0500÷4) for declaring statistical significance.

IM Olanzapine 5, 7.5, and 10mg were superior to placebo to a highly significant degree ($p<0.001$) on the PANSS Excited Component at 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis. The 2.5mg dose was superior to placebo at 120 minutes post-injection in both OC and LOCF analyses.

The Agitation-Calmness Evaluation Scale was examined as a supportive secondary efficacy variable. Data for this variable are displayed in Appendix 7.0, Tables 7.2.2.5. Results were the same as for the primary variable except that the low dose (2.5mg) was not superior to placebo.

Additionally, the results of the LOCF analysis of the mean change from baseline to 2 hours post-first injection for the Corrigan Agitated Behavior Scale are shown in Table 7.2.2.6 below. (Results for the observed cases analysis are expected to be similar since there were no dropouts in the 2 hour period after the first injection.) All active drug groups were superior to placebo on this variable at 120 minutes post-first injection, with the 5, 7.5, and 10mg doses of olanzapine highly superior.

TABLE 7.2.2.6 STUDY HGHV MEAN CHANGE FROM BASELINE IN THE CORRIGAN AGITATED BEHAVIOR SCALE AFTER FIRST INJECTION LOCF ANALYSIS				
	Baseline		120 minutes	p-value vs. placebo
	N	Mean	Mean Δ	
Olz 2.5	48	29.27	-5.81	0.012
Olz 5	45	31.38	-8.96	<0.001
Olz 7.5	46	31.24	-10.50	<0.001
Olz 10	46	30.76	-10.39	<0.001
Hal 7.5	39	30.13	-7.69	<0.001
Plac	45	29.98	-3.00	---

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine occurred without excessive sedation on average. The mean changes on this 9 point rating scale were in the range +1 to +3, from baseline means of just over 2 (indicating mild-moderate agitation) to generally over 4 (normal-mild calmness) at 120 minutes post-injection (LOCF).

There was no evidence to suggest a treatment-by-country interaction (p=0.135 in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of the optional injections, and 3) benzodiazepine use. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Conclusions

Data from study HGHV demonstrate the efficacy of IM olanzapine in doses of 5, 7.5, and 10mg in the acute treatment of agitation in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder. Data for the 2.5mg dose are weaker and less consistent but positive on the primary efficacy variable as well as the Corrigan Agitated Behavior Scale in the LOCF analysis.

7.2.3 Study HGHW

Investigators/Locations

This trial was conducted by 29 principal investigators, who are listed in Appendix 7.0, Table 7.2.3.1.

Objectives

The primary study objective was to evaluate the efficacy of IM olanzapine versus IM placebo in treating agitation as measured by the change from baseline to 2 hours post-first injection on the PANSS Excited Component.

Patient Sample

Study inclusion criteria included the following:

- male or female at least 18 years old.
- inpatient status.
- considered clinically agitated and appropriate candidates for treatment with IM medication.
- DSM-IV diagnosis of bipolar I disorder with an acute manic or mixed episode. Diagnosis was confirmed via SCID at some point during the double-blind treatment period.
- illness must not have been secondary to substance abuse, in the opinion of the investigator.
- prior to the first IM injection, a PANSS Excited Component total score ≥14 with at least one item score ≥4 on a 1-7 scale.

Important exclusion criteria were:

- previous participation in a Lilly short-acting intramuscular olanzapine trial.
- serious suicide risk.
- serious, unstable medical illness.
- DSM-IV substance dependence (except nicotine or caffeine) within 30 days.
- treatment with clozapine within the prior 6 weeks.
- benzodiazepine treatment (oral or IM) within 4 hours of the first IM administration of study drug.
- treatment with carbamazepine with 24 hours.
- treatment with short-acting IM injection or oral neuroleptics within 4 hours.

• treatment with psychostimulants or reserpine within one week of study drug.
• any other medication with primarily CNS activity within 48 hours.[9]

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

For a period of at least 2 hours prior to randomization, patients were screened for study eligibility. Eligible patients were then randomized to one of three treatment groups in a 2:1:1 ratio: IM olanzapine, IM lorazepam, or IM placebo. The double-blind treatment period was 24 hours in duration, during which the following rules for dosing applied:

• maximum number of IM injections was three.
• minimum number of IM injections was one.
• if a second injection was clinically indicated, it would be given at least 2 hours after the first injection and subsequent to the 2 hour post-first injection assessments.
• if a third injection was clinically indicated, it would be given at least 1 hour after the second injection.
• the maximum cumulative dose within 20 hours was 25mg for IM olanzapine and 5mg for IM lorazepam.

The decision whether to administer a second or third injection of study drug was made by the investigator based on clinical judgement.

The dosage for each injection is displayed in Table 7.2.3.2 below.

[9] Except for currently prescribed anti-manic medication and anticholinergics (benztropine, biperiden, procyclidine) for control of EPS.

TABLE 7.2.3.2 STUDY HGHW INTRAMUSCULAR DOSING			
Treatment	Injection #1	Injection #2	Injection #3
Olanzapine	10mg	10mg	5mg
Lorazepam	2mg	2mg	1mg
Placebo	0mg	0mg	Olanzapine 10mg

The study drug was supplied in unblinded form (open-label vials). Blinding of the patient and personnel involved in clinical assessments was preserved by utilizing an unblinded third party to prepare and administer the injections. Olanzapine powder for injection was reconstituted using sterile water provided by the study site. All injections prepared on-site must have been used within 30 minutes of preparation.

The use of concurrent anti-manic medication (lithium or valproate) and other non-pharmacologic interventions (hospitalization, quiet room, psychotherapy) were permitted.

Anticholinergic medication (specifically benztropine, biperiden, or procyclidine) was allowed to control extrapyramidal symptoms. However, their use as prophylaxis was not permitted.

The concomitant use of benzodiazepines was not allowed in this trial.

Analysis

The primary analysis was performed on an intent-to-treat basis, i.e., by the groups randomly assigned even if the assigned medication was not taken or the protocol was not followed. LOCF analyses included only patients with both a baseline and a post-baseline assessment.

The primary efficacy variable was the change from baseline to 2 hours post-first IM dose on the PANSS Excited Component, which was assessed pre-dose and at 30, 60, 90 and 120 minutes after the first injection. A baseline measure was the score obtained immediately prior to the first IM injection.

TABLE 7.2.3.4: STUDY HGHW PATIENT DISPOSITION			
Reason	Olanz	Lor	Placebo
Randomized	99	51	51
Dropouts (by reason)			
Lack of Efficacy	0	2	0
Patient Decision	1	0	2
Criteria/Compliance	0	1	1
Crossover (Plac→Olanz)	0	0	21
Completed Study	98	48	27

Protocol Violations

Over 260 protocol violations occurred in this study. Except as discussed below, the types of violations were not likely to bias the efficacy findings, in my opinion.

A total of 9 patients who completed the study received medication in violation of the study entry criteria: 3 were in the olanzapine group, 2 in the lorazepam group, and 3 in the placebo group. While it is difficult to estimate the influence of this use on the efficacy results, it is likely to be minimal given the small number of violators.

One placebo patient (009-0902) received IM olanzapine as injection #1 by mistake. This error is unlikely to bias the results in favor of olanzapine.

Violations in the use of concomitant anti-manic medication occurred in 9 patients: 4 olanzapine patients, 3 lorazepam patients, and 2 placebo patients. The timing of these violations in not known (i.e., ≤2 hours of first injection versus >2 hours after first injection). The effect of these violations on the efficacy results is unknown but, given the relatively small number of violations, it seems unlikely that the results were significantly biased.

Concomitant Medications

The percentages of patients who used various anti-manic agents concomitantly are provided in Table 7.2.3.5 below.

The only statistically significant difference between treatment groups was noted for the use of lithium carbonate (p=0.019): 2 olanzapine and 5 placebo patients used this agent concomitantly. This use is unlikely to bias the efficacy results in favor of olanzapine.

TABLE 7.2.3.5
STUDY HGHW
PERCENTAGE OF PATIENTS USING CONCOMITANT ANTI-MANIC AGENTS

	Olanz N=99	Lor N=51	Plac N=51
Gabapentin[10]	0.0%	3.9%	0.0%
Lithium	10.1%	9.8%	19.6%
Lithium Carbonate	2.0%	0.0%	9.8%
Lithium Citrate	1.0%	0.0%	0.0%
Valproate Semisodium	30.3%	19.6%	23.5%
Valproate Sodium	2.0%	0.0%	0.0%
Valproic Acid	0.0%	3.9%	2.0%

Efficacy Results

The efficacy results at 2 hours after the first injection of study drug on the PANSS Excited Component, the primary efficacy variable, are presented in Appendix 7.0, Table 7.2.3.6.

IM Olanzapine was superior to placebo to a highly significant degree ($p \leq 0.003$) on the PANSS Excited Component at 30, 60, 90, and 120 minutes post-injection for the observed cases dataset and at 120 minutes using an LOCF analysis.

The Corrigan Agitated Behavior Scale and the Agitation-Calmness Evaluation Scale were examined as supportive secondary efficacy variables. Data for these variables are displayed in Appendix 7.0, Tables 7.2.3.7 and 7.2.3.8, respectively. Results were the same as for the primary variable.

Data for the Agitation-Calmness Evaluation Scale suggest that improvement with IM olanzapine occurred without excessive sedation on average. The mean change on this 9 point rating scale was +2.90 (range 0.0 to +6.0): from a

[10] Gabapentin is not approved by the Agency as an anti-manic agent. However, it is listed since some feel that it has anti-manic properties.

baseline mean of 2.24 (indicating mild-moderate agitation) to 5.14 (mild-moderate calmness) at 120 minutes post-injection (LOCF).

There was no evidence to suggest a treatment-by-country interaction (p=0.362 in the LOCF analysis of the PANSS Excited Component at 120 minutes).

Efficacy assessments conducted subsequent to the 2 hour period following the first injection are potentially confounded by 1) a variable number of doses of study medication, 2) variable timing of optional dosing, and 3) possible olanzapine administration to placebo patients as a third injection. These efficacy data cannot be reliably interpreted and are not germane to the primary study objectives. These data will be summarized in section 7.3.4.

Conclusions

Study HGHW provides strong evidence for the efficacy of IM olanzapine 10mg versus placebo in the acute treatment of agitation in patients with bipolar I disorder.

7.2.4 ———

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Attachment B

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

The sponsor conducted subgroup analyses within each of the four key efficacy studies to detect significant treatment-by-subgroup interactions ($p<0.10$) for the following demographic variables: gender, age (<40 vs. ≥40 years for HGHB, HGHV, and HGHW [redacted], and origin (Caucasian vs. other racial groups). These analyses examined the changes in the PANSS Excited Component for all four studies as well as the Corrigan Agitated Behavior Scale (for HGHB, HGHV, and HGHW) [redacted] This review focused on possible interactions at the 2 hour post-first injection timepoint.

Only two such interactions were reported. In both HGHV and HGHW, there were significant treatment-by-origin interactions.

In HGHV, there were greater improvements on the PANSS Excited Component in the IM haloperidol- and IM placebo-treated patients of non-Caucasian origin compared to Caucasian patients ($p=0.013$).[12]

In HGHW, there were greater improvements on both the PANSS Excited Component and the Corrigan Agitated Behavior Scale in olanzapine-treated patients of Caucasian origin compared to non-Caucasian patients (p-values of 0.074 and 0.034, respectively).[13]

Overall, there were no significant differences between demographic subgroups that were consistent across the four key efficacy studies.

7.3.2 Size of Treatment Effect

The mean differences between drug and placebo on the primary efficacy variable (PANSS Excited Component) at 2 hours post-first injection for each of the four key efficacy studies are displayed in Table 7.3.2 below.[14]

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[12] Data are displayed in volume 1.55, page 149.
[13] Data are displayed in volume 1.60, pages 140-143.
[14] The drug-placebo difference equals the mean change from baseline for drug minus the mean change from baseline for placebo in the LOCF

TABLE 7.3.2 MEAN DRUG-PLACEBO DIFFERENCES ON THE PANSS EXCITED COMPONENT AT TWO HOURS POST-FIRST INJECTION		
Study	Olanzapine Dose	Mean Difference
HGHB	10mg	-4.27
HGHV	2.5mg	-2.59
	5mg	-5.18
	7.5mg	-5.74
	10mg	-6.44
HGHW	10mg	-4.76
[		]

It is difficult to evaluate the size of the drug-placebo differences for these studies since there exists no historical standard for comparison.

Also, a given change on the Excited Component of the PANSS might represent a large change in one of the five items comprising this score, a much smaller change in each of the five items, or something in between these two extremes. This renders an assessment of the clinical relevance of a change in this measure uncertain.

Finally, the clinical importance of a change in any of the individual items may depend on the baseline rating for that item. For example, a change of -1 on the hostility item may reflect a severely hostile patient becoming moderately severely hostile or, on the other hand, a mildly hostile patient becoming minimally hostile.

The only other approach which is reasonable, albeit not ideal, is to compare these differences with those observed in the comparator treatment arms since both IM haloperidol and IM lorazepam have been found to be useful in treating agitation in clinical settings If the comparator data are used as a standard for clinically important effect sizes, then the above differences for olanzapine at doses of 5mg and higher can be considered clinically relevant and for the 2.5mg dose possibly relevant.

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database; thus, negative differences indicate superiority of drug over placebo.

7.3.3 Choice of Dose

Study HGHV examined the relationship between dose and therapeutic response in patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder. A series of step-down linear contrasts was used to determine the minimum effective dose based on the PANSS Excited Component during the two hour post-first injection period while protecting the overall experiment-wise error rate at $\alpha=0.05$. From among the four doses examined (2.5, 5, 7.5, and 10mg), the minimum effective dose was shown to be 2.5mg and a statistically significant monotonic dose response relationship was seen across the dose range of 2.5 to 10mg ($p<0.001$).

Data were not available to perform a similar analysis in the studies in bipolar disorder patients (HGHW) [redacted] The above data do support the sponsor's proposal to use the 10mg IM dose in agitation associated with bipolar disorder and both the 2.5 and 5mg IM doses in patients [redacted]

7.3.4 Duration of Treatment

Most (59% to 76%) of the olanzapine-treated patients in each of the dose groups of the four key efficacy studies required only one injection of olanzapine during the entire injectable treatment phase, except for patients in the 2.5mg dose group of study HGHV, where 52% needed more than one dose. All olanzapine dose groups in these studies, except for the 2.5mg dose in study HGHV, were statistically superior to placebo at 24 hours post-first injection based on an LOCF analysis of change in the PANSS Excited Component at the end of the injectable treatment phase. The 2.5mg dose group in HGHV showed a trend toward superiority.[15]

However, conclusions about the multiple dose efficacy of IM olanzapine based on these data must be drawn with a measure of caution because these studies were not adequately designed to rigorously assess the efficacy of repeated doses of intramuscular olanzapine in the treatment of acute agitation. In addition to the fact that most olanzapine patients received only one IM dose and that those who received more than one injection were probably poorly

[15] These data are summarized in volume 1.83, pages 133-136.

responsive to the initial dose, there are multiple confounding factors: 1) a variable number of doses of study medication, 2) variable timing of optional doses, 3) use of concomitant benzodiazepines after the first injection in two studies (HGHB and HGHV), and 4) the switching of some placebo patients to olanzapine for the third injection in two studies (HGHW ———).[16]

On a more intuitive level, if the efficacy of a single IM dose for acute agitation is established, then it may be reasonable to infer the efficacy of subsequent IM doses for this condition.

7.3.5 Transition from Intramuscular to Oral Dosing

Study HGHB was comprised of a 24 hour IM treatment period followed by a period of oral treatment for 4 additional days.

IM treatment consisted of 1 to 3 injections of olanzapine 10mg, haloperidol 7.5mg, or placebo.

Immediately after the assessments at 24 hours post-first injection, the oral treatment phase commenced. Patients who had been randomized to IM olanzapine or IM placebo were switched to oral olanzapine, 5-20 mg/day. Patients who had been randomized to IM haloperidol were switched to oral haloperidol, 5-20 mg/day. Oral doses were administered in the morning and were selected by the investigator as being clinically appropriate, within the above ranges.

Benzodiazepines were discouraged but permitted only in oral form during the oral treatment period according to the following maximum doses:

Lorazepam	8 mg/day
Diazepam	40 mg/day
Oxazepam	60 mg/day
Chlorazepate	100 mg/day

[16] The proportion of olanzapine patients who received a benzodiazepine during the injectable treatment phases of studies HGHB and HGHV ranged from 4% to 16%. Usage among placebo patients was greater: 39% (HGHB) and 36% (HGHV). Benzodiazepine use in studies HGHW ———, where concomitant benzodiazepine use was prohibited, was less, e.g., 5% or less among olanzapine patients. In studies HGHW ——— 41% ——— respectively, of the placebo patients were switched to olanzapine for their third injection of study drug.

Roughly 90% of the patients randomized to each IM treatment group continued into the oral treatment period: 122 IM olanzapine, 47 IM placebo, and 116 IM haloperidol patients entered the oral treatment phase. About 91% of the patients in each of these groups completed the oral treatment period.

The modal daily dose for all patients receiving oral olanzapine was 10 mg/day and for those receiving oral haloperidol also 10 mg/day.

Among the IM olanzapine and IM haloperidol patients who entered the oral treatment phase, 43% and 53%, respectively, used a benzodiazepine during oral treatment.

An LOCF analysis of the change from baseline, which was the beginning of the oral treatment phase for purposes of this analysis, to the end of the oral treatment period for the PANSS Excited Component revealed no significant difference between the IM olanzapine patients who received oral olanzapine and the IM haloperidol patients who received oral haloperidol. Data are summarized in Table 7.3.5 below. An examination of the mean changes for these patients by each day of the study revealed no major difference at any timepoint.[17]

TABLE 7.3.5
STUDY HGHB
ORAL TREATMENT PHASE
MEAN CHANGE FROM BASELINE IN PANSS EXCITED COMPONENT (LOCF)

Treatment Group	Baseline		Mean Δ	p-value Olanz vs. Hal
	N	Mean		
Olanzapine	119	6.31	-0.60	0.307
Haloperidol	115	6.44	-1.26	

Interpretation of this analysis is complicated by the lack of a placebo control group and by the concomitant use of benzodiazepines. However, it does suggest there was a continued effect of oral therapy on agitation over the 4 day period following intramuscular treatment with both olanzapine and haloperidol.

[17] These data are plotted in volume 1.83 on page 141.

7.3.6 Pediatric Use

The sponsor has requested a deferral for submitting pediatric data for IM olanzapine until after approval of the adult indication. A post-marketing pediatric study to address the requirements of the Pediatric Rule (21 CFR 314.55) is planned.

7.4 Conclusions Regarding Efficacy

Table 7.4 in Appendix 7.0 summarizes the efficacy results for the four key efficacy studies at the primary endpoint, i.e., 2 hours after the first injection of study medication. These data demonstrate the superiority of single doses of intramuscular olanzapine over the range of 2.5 to 10mg versus intramuscular placebo in the treatment of acute agitation across the — classes of diagnostic patient groups studied.

8.0 Integrated Review of Safety

The intramuscular olanzapine safety database is comprised of 11 human studies with a cutoff date of April 1, 2000, for 9 of these trials. For the remaining 2 studies (HGJA and HGIO), which were completed later than the other trials, the cutoff date is considered to be June 2000.

The evaluation of safety consisted of two general approaches:

1) an examination of the pool of all 11 studies, referred to as the overall IM safety database (848 IM olanzapine-treated patients), for more serious adverse events, specifically deaths (section 8.1.1), other serious adverse events (section 8.1.2), and dropouts related to unexpected, clinically important adverse events (section 8.1.3).

2) an examination of less serious safety findings within two pools of the placebo-controlled Phase 2/3 trials: a pool of those studies that enrolled younger patients (HGHB, HGHV, and HGHW), referred to as the placebo-controlled IM safety database, and the single study — that enrolled older patients [ ] referred to as the geriatric study. This examination entailed an evaluation of common adverse events (section 8.1.4), laboratory test data (section 8.1.5), vital signs (section 8.1.6), and ECG data (section 8.1.7). Finally, the results of three studies

conducted to evaluate special issues relevant to IM olanzapine will be summarized (section 8.1.8).

8.1 Safety Findings

8.1.1 Deaths

There were no deaths during or within five days of participation in any study. However, three patients did expire several days after study completion:

- Patient 016-1606 received IM lorazepam in study HGHW and was found dead 11 days after the study. The cause of death was determined to be an accidental intoxication with morphine, cocaine, and alcohol.
- Patient 007-0701, a 90 year old male, had received IM olanzapine 5mg in study [redacted] and was found dead 9 days after completing the trial.
- Patient 036-3637, a 77 year old male, received two IM injections of placebo and a final IM injection of olanzapine 5mg in study [redacted] The patient was found without respiration 8 days after the study and Advanced Cardiac Life Support was administered, with no success. No autopsy was conducted.

None of these deaths are felt to be reasonably attributable to IM olanzapine.

8.1.2 Other Serious Adverse Events

In the overall IM safety database, there were five subjects who experienced adverse events classified as serious.[18] Narrative summaries for these cases were reviewed and each is summarized below:

#1 Subject 2843 in study LOAV was a 37 year old healthy male volunteer smoker who experienced loss of consciousness, extremity shaking (for 10 seconds), and respiratory depression one hour after receiving an intramuscular injection of olanzapine 5mg and after standing to urinate. Plasma level data indicate that this subject had a Cmax at about 30 minutes post-dose; Cmax was

[18] An event was considered serious if it resulted in death, caused or prolonged inpatient hospitalization, was life-threatening, produced severe or permanent disability, was a cancer or congenital anomaly, or was significant for some other reason.

about two-fold higher than the mean for other subjects in this study (one other subject had a slightly higher Cmax). Pre-treatment vital signs were BP=120/51, heartrate=82 bpm, and respiratory rate(RR)=16/min. Following this event, supine blood pressure was 104/68, pulse was 33 bpm, and RR was 4-7/min. There were no obvious vasovagal signs. Most of the bradycardia was sinus bradycardia with a question of a few junctional escape beats. However, the sponsor also indicated that this subject probably experienced a sinus pause.[19] He was assessed as experiencing respiratory depression and was given one breath mouth-to-mouth. He responded after a second breath was attempted and was briefly agitated on recovery. Thereafter, he was alert and oriented. Heartrate was about 50 bpm at that point but subsequently fell to 37 bpm with RR=13/min and BP=107/65. Atropine 0.2mg IV was administered but his pulse had spontaneously increased. There was a drop in oxygen saturation during the event, the lowest recording being 94%; however, he was off oximetry for a short period surrounding the time of the event. This subject had received olanzapine 2.5mg IM and lorazepam 2mg IM 14 days and 7 days, respectively, prior to this occurrence without remarkable incident. His medical history was unremarkable and there were no concomitant medications. He was discontinued from the trial after this event.

The etiology of case #1 is difficult to know with certainty but the clinical picture strongly suggests that this event most likely represents a syncopal seizure.[20] This healthy volunteer may have been unusually susceptible to olanzapine-induced orthostatic hypotension, which may have played a causative role in this event along with increased cholinergic tone and vasodilatation associated with micturition. But, the sponsor also raises the possibility that this patient experienced a sinus pause, which was noted in other healthy volunteers (see below).

#2 Subject 32 in study LOAC was a 26 year old non-smoking male with no significant medical history except for seasonal allergies.[21] Prior to dosing, this subject

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[19] See comment in volume 1.84, page 230. The evidence for this statement was not provided.

[20] This opinion is based in large part on an informal consultation with a neurologist within the Division, Armando Oliva, M.D.

[21] It should be noted that the experience of this subject is not listed as "serious" in the ISS (vol. 1.84, page 223) but it is designated as a serious adverse event in the study report (vol. 1.33, page 205) and did

manifested an orthostatic decrease in systolic blood pressure. He received an oral dose of olanzapine 10mg and, about 2 hours later, complained of nausea. Supine blood pressure and pulse were 128/61 and 60 bpm (116/66 and 59 bpm pre-dose). At 3 hours post-dose, supine vital signs were 84/34 and 50 bpm (no standing measurements were taken). The foot of his bed was elevated. At 4 hours, 35 minutes post-dose, the subject collapsed returning from the toilet and was helped back to bed. At 5 hours post-dose, supine vital signs were 113/59 and 50 bpm. Telemetry revealed that this subject had experienced a 5 second sinus pause on 2 occasions. The first was 2 hours post-dose and the second occurred about 4.5 hours after dosing and 4 minutes prior to his collapse. Two unifocal PVC's were noted preceding the latter sinus pause. A cardiology consult that the subject was "vagotonic" and inclined to sinus bradycardia. Pharmacokinetic data indicated that the olanzapine plasma concentrations for this subject were not remarkably different from the means of other subjects in this trial. Tmax was about 4 hours.

The occurrence of 2 sinus pauses in this reasonably healthy subject, one of which occurred as plasma levels were beginning to rapidly rise and the second shortly after Tmax and associated with collapse, suggest that these events were related to olanzapine.

This case was considered by the Division review team at the time the original IND application was evaluated (see the April 1, 1998, clinical review of IND 55,342).

#3 Patient 0272 in study HGHB was a 27 year old Hispanic male with schizophrenia who received one injection of olanzapine 10mg. Twenty minutes later, he experienced markedly increased levels of anxiety and nervousness as well as a number of somatic complaints such as difficulty breathing, hyperventilation, palpitations, and sweating. He was discontinued from the study 3.5 hours after the injection and treated with Seroquel and lorazepam, with complete resolution 4-5 hours later. Based on the temporal association with the study drug injection, the investigator concluded that the severe anxiety was caused by an allergic reaction to the drug. However, no steroids, epinephrine, or antihistamines were required to treat this event and no other symptoms consistent with an allergic reaction (e.g.,

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lead to discontinuation from the study (vol. 1.33, page 405). Hence, it will be discussed in this section.

rash) were reported. Medical history was remarkable only for back pain and there were no concomitant medications at the time of the event.

The clinical presentation and course of events in Case #3 are more consistent with worsening anxiety and agitation than an allergic reaction to olanzapine.

#4 Patient 2610 in study HGHV was a 48 year old female who experienced a decrease in supine blood pressure from 110/70 (pulse=72 bpm) pre-dose to 90/60 (pulse=62 bpm) 60 minutes after an intramuscular injection of olanzapine 10mg. At 90 and 120 minutes post-injection, her blood pressure remained 90/60 (pulse increased to 80 bpm at both points). By 240 minutes post-injection, her blood pressure had returned to pre-dose values and remained essentially unchanged thereafter. This patient also had an abnormal ECG, anemia, and a high TSH before treatment. Additionally, 24 hours post-injection, she experienced acute urinary retention. A catheter was placed and the event resolved within 24 hours. An endocrinology evaluation revealed a diagnosis of myxedema, which was suggested to be the probable cause of her ECG changes, anemia, and urinary retention.

The patient in case #4 did experience a slight decrease in supine blood pressure, which could be related to olanzapine. This is not considered a serious event. However, it seems that the other events, which were attributable to a pre-existing thyroid disorder, were classified as serious because their evaluation prolonged hospitalization.

#5 Patient 0909 in study HGHW was a 53 year old male with bipolar disorder who had received two IM doses of placebo followed by an injection of olanzapine 10mg. Approximately 4 hours after the latter, he experienced tachycardia (standing pulse=100 bpm) and an increase in hypertension (standing BP=210/110)(pre-IM olanzapine pulse=60 bpm and BP=192/90). Due to increased agitation, he was administered rescue medication (IM lorazepam, IM haloperidol, and IM diphenhydramine) over the next several hours. Vital signs 9 hours after IM olanzapine and after four doses of rescue medication revealed a pulse of 138 bpm and BP=192/114. At that point, the patient was cool and clammy and was transferred to the emergency room, where IV diltiazem was given and an ECG revealed poor R wave progression but no evidence suggesting a myocardial

infarction. Within 4 hours, blood pressure had stabilized and tachycardia had resolved. Hypertension had been documented at several timepoints prior to olanzapine injection and tachycardia was attributed by the investigator to increased agitation. The patient had a history of hypertension and postural hypotension and concomitant medications consisted of enalapril and glyceryl trinitrate, both of which were continued during the study.

The patient in case #5 had substantially elevated blood pressure readings prior to olanzapine treatment which were not much worse after treatment. His tachycardia, especially 9 hours after olanzapine injection, seems more likely related to his agitated state than to olanzapine.

In summary, cases #1 and #2 may represent an unexpected hazard (sinus pause) attributable to olanzapine. The other three cases are not felt to suggest an unexpected safety risk associated with IM olanzapine.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

Table 8.1.3.1 below depicts the percentages of patients dropping out from the placebo-controlled IM safety database by reason for dropout. This table excludes 21 patients from the HGHW IM placebo group who received IM olanzapine as a third injection: among these, 2 patients discontinued due to an adverse event.

TABLE 8.1.3.1
PLACEBO-CONTROLLED IM SAFETY DATABASE
DROPOUTS BY REASON (N(%))

Reason for Dropout	IM Olanzapine (N=415)	IM placebo (N=129)
Adverse Event	2(0.5%)	0
Lack of Efficacy	3(0.7%)	5(3.9%)
Patient Decision	6(1.4%)	4(3.1%)
Criteria not met/Compliance	0	1(0.8%)
Physician Decision	1(0.2%)	0

In the geriatric study — there was only one dropout due to an adverse event. This occurred in a placebo patient who received olanzapine as the third injection. The most

common reason for premature discontinuation in this study was due to lack of efficacy.

8.1.3.2 Dropouts Due to Adverse Events

Among the 11 studies in the overall IM safety database, there were 9 subjects who received IM olanzapine and 1 subject who received oral olanzapine who dropped out due to an adverse event. These patients are listed in Table 8.1.3.2 below.

Four of these patients (0272, 0909, 2843, and 32) were discussed section 8.1.2 as having serious adverse events. The narrative summary for each of these 9 dropouts was reviewed. There are an additional two cases that could represent an unexpected hazard associated with olanzapine; these are described below.

TABLE 8.1.3.2
OVERALL IM SAFETY DATATBASE
LISTING OF DROPOUTS DUE TO ADVERSE EVENTS

Study	Subject #	Event Leading to Dropout
HGHB	0272	Anxiety
HGHB	3051	Rash
HGHW	0909	Agitation
HGHW	1801	Hostility
—	3602	Tachycardia
LOAV	2843	Respiratory Depression/ Syncope/? Sinus pause
LOAC	32	Sinus pause
LOAW	002	Sinus pause
LOAW	015	Sinus pause

Case #1 Subject 002 in study LOAW was a 55 year old healthy male non-smoker who received olanzapine 5mg IM and, about one hour later, experienced loss of consciousness (LOC) after standing for 1-2 minutes. Supine vital signs were BP=103/70 with a pulse of 39 bpm (pre-dose supine BP=105/73 and pulse=53). He was placed in bed with feet elevated and gradually recovered. However, he lost consciousness a second time about 6 hours post-dose, again after standing for 1-2 minutes. Vital signs 5 minutes prior to this event revealed a 47 and 30 mmHg orthostatic decrease in systolic and diastolic pressures with a 4 bpm orthostatic decrease in pulse. The subject was laid down and his vital signs

spontaneously normalized. Telemetry was remarkable for 2 episodes of vagal sinus arrest (longest duration was 5-6 seconds) associated with sinus bradycardia.[22] The first occurred 1 hour post-injection and the second 6 hours post-injection; both were temporally associated with syncope. His olanzapine plasma level was slightly higher than the mean for most other subjects (i.e., excluding subjects 2 and 15) at Tmax, about the time of the first LOC; however, 8 other subjects had higher Cmax's. His level at the time of the second LOC was much lower.

Case #2 Subject 015 in study LOAW was a 47 year old male smoker (5 cigarettes/day) who was healthy except for an upper respiratory tract infection. He received an intramuscular dose of olanzapine 5mg. About 50 minutes later, he complained of nausea and 60 minutes post-dose experienced dizziness and had to lie down with his bed elevated. Supine blood pressure and pulse were 106/61 and 55 bpm (101/68 and 80 bpm pre-dose). Four hours after his first IM dose, he received a second intramuscular dose of olanzapine 5mg. An hour after that dose, he again experienced dizziness and had to lie down. Supine blood pressure and pulse were 95/60 and 92 bpm (108/73 and 86 bpm pre-dose). He remained lying for at least 4 hours. Telemetry data revealed that he had experienced a series of two sinus pauses approximately 3 1/4 hours after his second injection; these were 5.2 and 6.4 seconds in duration. This was associated with hypotension and bradycardia: supine BP and pulse were 71/41 and 45 bpm; no standing vital signs were taken. Due to the sinus pause and dizziness which occurred one hour after each injection, the patient was withdrawn from the study but he continued to be monitored. About 1 hour and 10 minutes after the first series of pauses, he experienced a second episode of sinus bradycardia with two additional sinus pauses (6.2 and 4.7 seconds in duration) within a 2 minute interval. This was immediately followed by a 1-2 minute period of sinus tachycardia (103-143 bpm). Olanzapine plasma levels indicate that this subject experienced Cmax levels roughly 30% higher than the mean for most other subjects (i.e., excluding subjects 2 and 15) after both injections.

Overall, there were 3 normal volunteers who manifested at least one sinus pause on telemetry, and an additional subject with a suspected sinus pause, associated with the

[22] The association with bradycardia and syncope is documented in the Post-Study Discharge note in the CRF.

administration of olanzapine, usually by the intramuscular route but in one case orally. These pauses were associated with bradycardia and variably with collapse and loss of consciousness.

8.1.4 Adverse Event Incidence

8.1.4.1 Categorization of Adverse Events

Adverse events were recorded as COSTART terms. The accuracy of the translation of actual adverse event terminology to COSTART terms was assessed by examining line listings of adverse events in the reports for studies HGHB, HGHV, HGHW, and —

This examination revealed two instances in which the event coding was not felt to be reasonably accurate:

- For patient 35-3502 in study HGHW, the actual term "hypothyroid" was coded to "hyperthyroidism."
- For patient 13-1309 in study — the actual term "premature atrial contraction" was coded to "ventricular arrhythmia."

It is unlikely that these errors will substantially affect conclusions drawn from the submitted data about the safety of IM olanzapine.

8.1.4.2 Appropriateness of Data Pooling

Assessment of adverse event incidence is based on data from two groups of studies from the pool of Phase 2/3, double-blind, placebo-controlled trials:

- the placebo-controlled IM safety database: studies HGHB, HGHV, and HGHW, which enrolled patients in the age range 18-79 years (mean age 38) with schizophrenia, schizophreniform disorder, schizoaffective disorder, or bipolar I disorder.
- the geriatric study: study — which enrolled patients 54-97 years old (mean age 78) [ ]

Based on the difference in patient age ranges in these two groups and, to a lesser extent, the difference in diagnoses, this pooling of studies is reasonable.

8.1.4.3 Common, Drug-Related Adverse Events

The incidence of treatment-emergent adverse events in the placebo-controlled IM safety database during the 24 hour injectable treatment phase is displayed in Table 8.1.4.3 in Appendix 8.0 for those events reported by at least 1.0% of the patients in the IM olanzapine treatment group. Please note that data subsequent to the third injection for 21 placebo patients in study HGHW who received olanzapine as the third injection are excluded.

None of these events meet the customary criteria for common, drug-related adverse events (i.e., reported by at least 5% of the drug-treated patients at a rate at least twice that among the placebo-treated patients).[23]

A similar analysis in the geriatric study also revealed no common, drug-related adverse events utilizing the above criteria.

8.1.4.4 Dose-Relatedness

Study HGHV employed four fixed doses of IM olanzapine (2.5, 5, 7.5, and 10mg) with approximately 45 patients per dose. Visual inspection of the proportions of patients reporting treatment-emergent adverse events across these dose groups revealed no obvious dose relationship for any events.

8.1.4.5 Demographic Effects on Adverse Events

Treatment-emergent adverse event occurrence was examined by various demographic subgroups for the placebo-controlled IM safety database: age (<40 vs. ≥40), gender (male vs. female), and racial origin (Caucasian vs. other). Odds ratios (IM olanzapine:IM placebo) were computed and compared across subgroups using the Breslow-Day test for homogeneity of odds ratios.[24]

Although the odds ratios for several events were significantly different statistically (Breslow-Day p-value ≤0.10), none of these differences were deemed by this reviewer to be clinically significant.

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[23] Based on percentages rounded to the nearest 0.1%.
[24] Data are displayed in volume 1.85, page 117ff.

8.1.4.6 Additional Analysis of Adverse Events

Additional analyses of adverse events which are of special interest with the acute use of an intramuscular antipsychotic were examined.

Injection Site Reactions
In two studies (LOAC and LOAR), subjects were systematically monitored for injection site reactions.

Three subjects in LOAC (N=30) reported "severe pain" after IM injection, one after receiving IM olanzapine 0.2mg and two after IM placebo. Overall, inspection of the injection sites revealed occasional minor bruising.

Study LOAR (N=26) revealed no adverse events related to the injection site.

In studies HGHB, HGHV, HGHW, and [redacted] there were reports of injection site pain (burning and stinging sensations) in 3/604 IM olanzapine patients, 2/119 IM lorazepam patients, 0/166 haloperidol patients, and 0/217 IM placebo patients.

In sum, there was no evidence of significant injection site reactions associated with IM olanzapine.

Dystonic Reactions/Extrapyramidal Symptoms
The sponsor surveyed the placebo-controlled IM safety database and the geriatric study for adverse events potentially representing dystonia (events terms dystonia, oculogyric crisis, opisthotonus, and torticollis). No such adverse events were reported among IM olanzapine- or IM placebo-treated patients in these trials.

The sponsor also searched the two fixed-dose studies HGHV and [redacted] for other treatment-emergent extrapyramidal events by event category: Parkinsonian events, akathisia events, dyskinetic events, and residual events (e.g., myoclonus, twitching). Very few patients experienced these events and there was no evidence to suggest a dose-relationship for any of these event categories.

Sedation/Tranquilization
Among patients in the placebo-controlled IM safety database, 4.3% (18/414) of IM olanzapine and 0.7% (1/149) of IM placebo patients had a maximum ACES (Agitation-Calmness Evaluation Scale) score of 8 (deep sleep); this

difference was statistically significant (p=0.033). No patient in either group had a maximum ACES score of 9 (unarousable). The proportion of IM olanzapine patients reporting treatment-emergent somnolence was not significantly greater than that in the IM placebo group (5.5% vs. 3.3%).

In the geriatric study, 7.3% (10/137) of IM olanzapine and 4.5% (3/67) of IM placebo patients had a maximum ACES score of 8 (p=0.552).[25] None had a maximum score of 9. The fraction of IM olanzapine patients reporting somnolence was almost identical to that in the IM placebo group (about 3%).

No patient in either study pool had treatment-emergent CNS depression, stupor, or coma.

Thus, it does not appear that IM olanzapine is associated with excessive sedation.

Seizures

During pre-marketing studies with oral olanzapine, seizures occurred in 0.9% of olanzapine-treated patients. No patient in the placebo-controlled IM safety database or geriatric study was reported as having experienced a seizure.

8.1.5 Laboratory Data

8.1.5.1 Laboratory Assessments

Laboratory studies (clinical chemistry, CBC with differential WBC count, and urinalysis) were conducted at screening and 24 hours after the first IM injection in studies HGHV, HGHW, and [redacted].[26]

Patients from study HGHB were excluded from the following analyses since laboratory tests were not performed during the 24 hour injectable treatment period in that study. Thus, the placebo-controlled IM safety database refers to the pool of studies HGHV and HGHW in this section.

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[25] The 2.5 and 5mg dose groups were pooled for these analyses.

[26] Clinical chemistry parameters included electrolytes, SGOT, SGPT, GGT, total bilirubin, alkaline phosphatase, BUN, creatinine, uric acid, calcium, nonfasting glucose, creatine phosphokinase, phosphorus, total protein, albumin, and cholesterol.

8.1.5.2 Potentially Clinically Significant Lab Changes

The sponsor examined the proportions of patients meeting criteria for potentially clinically significant changes in laboratory analytes during the 24 hour injectable treatment phase. These criteria are displayed in Appendix 8.0, Table 8.1.5.2. The analysis excluded patients who met the criteria at baseline for any particular analyte. In the placebo-controlled IM safety database and in the geriatric study, there were no significant differences (α=0.100) in pairwise comparisons of the IM olanzapine and IM placebo treatment groups with respect to the fraction of patients who met these criteria.[27]

There were 4 patients in the pool of studies HGHV and HGHW who met criteria for potentially clinically significant increases in SGPT.[28] All had considerable SGPT elevations pre-treatment with no substantial increase after receiving IM olanzapine.

Also in this pool, there was one IM olanzapine patient who met criteria for a potentially clinically significant low neutrophil count (<15% of the WBC count): Patient 3607 was a 32 year old male in study HGHW received olanzapine 10mg IM. Baseline WBC count was 8.98 GI/L with 29% neutrophils; At study endpoint, WBC count was 8.01 GI/L with 14% neutrophils (ANC=1.12 GI/L). There were no pre-existing conditions, concomitant medications, or adverse events reported. Further information was not reported. No other patient in this study pool or in the geriatric study met criteria for a potentially clinically significant low WBC or neutrophil count.

8.1.5.3 Mean Change from Baseline in Lab Values

Laboratory analyte mean changes from baseline to LOCF endpoint during the 24 hour injectable treatment phase were compared between IM olanzapine and IM placebo treatment groups in the placebo-controlled IM safety database and in the geriatric study.[29] Although the changes for some analytes were different to a statistically significant

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[27] These data are displayed in volume 1.84, pages 88-93 and 147-155, respectively.
[28] HGHV: patients 1315 and 9075; HGHW: patients 1605 and 2512.
[29] Data are displayed in volume 1.84, pages 83-85, and in volume 1.85, pages 318-352, respectively.

degree (α=0.100), the magnitude of these changes was small and none were deemed to be clinically important.

8.1.5.4 Dropouts Due to Lab Abnormalities

No IM olanzapine-treated patient in the placebo-controlled IM safety database nor in the geriatric study reportedly dropped out because of a laboratory abnormality (see section 8.1.3.2).

8.1.6 Vital Sign Data

8.1.6.1 Vital Sign Assessments

Heartrate and blood pressure assessments were conducted at screening, pre-dose, and at 30 min, 60 min, 90 min, 120 min, 4 hrs, and 6 hrs after the first, second, and third injections and at 12 hrs and 24 hrs after the first injection in the placebo-controlled IM safety database studies and the geriatric study.

8.1.6.2 Potentially Clinically Significant VS Changes

Table 8.1.6.2.1 in Appendix 8.0 displays the criteria for identifying a vital sign measure as potentially clinically significant during the 24 hour injectable treatment phase. In both the placebo-controlled IM safety database and the geriatric study, the proportions of patients meeting these criteria at any time during the 24 IM treatment period were compared between the IM olanzapine and IM placebo treatment groups for each vital sign variable.

Statistically significant differences (α=0.100) between IM olanzapine and IM placebo in the placebo-controlled IM safety database are displayed in Table 8.1.6.2.2 below. No such differences were noted in the geriatric study.

TABLE 8.1.6.2.2 PLACEBO-CONTROLLED IM SAFETY DATABASE POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGN VARIABLES AT ANY TIME DURING IM TREATMENT					
Vital Sign Variable	TX	N total	Abnormal		p-value Olz vs. Pl
			n	%	
Low Standing Diastolic BP	Olz	406	20	4.9%	0.021
	Plac	146	1	0.7%	
Low Standing Systolic BP	Olz	396	43	10.9%	0.017
	Plac	144	6	4.2%	
Low Supine Diastolic BP	Olz	413	26	6.3%	0.003
	Plac	149	1	0.7%	

The low standing blood pressures are consistent with the well-known orthostatic hypotensive effect of olanzapine, which is probably due to the α-1 adrenergic blockade. This mechanism is likely to also play a role in the low supine diastolic blood pressure finding. While a larger fraction of IM olanzapine patients experienced potentially significant orthostatic hypotension compared to IM placebo patients (8.7% vs. 4.9%), this difference was not statistically significant (p=0.200).

Normally, hypotension results in a reflexive increase in heartrate and vascular tone to maintain adequate perfusion. To assess the extent to which this reflex may be impaired, the sponsor searched the eleven studies comprising this NDA for instances of bradycardia with hypotension or bradycardia without a reflexive increase in pulse on standing. The criteria used for identifying such cases are listed in Appendix 8.0, Table 8.1.6.2.3.

This search revealed 13 olanzapine-treated patients, who are listed in Appendix 8.0, Table 8.1.6.2.4. The vast majority of these subjects experienced low supine blood pressure in conjunction with low heartrate compared to pre-dose readings. Many did not have corresponding standing vital sign data due to symptoms in the supine position or inability to remain standing, but the occurrence of poorly compensated orthostatic hypotension would be a reasonable assumption. Many of these individuals experienced symptoms, usually dizziness or syncope. The sponsor reported one IM placebo-treated patient meeting these criteria, Patient 3634 in study — who experienced a low supine systolic blood pressure with a low supine pulse.

In particular, Dr. [ ] review of the QTc data revealed several findings that caused him to question the accuracy of the QTc measurements: 1) there was a meaningful difference in QTc at baseline among the four treatment groups, 2) baseline variability of QTc values was large, 3) a small number of the placebo patients experienced large increases in QTc at 2 hours post-injection. Pursuant to these concerns, Dr. [ ] randomly read several ECG tracings and noted discrepancies between his measurements and the reported measurements.

On the basis of the above, Dr. [ ] recommended to Lilly that all ECG tracings from [ ] should be independently re-read by two established laboratories. The sponsor chose the [ ] and the [ ] Each lab developed a priori measurement guidelines which were applied to the tracings under blinded conditions.

It was decided a priori that the data from the two labs would be combined. Results from the two labs were examined separately and found to be closely correlated (r=.807), suggesting that it was appropriate to combine them.[32] The following review of ECG data from [ ] is based on this combined dataset.

8.1.7.2 Potentially Clinically Significant ECG Changes

Criteria used by the sponsor to identify potentially clinically significant ECG measures during the 24 hour injectable treatment phase are displayed in Appendix 8.0, Table 8.1.7.2. With two exceptions, the proportions of patients meeting any of these criteria at any time during the 24 hour IM treatment period were not significantly different (α=0.100) between IM olanzapine and IM placebo patients in either the placebo-controlled IM safety database or the geriatric study.[33] One exception occurred in the placebo-controlled IM safety database, where 0.7% of the IM olanzapine and 2.8% of IM placebo patients met criteria for a prolonged PR interval. Also, the percentage of patients in — with a prolonged QTc was 21.4% in the 2.5mg IM olanzapine group and 44.4% in the IM placebo group (p=0.089). In both cases, the finding was not of concern

[32] In the amended study report, the combined data are referred to as the combined [ ] data.

[33] Data are displayed in volume 1.84, page 100, and in the amended study report for — pages 279-280, respectively.

since the placebo incidence was higher than that for olanzapine.

In the placebo-controlled IM safety database, no IM olanzapine (N=411) nor IM placebo (N=149) patient with a baseline QTc<500 msec had a post-baseline QTc ≥500 msec.

In the geriatric study, a few patients with baseline QTc values <500 msec had post-baseline values ≥500 msec:

Treatment Group	Ntotal	n≥500	%≥500
IM Olz 2.5	65	1	1.5%
IM Olz 5	61	2	3.3%
IM Placebo	62	3	4.8%
IM Lorazepam	64	3	4.7%

None of the intergroup differences were statistically significant. It is notable that a few of the IM lorazepam patients met these criteria in this study, since benzodiazepines are not generally thought to prolong the QTc interval.

8.1.7.3 Mean Change from Baseline in ECG Values

The mean changes from baseline to LOCF endpoint during the 24 hour injectable treatment phase were compared between the IM olanzapine and IM placebo treatment groups for ECG parameters in the placebo-controlled IM safety database and the geriatric study.[34] Statistically significant differences were found only in the geriatric study: relative to placebo, there was a small shortening of the mean PR interval in the IM olanzapine 5mg group and shortening of the mean QT, QTc, and JTc intervals in the olanzapine 2.5mg group.[35] A lengthening of these intervals among drug-treated patients relative to placebo would be a potential concern but a shortening is of questionable clinical significance.

Further analyses of changes in QTc were conducted by the sponsor. Changes in ECG parameters from baseline to 24 hours after the first injection are difficult to interpret

[34] Data are displayed in volume 1.84, page 99, and in the — amended study report, pages 265-270, respectively.
[35] There was no analysis of the PR interval in the amended — study report.

because of the variable number and timing of doses administered after the first injection and the fact that plasma drug levels are only one-third to one-half of Cmax at 24 hours. Thus, the analyses presented here are from 2 hours post-first injection.

In the placebo-controlled IM safety database, QTc change from baseline to 2 hours post-first injection (LOCF) reflected a greater mean decrease in the IM olanzapine group relative to placebo (-3.04 (N=408) vs. -0.70 msec (N=148)). The percentage of patients with various degrees of QTc prolongation at 2 hours is displayed in Table 8.1.7.3.1 below. At each level of prolongation, the percentage of IM placebo patients was slightly greater than for IM olanzapine.

TABLE 8.1.7.3.1
PLACEBO-CONTROLLED IM SAFETY DATABASE
NUMBER (%) OF PATIENTS WITH QTc PROLONGATION
AT TWO HOURS POST-FIRST DOSE

QTc Prolongation	TX	N-total	n-prolonged	% prolonged
≥30 msec	IM Olz	408	17	4.2%
	IM Plac	148	10	6.8%
≥60 msec	IM Olz	408	2	0.5%
	IM Plac	148	1	0.7%
≥75 msec	IM Olz	408	0	0.0%
	IM Plac	148	1	0.7%

In the geriatric study, there was a small mean increase in the change from baseline to two hours post-first injection (LOCF) for the 5mg IM olanzapine group:

Treatment Group	Mean Change	N
IM Olz 2.5mg	-4.53 msec	68
IM Olz 5mg	+3.05 msec	61
IM Placebo	+3.29 msec	61

This increase was not significantly different compared to the change in the placebo group. The mean change in the IM lorazepam group (N=63) was -6.18 msec. Findings were

similar for the mean change in the JTc interval.[36]

The percentage of patients experiencing various degrees of QTc prolongation at 2 hours post-first injection in the geriatric study is shown in Table 8.1.7.3.2 below.

TABLE 8.1.7.3.2
GERIATRIC STUDY
NUMBER (%) OF PATIENTS WITH QTc PROLONGATION AT TWO HOURS POST-FIRST DOSE

QTc Prolongation	TX	N-total	N-prolonged	% Prolonged
≥30 msec	IM Olz 2.5	68	4	5.9%
	IM Olz 5	61	4	6.6%
	IM Plac	61	7	11.5%
	IM Lor	63	2	3.2%
≥60 msec	IM Olz 2.5	68	0	0.0%
	IM Olz 5	61	2	3.3%
	IM Plac	61	0	0.0%
	IM Lor	63	1	1.6%
≥75 msec	IM Olz 2.5	68	0	0.0%
	IM Olz 5	61	1	1.6%
	IM Plac	61	0	0.0%
	IM Lor	63	0	0.0%

Neither olanzapine group differed significantly from placebo for any category of QTc change. One olanzapine 5mg patient experienced a QTc prolongation of at least 75 msec.

As a further exploration of potential QTc prolongation, data from the fixed dose study HGHV was examined. The mean QTc change from baseline to two hours post-first injection (LOCF) in this study was as follows:

Treatment Group	Mean Change	N
IM Olz 2.5	-2.87 msec	47
IM Olz 5	-3.27 msec	45
IM Olz 7.5	-2.33 msec	46
IM Olz 10	+0.33 msec	46
IM Placebo	+3.03 msec	44

[36] These data are presented in the amended — study report, page 260.

These data do not suggest dose-related prolongation of QTc associated with IM olanzapine albeit in a younger, probably healthier patient sample vis-à-vis the geriatric study. Even at the highest dose (10mg), the mean change for drug was less than that for the placebo group.

8.1.7.4 Dropouts Due to ECG Abnormalities

No patient in the placebo-controlled IM safety database or in the geriatric study dropped out due to an ECG abnormality.

However, as discussed in sections 8.1.2 and 8.1.3.2 above, there were three healthy volunteers who manifested at least one sinus pause on telemetry, and an additional volunteer with a suspected sinus pause, associated with the administration of olanzapine in clinical pharmacology studies.

8.1.8 Special Studies

8.1.8.1 Study HGJA

Study HGJA was an open-label trial conducted to evaluate the pharmacokinetics (N=20) and tolerability (N=37) of IM olanzapine 10mg given as three doses four hours apart. There was a step-wise pattern of increasing concentrations, with mean Cmax and AUC(0-4) slightly higher with each dose:

	Dose 1	Dose 2	Dose 3
Cmax(ng/ml)	27.1	29.5	41.5
AUC(0-4)(ng-hr/ml)	45.2	79.5	115

The mean concentrations at 2 and 4 hours after each injection were very similar by virtue of the long elimination half-life. Thus, dosing every 2 hours should produce similar cumulative concentrations as dose administration every 4 hours.[37]

In this study, 37 patients (ages 19-62) with chronic schizophrenia received 3 injections of olanzapine 10mg within 24 hours, the majority receiving injections at approximately 4 hour intervals. There were no serious adverse events or adverse experiences that led to dropout.

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[37] Please see page 74 of the study report.

Somnolence, postural hypotension, and dizziness were common adverse events, each occurring in more than 5% of the patients. Also, about one-third of all patients in this study (32.6%) experienced significant orthostatic hypotension at some point during the study (≥30 mmHg decrease in systolic blood pressure from supine to standing). One patient (#2014) had a QTc ≥500 msec (512 msec); this was discovered 24 hours after receiving a single dose and was considerably higher than the QTc found at 2 hours post-dose (479 msec). Thus, this finding is unlikely to be drug-related.

8.1.8.2 Study ——

8.1.8.3 Study LOAV

Study LOAV was conducted to evaluate the potential pharmacokinetic and pharmacodynamic interaction of IM olanzapine and IM lorazepam. Basically, this was a three-way crossover study in 15 healthy males and females who received, in randomized order, IM olanzapine 5mg, IM lorazepam 2mg, or IM olanzapine 5mg followed one hour later by IM lorazepam 2mg. There was a 6-17 day washout between treatment periods.

The pharmacokinetics of olanzapine, unconjugated lorazepam, and total lorazepam were not affected by co-administration of these drugs.

Pharmacodynamic effects (performance on the Digit Symbol Substitution Test and onset and duration of somnolence)

tended to be additive with combined use. With the exception of one subject (#2843) who experienced syncope and apnea after IM olanzapine 5mg alone, there were no serious adverse events in this study. Subject 2843 was discussed in section 8.1.2 above.

8.2 Adequacy of Patient Exposure and Safety Assessments

There are a number of factors pertaining to the short-term administration of IM olanzapine that potentially impact on its safety: 1) the size of the individual injected dose, 2) the number of injections administered, and 3) the timing of those injections. Ideally, an assessment of the adequacy of patient exposure would simultaneously consider all of these factors. However, such an approach is not fruitful in this case because of the dosing strategy used in the four key studies: the number of IM doses given and the timing of those doses were dependent on the clinical status of the patient. If patients tend to respond after a single dose, as apparently was the case here, then safety experience from an adequate number of patients exposed to more extreme dosing (multiple doses injected at rapid frequency), which is more likely to reveal safety problems, is not available.

Among the 415 IM olanzapine-treated patients in the placebo-controlled IM safety database, the total olanzapine dose during the 24 hour injectable period was greater than 20mg for only 14 patients; five of these patients received the maximum dose, 30mg. Only 18 patients received three injections.[38]

Considering the 137 patients in the geriatric study — 13 patients received a total olanzapine dose of 10mg during the 24 hour injectable period; another 11 patients received 12.5mg. Twenty-nine patients received three injections.[39]

The relatively safe passage of patients in study HGJA, where 37 patients received three doses of 10mg, generally separated by 4 hour periods, provides some evidence supporting the safety of multiple dosing with IM olanzapine. Pharmacokinetic data from that study also suggests that dosing at 2 hour intervals could be expected

[38] These figures exclude the 21 placebo patients in HGHW who crossed over to olanzapine for their final dose.
[39] These figures do not reflect the 31 placebo patients who received olanzapine as their third dose.

to produce plasma levels of olanzapine comparable to those seen at 4 hour intervals.

Few patients in the other open-label studies, LOAR and LOAT, received dosing with IM olanzapine similar to that in study HGJA.
Overall, safety exposure with multiple dosing is adequate, although marginally so given the small number of patients who received more than one injection of olanzapine.

In terms of safety assessments, there are two issues worth mentioning. First, in light of the sinus pauses documented in healthy volunteers in the Phase 1 studies, it would have been helpful for the sponsor to conduct cardiac telemetry in some portion of the patients studied in the placebo-controlled Phase 2/3 trials. It must be acknowledged, however, that it may have been difficult to obtain reliable tracings in these agitated patients. The lack of this information leaves unanswered the question of whether sinus pauses also occur in patients with psychiatric illness although, as will be discussed below, an evaluation of relevant adverse events in these trials mitigates against the occurrence of symptomatic sinus pauses; asymptomatic pauses are felt to have no clinical significance.[40]

Second, the first post-baseline 12-lead ECG in the Phase 2/3 studies was obtained 2 hours after the first injection. After injection of olanzapine, Tmax is 15-45 minutes, with a rapid decline in plasma concentration thereafter see Figure 6.0 in section 6.0). Hence, at 2 hours post injection, plasma levels are likely to be well below Cmax (~50% of Cmax) and maximal changes from baseline in ECG parameters (such as QTc) may be considerably underestimated. However, considerable reassurance is derived from an analysis performed by OCPB of Cmax with IM and oral dosing of olanzapine: a comparison of the range of values for Cmax under maximal dosing with IM olanzapine (10mg IM q4 hrs × 3 in study HGJA) with the range for Cmax at steady state under dosing with oral olanzapine 20 mg/day (from study HGAJ) revealed no substantial difference. Also, data from previous studies do not suggest that oral olanzapine prolongs the QTc interval to any important

[40] This is based on the opinion of Jean Barbey, M.D., cardiology consultant to the PDAC, which was expressed during the 2-14-01 PDAC meeting.

extent.[41] Thus, assuming that the rate of rise in plasma levels would not itself produce a QTc lengthening, it seems reasonable to infer that IM olanzapine will likewise not prolong QTc.

Otherwise, the safety assessments seem reasonable.

8.3 Assessment of Data Quality and Completeness

Data contained in this NDA submission appear to be reasonably reliable and complete.

Twenty percent (4/20) of the Case Report Forms (CRF's) that were electronically submitted in the original NDA submission were audited by comparing adverse event data in those CRF's with the corresponding data contained in the Narrative Summaries. These four patients are identified in section 1.1. Each Narrative Summary was deemed to completely and accurately reflect the adverse event data in the CRF.

8.4 Summary of Potentially Important Safety Issues

8.4.1 Hypotension with Bradycardia

Using the criteria listed in Appendix 8.0, Table 8.1.6.2.3, 12 cases of supine hypotension with bradycardia and one case of orthostatic hypotension without a heartrate increase were identified in the entire NDA database. These occurrences were often accompanied by symptoms such as dizziness and syncope.

This combination of findings was much more common in healthy volunteers (7/83=8.4%) compared to patients with psychiatric disorders (6/765=0.8%). Of the 13 total cases, which are listed in Appendix 8.0, Table 8.1.6.2.4, only one occurred among the four large Phase 2/3 studies in this NDA database (604 IM olanzapine-treated patients).

The sponsor has proposed that the observed hypotension and bradycardia are consistent with a physiologic phenomenon known as "neurally-mediated reflex bradycardia" or NMRB. According to this mechanism, venous pooling, probably due in large part to the alpha-1 adrenergic blockade associated with olanzapine, triggers this process. Such pooling leads

[41] For example, see Study 054, which was conducted by Pfizer and presented to the PDAC at a meeting on 7-19-00.

to decreased left ventricular filling and, as a consequence, more vigorous contraction of the underfilled chamber. This then stimulates mechanoreceptors in the ventricle which stimulate afferent nerve pathways to centers in the medulla, which in turn lead to increased vagal tone and a reduction in heartrate. This chain of events is generally considered benign and is reversed by the assumption of a supine posture and elevation of the legs. Symptomatic NMRB can be produced in 5-10% of the population with a tilt table test. A small proportion of patients with NMRB will have sinus pauses.[42]

While it would be difficult to prove the mechanism for these findings, NMRB does appear to be a plausible explanation.

Also, the sponsor reported that data from HGJA suggest that the frequency and magnitude of blood pressure changes may be related to recent antipsychotic medication. At one site, only 1 of 23 non-agitated patients was receiving antipsychotic medication at baseline whereas, at the other site, 17 of 20 such patients were receiving an antipsychotic. More decrements in blood pressure of greater magnitude were experienced by the patients acutely naive to antipsychotic medication.[43]

Finally, they also speculate that the infrequent occurrence of these events among agitated patients in the Phase 2/3 studies might be explained by the increased sympathetic tone presumably experienced in the context of agitation; in other words, the agitation may have played a protective role against bradycardia.[44]

Of course, the use of IM olanzapine in patients with more concomitant illnesses and medications than those in these studies and in patients naive to psychotropics may be associated with an appreciably higher risk of hypotension with bradycardia. Thus, it is prudent to prominently mention the possibility of such occurrences in product labeling.

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[42] This is explained in the revised ISS, pages 254-255 and 276-279.
[43] This is reported in the revised ISS, page 255, submitted on 12-20-00.
[44] Please see the revised ISS, page 278.

8.4.2 Sinus Pause

There were three healthy volunteers in two clinical pharmacology studies with documented pauses in sinus rhythm subsequent to olanzapine administration. See sections 8.1.2 and 8.1.3.2 for a description of these cases.[45] The pauses were preceded by bradycardia and accompanied by collapse and loss of consciousness in one subject each. The longest reported duration of pause was 6 seconds. All resolved without specific intervention.

The two studies in which these three subjects participated were the only trials in the IM development program in which telemetry was performed. Hence, the fact that there are no documented cases of sinus pause in other studies may be due to lack of detection as opposed to an actual absence of such events.

Adverse events that might have accompanied the occurrence of a sinus pause in other trials include syncope, bradycardia, and dizziness. The placebo-controlled IM safety database as well as the geriatric study were examined for the proportion of patients who reported these adverse experiences in the IM olanzapine and IM placebo treatment groups. For none of these events was the proportion of IM olanzapine patients reporting the event significantly greater than that for IM placebo (α=0.100).

Only one patient in the placebo-controlled Phase 2/3 studies (604 patients treated with IM olanzapine) experienced syncope: Patient 1503 in study HGHW was a 30 year old male who experienced syncope about 20 minutes after receiving IM olanzapine 10mg. This event was likely due to severe orthostatic hypotension: supine blood pressure shortly after the episode was 97/67 but the first standing blood pressure obtainable after this experience (6 hours later) was 81/55.

Additionally, the mean change from baseline in ECG heartrate and the percentages of patients meeting criteria for potentially clinically significant decreases in pulse or heartrate were examined. Again, there were no significant differences between IM olanzapine and IM placebo.

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[45] In an additional case (LOAV Subject 2843), sinus pause was suspected by the sponsor.

There is one postmarketing report of a patient experiencing sinus pause associated with an olanzapine overdosage.[46] There was spontaneous resumption of normal rhythm.

Thus, these examinations did not produce a signal suggesting the occurrence of sinus pauses in the placebo-controlled Phase 2/3 studies. Of course, it must be borne in mind that the above analyses are not particularly sensitive for this purpose and certainly cannot rule out the possibility of sinus pauses, especially asymptomatic pauses, in these studies. However, as discussed above, asymptomatic pauses are felt to have no clinical importance.

These events were discussed at some length by two cardiology consultants to the PDAC at the 2-14-01 meeting (Drs. Jean Barbey and Edward Pritchett). As explained in the previous section, neurally-mediated reflex bradycardia or NMRB was deemed to be a plausible explanation for these events.

Given the lack of a signal for sinus pauses in the target population (i.e, among the agitated psychiatric patients) and the spontaneous resolution of the pauses in the normal volunteers, these occurrences do not contraindicate approval of IM olanzapine and special monitoring (e.g., telemetry) during treatment is not warranted. However, as for hypotension with bradycardia, it is wise to mention these events in product labeling.

8.5 Conclusions Regarding Safety

These data reveal no evidence of any significant toxicities or previously unrecognized hazards that can be reasonably attributed to IM olanzapine and expected in the target population.

The PDAC was quite clear in recommending, primarily for safety reasons, that IM olanzapine be approved for the treatment of acute agitation only in the diagnostic groups studied in the Lilly development program. The safety of this product in other disorders, such as drug intoxication and acute medical illness, cannot be extrapolated from the experience in the studied populations.

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[46] See the Overdosage/Human Experience section of Zyprexa labeling. No other information about this case was reported.

9.0 Labeling

The following comments are based on the revised draft labeling submitted by the sponsor on 12-20-00, as well as the most recently approved labeling for Zyprexa.[47]

DESCRIPTION

[redacted]

CLINICAL PHARMACOLOGY, Clinical Efficacy Data, Agitation

[redacted]

This subsection should end with a sentence indicating that an examination of population subgroups (age, gender, and racial origin) did not reveal any differential responsiveness on these variables.

INDICATIONS AND USAGE, Agitation

The section should be modified to indicate use for the rapid control of agitation in the diagnostic groups studied (i.e., schizophrenia, schizophreniform disorder, or schizoaffective disorder; bipolar I disorder in an acute manic or mixed state; [redacted]).

[47] The most recently approved labeling was attached to the approval letter for supplement SE1-011 to NDA 20-592.

This section should end with a sentence indicating that the safety and efficacy of Zyprexa ~ beyond 24 hours have not been studied.

PRECAUTIONS

I concur with the sponsor's proposal for a subsection under General PRECAUTIONS regarding hemodynamic effects associated with olanzapine.

A subsection that describes the occurrence of sinus pauses should be added:

PRECAUTIONS

ADVERSE REACTIONS

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DOSAGE AND ADMINISTRATION, Agitation, Administration of Zyprexa

HOW SUPPLIED

10.0 Conclusions

This NDA presents adequate evidence supporting the clinical safety and efficacy of IM olanzapine for the treatment of acute agitation across three diagnostic categories: schizophrenia, schizophreniform disorder, or schizoaffective disorder; bipolar I disorder in an acute manic or mixed state

11.0 Recommendations

It is recommended that this NDA be deemed approvable, with final approval contingent on: 1) satisfactory resolution of CMC and microbiology deficiencies and 2) agreement on the above labeling issues.

Gregory M. Dubitsky, M.D.
March 10, 2001

Cc: NDA 21-253
HFD-120 (Division File)
HFD-120/TLaughren
/GDubitsky
/PAndreason
/SHardeman

3-13-01
I agree that this NDA is approvable. See memo to file for more detailed comments.
T. Laughren

APPENDIX 5.0

DATA SOURCES

TABLE 5.1.1.1 TABLE OF COMPLETED STUDIES	
Clinical Pharmacology Studies (healthy volunteers)	
LOAC	Single blind, ascending dose tolerance, safety, and pharmacokinetic study in 31 healthy males (age 18-65) using single doses of IM olanzapine up to 4mg.
LOAW	Open-label, randomized, 2 period crossover study comparing the bioavailability of IM olanzapine (two 5mg injections given 4 hours apart) with PO olanzapine (2×5mg tablets) in 24 healthy males (age 18-65).
LOAV	Open-label, randomized, 3 period crossover study comparing the safety and pharmacokinetics of IM olanzapine 5mg and IM lorazepam 2mg, each given separately and together as single doses, in 15 healthy subjects (4 males, 11 females)(age 21-40) to evaluate PK/PD interactions.
Open-Label Clinical Studies	
LOAR	Open-label, ascending dose range, pilot study of the safety, efficacy, and PK of IM olanzapine in 26 male inpatients (age 18-65) with acute non-organic psychosis treated with 2-5 doses of IM olanzapine, up to 10mg each, over 3 days.
LOAT	Open-label study of the safety and efficacy of IM olanzapine in 92 male and female inpatients (age ≥18) with acute non-organic psychosis treated with at least two doses of IM olanzapine (2.5, 5, 7.5, or 10mg each) over 3 days.
HGJA	Open-label study in 43 inpatients with chronic schizophrenia to evaluate the tolerance and pharmacokinetics of up to 3 intramuscular doses of olanzapine 10mg within 20 hours during each of two phases of this trial.

TABLE 5.1.1.1 TABLE OF COMPLETED STUDIES	
Placebo-Controlled Studies	
HGHB	Randomized, double-blind, placebo- and haloperidol-controlled parallel group study in 311 inpatients (age ≥18) with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with 1-3 IM injections of olanzapine 10mg, haloperidol 7.5mg, or placebo (2:2:1 ratio) over 24 hours followed by oral olanzapine (5-20 mg/d) or haloperidol (5-20 mg/d) for 4 days.
HGHV	Randomized, double-blind, placebo- and haloperidol-controlled parallel group study in 270 inpatients (age ≥18) with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with 1-3 IM fixed dose injections of olanzapine (2.5, 5, 7.5, or 10mg), haloperidol 7.5mg, or placebo over 24 hours.
HGHW	Randomized, double-blind, placebo- and lorazepam-controlled parallel group study in 201 inpatients (age ≥18) with bipolar I disorder, with an acute manic or mixed episode, treated with 1-3 IM injections of olanzapine (10, 10, and 5mg, respectively), lorazepam (2, 2, and 1mg, respectively), or placebo (0, 0, and IM olanzapine 10mg, respectively) over 24 hours.
—	C J

TABLE 5.1.1.2: PATIENT ENUMERATION BY STUDY TYPE				
Study Type	**IM Olanzapine**	**Placebo**	**Haloperidol**	**Lorazepam**
Clinical Pharmacology Trials	83	18	0	12
Open-Label Trials	161	0	0	0
Placebo-Controlled Trials	604	217	166	119
Total	848	235	166	131

TABLE 5.1.2.1: PLACEBO-CONTROLLED IM SAFETY DATABASE PATIENT DEMOGRAPHIC CHARACTERISTICS						
	Age (yrs)		Sex (%)		Race (%)	
	Mean	Range	Male	Female	White	Non-white
IM Olanzapine (N=415)	37.69	18-79	61%	39%	69%	31%
IM Placebo (N=150)	38.31	18-70	57%	43%	70%	30%

TABLE 5.1.2.2: GERIATRIC STUDY (HGHX) PATIENT DEMOGRAPHIC CHARACTERISTICS						
	Age (yrs)		Sex (%)		Race (%)	
	Mean	Range	Male	Female	White	Non-white
IM Olanzapine 2.5	77.36	54-95	44%	56%	92%	8%
IM Olanzapine 5.0	79.21	56-97	35%	65%	92%	8%
IM Placebo	76.98	56-96	40%	60%	94%	6%
IM Lorazepam	76.97	55-95	37%	63%	91%	9%

TABLE 5.1.3: PATIENT EXPOSURE TO IM OLANZAPINE				
Placebo-Controlled IM Safety Database		Geriatric Study		
Dose (mg/24 hours)	% Receiving Dose N=415	Dose (mg/24 hours)	% Receiving Dose	
			IM Olanz 2.5mg N=71	IM Olanz 5.0mg N=66
2.5	5.5%	2.5	59.2%	0%
5.0	12.3%	5.0	15.5%	63.6%
7.5	8.7%	6.2	25.4%	0%
10.0	53.7%	10.0	0%	19.7%
15.0	3.1%	12.5	0%	16.7%
20.0	13.3%			
22.5	0.2%			
25.0	1.9%			
30.0	1.2%			

APPENDIX 7.0

EFFICACY

TABLE 7.2.1.1: STUDY HGHB INVESTIGATORS/LOCATIONS	
Principal Investigator (Site #)	**Location**
Battaglia (001)	Anchorage, Alaska
Kang (003)	Center Township, Pennsylvania
Plopper (004)	San Diego, California
Reinstein (005)	Chicago, Illinois
Riesenberg (006)	Decatur, Georgia
Sack (007)	Cerritos, California
Adityanjee (008)	Cleveland, Ohio
Wang (009)	Milwaukee, Wisconsin
Chappell (011)	Olympia, Washington
Mofsen (012)	St. Louis, Missouri
Small (013)	Indianapolis, Indiana
Lerman (014)	Oak Brook, Illinois
Fabre (015)	Houston, Texas
Levine (016)	Torrance, California
Figueroa (017)	Torrance, California
Dantendorfer, [ ] (100)	Austria
Geretsegger (101)	Austria
Zapotoczky (102)	Austria
Fleischhacker (103)	Austria
Seifertova (121)	Czech Republic

TABLE 7.2.1.1: STUDY HGHB INVESTIGATORS/LOCATIONS	
Principal Investigator (Site #)	**Location**
Tuma (131)	Czech Republic
Janka (141)	Hungary
Bartko (142)	Hungary
Bitter (143)	Hungary
Peuskens (200)	Belgium
Renier (202)	Belgium
Seghers (203)	Belgium
Herregodts (204)	Belgium
DeClercq (205)	Belgium
Daumer (301)	France
Kannas (302)	France
Gudej (303)	France
Passamar (304)	France
Bonnafoux (305)	France
Wertenschlag (306)	France
Chinchilla (600)	Spain
Bernardo (601)	Spain
Peralta (602)	Spain
De la Gandara (603)	Spain
San Molina (604)	Spain

TABLE 7.2.1.1: STUDY HGHB INVESTIGATORS/LOCATIONS	
Principal Investigator (Site #)	**Location**
McCreadie (801)	Scotland
Chouinard (850)	Canada
Labelle (851)	Canada
Siekiersky (853)	Canada
Brook (900)	South Africa
Hart (903)	South Africa
Belmaker (920)	Israel
Grunhaus (921)	Israel
Elizur (922)	Israel
Christodoulou (930)	Greece
Morris (960)	Australia

TABLE 7.2.1.2:
STUDY HGHB
PATIENT DEMOGRAPHICS
INJECTABLE PERIOD

Treatment	IM Olanz	IM Hal	IM Placebo
N	131	126	54
AGE (years)			
Mean	38.17	38.54	37.60
Range	18-72	18-70	19-70
GENDER (%)			
Male	64.9	68.3	61.1
Female	35.1	31.7	38.9
RACE (%)			
Caucasian	72.5	77.0	63.0
African	18.3	17.5	24.1
Hispanic	6.1	3.2	9.3
E/SE Asian	0.8	1.6	0.0
Other	2.3	0.8	3.7

TABLE 7.2.1.5
STUDY HGHB
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
IM Olanz	131	13.35	130	-6.33	130	-8.10	129	-8.50	129	-8.09	131	-8.01
IM Hal	126	13.17	126	-4.27	126	-7.22	125	-7.96	126	-7.83	126	-7.83
IM Plac	54	13.37	54	-2.39	54	-3.50	54	-3.69	54	-3.74	54	-3.74
2-sided p-values for pairwise comparisons												
IM Olanz vs. IM Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
IM Hal vs. IM Plac			0.007		<0.001		<0.001		<0.001		<0.001	
IM Olanz vs. IM Hal			<0.001		0.171		0.422		0.793		0.868	

TABLE 7.2.1.6
STUDY HGHB
MEAN CHANGE FROM BASELINE IN THE CORRIGAN AGITATED BEHAVIOR SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
IM Olanz	131	27.60	129	-6.53	130	-8.12	128	-8.34	129	-8.01	131	-7.89
IM Hal	126	26.92	126	-5.20	125	-7.37	125	-7.98	126	-7.79	126	-7.79
IM Plac	54	28.52	54	-3.37	54	-4.81	54	-5.06	54	-4.39	54	-4.39
2-sided p-values for pairwise comparisons												
IM Olanz vs. IM Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
IM Hal vs. IM Plac			0.020		0.003		0.001		<0.001		<0.001	
IM Olanz vs. IM Hal			0.036		0.290		0.644		0.849		0.940	

TABLE 7.2.1.7
STUDY HGHB
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
IM Olanz	131	2.59	131	+1.34	131	+1.95	131	+1.95	130	+1.81	131	+1.79
IM Hal	126	2.48	126	+0.96	126	+1.67	126	+1.81	126	+1.65	126	+1.65
IM Plac	54	2.43	54	+0.48	54	+0.74	54	+0.87	54	+0.74	54	+0.74
2-sided p-values for pairwise comparisons												
IM Olanz vs. IM Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
IM Hal vs. IM Plac			0.024		<0.001		<0.001		<0.001		<0.001	
IM Olanz vs. IM Hal			0.017		0.114		0.439		0.406		0.448	

TABLE 7.2.2.1: STUDY HGHV INVESTIGATORS/LOCATIONS	
Principal Investigator (Site #)	**Location**
Folnegovic-Smalc (131)	Croatia
Dodig (132)	Croatia
Mandic (133)	Croatia
Jakovljevic (134)	Croatia
Prelipceanu (260)	Romania
Boisteanu (261)	Romania
Lazarescu (262)	Romania
Caserta (502)	Italy
Rataemane (901)	South Africa
Brook (902)	South Africa
Van Wyk (904)	South Africa
Hart (905)	South Africa
Strauss (906)	South Africa
Emsley (907)	South Africa

TABLE 7.2.2.2:
STUDY HGHV
PATIENT DEMOGRAPHICS

Treatment Group	IM Olanzapine				IM Hal 7.5mg	IM Plac
	2.5mg	5mg	7.5mg	10mg		
N	48	45	46	46	40	45
AGE (years)						
Mean	36.24	35.08	35.87	36.73	37.41	36.65
Range	19-70	18-54	20-71	18-71	21-73	19-58
GENDER (%)						
Male	64.6	60.0	56.5	56.5	55.0	51.1
Female	35.4	40.0	43.5	43.5	45.0	48.9
RACE (%)						
Caucasian	60.4	68.9	63.0	69.6	62.5	71.1
African	22.9	24.4	26.1	23.9	30.0	17.8
W Asian	4.2	0.0	0.0	0.0	0.0	4.4
Other	12.5	6.7	10.9	6.5	7.5	6.7

TABLE 7.2.2.4
STUDY HGHV
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olz 2.5	48	13.25	48	-1.71	48	-3.98	48	-5.15	48	-5.50	48	-5.50
Olz 5	45	14.71	45	-2.93	45	-5.82	45	-7.18	45	-8.09	45	-8.09
Olz 7.5	46	13.85	46	-3.26	46	-6.28	46	-8.35	46	-8.65	46	-8.65
Olz 10	46	14.30	45	-2.87	46	-6.83	46	-9.15	46	-9.35	46	-9.35
Hal 7.5	40	14.28	40	-2.00	40	-5.38	40	-6.40	39	-7.69	40	-7.53
Placebo	45	13.78	45	-1.40	45	-2.22	45	-2.80	45	-2.91	45	-2.91
2-sided p-values for pairwise comparisons												
Olz 2.5 vs. Placebo			0.646		0.050		0.016		0.010		0.010	
Olz 5 vs. Placebo			0.029		<0.001		<0.001		<0.001		<0.001	
Olz 7.5 vs. Placebo			0.007		<0.001		<0.001		<0.001		<0.001	
Olz 10 vs. Placebo			0.046		<0.001		<0.001		<0.001		<0.001	
Hal 7.5 vs. Placebo			0.343		<0.001		<0.001		<0.001		<0.001	

TABLE 7.2.2.5
STUDY HGHV
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olz 2.5	48	2.42	48	+0.31	48	+0.85	48	+1.25	48	+1.27	48	+1.27
Olz 5	45	2.18	45	+0.56	45	+1.49	45	+1.91	45	+2.31	45	+2.31
Olz 7.5	46	2.26	46	+0.67	46	+1.48	46	+2.15	46	+2.37	46	+2.37
Olz 10	46	2.26	45	+0.84	46	+1.91	46	+2.59	46	+2.57	46	+2.57
Hal 7.5	40	2.15	40	+0.28	40	+1.20	40	+1.60	39	+1.82	40	+1.78
Placebo	45	2.38	45	+0.24	45	+0.44	45	+0.62	45	+0.69	45	+0.69
2-sided p-values for pairwise comparisons												
Olz 2.5 vs. Placebo			0.715		0.142		0.044		0.064		0.064	
Olz 5 vs. Placebo			0.112		<0.001		<0.001		<0.001		<0.001	
Olz 7.5 vs. Placebo			0.026		<0.001		<0.001		<0.001		<0.001	
Olz 10 vs. Placebo			0.004		<0.001		<0.001		<0.001		<0.001	
Hal 7.5 vs. Placebo			0.787		0.008		0.002		<0.001		0.001	

TABLE 7.2.3.1: STUDY HGHW INVESTIGATORS/LOCATIONS	
Principal Investigator (Site #)	**Location**
Bari (001)	Chula Vista, CA
Fossey (003)	Tulsa, OK
Janicak (004)	Chicago, IL
El-Mallakh (005)	Louisville, KY
Kwentus (006)	Madison, TN
Pavlinac (007)	Oceanside, CA
Plopper (008)	San Diego, CA
Ranjan (009)	Medina, OH
Reinstein (010)	River Park, IL
Small (011)	Indianapolis, IN
Charuvastra (012)	San Fernando, CA
Wang (013)	Milwaukee, WI
Achamallah (014)	Vallejo, CA
Brown (015)	Austin, TX
Feifel (016)	San Diego, CA
Maguire (017)	Orange, CA
Mee-Lee (018)	Honolulu, HI
Printz (019)	New York, NY
Vivek (020)	Jamaica, NY

TABLE 7.2.3.1: STUDY HGHW INVESTIGATORS/LOCATIONS	
Principal Investigator (Site #)	**Location**
Munoz (023)	Birmingham, AL
Rosenthal (025)	San Diego, CA
Oxenkrug (029)	Brighton, MA
Moss (030)	North Chicago, IL
Gupta (031)	Olean, NY
Beckett (035)	Oklahoma City, OK
Fabre (036)	Houston, TX
Prelipceanu (101)	Romania
Boisteanu (102)	Romania
Lazarescu (103)	Romania

TABLE 7.2.3.3:
STUDY HGHW
PATIENT DEMOGRAPHICS

Treatment	IM Olanzapine	IM Lorazepam	IM Placebo
N	99	51	51
AGE (years)			
Mean	40.24	38.96	40.54
Range	18-79	19-60	18-67
GENDER (%)			
Male	57.6	41.2	56.9
Female	42.4	58.8	43.1
RACE (%)			
Caucasian	69.7	74.5	76.5
African	17.2	13.7	15.7
E/SE Asian	3.0	0.0	3.9
W Asian	1.0	2.0	2.0
Hispanic	7.1	7.8	2.0
Other	2.0	2.0	0.0

TABLE 7.2.3.6
STUDY HGHW
MEAN CHANGE FROM BASELINE IN THE PANSS EXCITED COMPONENT
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanzapine	98	12.96	98	-5.58	98	-8.32	98	-9.41	98	-9.60	98	-9.60
Lorazepam	51	12.39	51	-3.45	50	-5.22	51	-6.61	51	-6.75	51	-6.75
Placebo	50	12.72	50	-3.24	50	-4.32	49	-4.84	48	-5.04	50	-4.84
2-sided p-values for pairwise comparisons												
Olanz vs. Plac			0.003		<0.001		<0.001		<0.001		<0.001	
Lor vs. Plac			0.862		0.345		0.066		0.088		0.053	
Olanz vs. Lor			0.005		<0.001		<0.001		<0.001		0.001	

TABLE 7.2.3.7
STUDY HGHW
MEAN CHANGE FROM BASELINE IN THE CORRIGAN AGITATED BEHAVIOR SCALE
AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanzapine	98	28.79	98	-7.34	98	-9.78	98	-11.02	98	-11.30	98	-11.30
Lorazepam	51	28.14	51	-4.35	50	-6.10	51	-8.00	51	-8.39	51	-8.39
Placebo	50	27.66	50	-3.56	50	-4.66	49	-4.98	48	-5.06	50	-4.78
2-sided p-values for pairwise comparisons												
Olanz vs. Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
Lor vs. Plac			0.535		0.199		0.009		0.007		0.003	
Olanz vs. Lor			0.003		<0.001		0.002		0.006		0.006	

TABLE 7.2.3.8
STUDY HGHW
MEAN CHANGE FROM BASELINE IN THE AGITATION-CALMNESS EVALUATION SCALE AFTER FIRST INJECTION

Treatment Group	Baseline		Observed Cases								LOCF	
			30 minutes		60 minutes		90 minutes		120 minutes		120 minutes	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Olanzapine	98	2.24	98	+1.68	98	+2.37	98	+2.76	98	+2.90	98	+2.90
Lorazepam	51	2.33	51	+0.75	50	+1.22	51	+1.67	51	+1.88	51	+1.88
Placebo	50	2.26	50	+0.62	50	+0.94	49	+0.80	48	+0.90	50	+0.82
2-sided p-values for pairwise comparisons												
Olanz vs. Plac			<0.001		<0.001		<0.001		<0.001		<0.001	
Lor vs. Plac			0.710		0.406		0.006		0.004		0.002	
Olanz vs. Lor			<0.001		<0.001		<0.001		<0.001		0.001	

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contains
trade secret
and/or
confidential information
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APPENDIX 8.0

SAFETY FINDINGS

TABLE 8.1.4.3
PLACEBO-CONTROLLED IM SAFETY DATABASE
TREATMENT-EMERGENT ADVERSE EVENTS DUIRNG THE INJECTABLE TREATMENT PHASE

	Percentage of Patients Reporting Adverse Event	
	IM Olanzapine (N=415)	IM Placebo (N=150)
Somnolence	5.5%	3.3%
Dizziness	4.1%	2.0%
Agitation	2.9%	8.7%
Headache	2.2%	2.0%
Hypotension	2.2%	0.0%
Insomnia	1.9%	3.3%
Asthenia	1.7%	0.7%
Anxiety	1.4%	4.0%
Dry Mouth	1.4%	0.7%
Hypertension	1.2%	1.3%
Nervousness	1.2%	1.3%
Postural Hypotension	1.2%	0.0%
Tremor	1.2%	0.0%
Akathisia	1.0%	0.0%

TABLE 8.1.5.2
CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN LABORATORY VALUES

Analyte		Units	Low Limit	High Limit
AST/SGOT		U/L		150
ALT/SGPT		U/L		165
CPK:	Female	U/L		507
	Male	U/L		594
Alkaline Phosphatase		U/L		420
GGT:	Female	U/L		135
	Male	U/L		195
Urea Nitrogen		mmol/L		10.71
Creatinine		µmol/L		176.8
Calcium		mmol/L	1.7465	2.994
Inorganic Phosphorous		mmol/L	0.48435	1.77595
Sodium		mmol/L	129	160
Total Protein		g/L	50	
Albumin		g/L	25	
Glucose (nonfasting)		mmol/L	2.4975	13.875
Uric Acid:	Female	µmol/L		505.58
	Male	µmol/L		624.54
Total Cholesterol		mmol/L		15.516
Total Bilirubin		µmol/L		34.2
Hematocrit:	Female	1	0.32	0.50
	Male	1	0.37	0.55
Hemoglobin:	Female	mmol/L (Fe)	5.8957	10.2399
	Male	mmol/L (Fe)	7.1369	11.4811
Erythrocyte Count		TI/L	3	6
Leukocyte Count		GI/L	2.8	16.0
Platelet Count		GI/L	75	700
Neutrophils, Segmented		% WBC	15	
Eosinophils		% WBC		10
UA-Specific Gravity			1.001	1.035
UA-pH			4.6	8.0
UA-RBC				Increase ≥2 and score ≥3
UA-WBC				Increase ≥2 and score ≥3
UA-Casts, Hyaline				Increase ≥2 and score ≥3
UA-Protein				Increase ≥2 and score ≥3
UA-Ketones				Increase ≥2 and score ≥3
UA-Glucose				Increase ≥2 and score ≥3

Abbreviations: AST/SGOT = aspartate transaminase/serum glutamic oxaloacetic transaminase; ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase; CPK = creatine phosphokinase; GGT = Gamma-glutamyl transferase; UA = urinalysis analyte.

TABLE 8.1.6.2.1 CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS[51]		
Variable	**Low**	**High**
Supine systolic BP	≤90 & ↓ ≥20	≥180 & ↑ ≥20
Standing systolic BP	≤90 & ↓ ≥20	≥180 & ↑ ≥20
Sitting systolic BP	≤90 & ↓ ≥20	≥180 & ↑ ≥20
Supine diastolic BP	≤50 & ↓ ≥15	≥105 & ↑ ≥15
Standing diastolic BP	≤50 & ↓ ≥15	≥105 & ↑ ≥15
Sitting diastolic BP	≤50 & ↓ ≥15	≥105 & ↑ ≥15
Supine pulse	<50 & ↓ ≥15	>120 & ↑ ≥15
Standing pulse	<50 & ↓ ≥15	>120 & ↑ ≥15
Sitting pulse	<50 & ↓ ≥15	>120 & ↑ ≥15
Orthostatic hypotension	≥30 ↓ in systolic BP[52]	---
Sitting orthostatic hypotension	≥30 ↓ in systolic BP[53]	---

[51] Blood pressure is measured is mmHg and pulse in beats per minute.
[52] Supine to standing (placebo-controlled IM safety database).
[53] Supine to sitting (geriatric study).

TABLE 8.1.7.2

CRITERIA FOR IDENTIFYING POTENTIALLY CLINICALLY SIGNIFICANT ECG MEASURES

Variable	Low	High
PR	---	200 msec
QRS	---	100 msec
QT	---	450 msec
QTc	---	430 msec
Heartrate	40 bpm	120 bpm

ADDENDUM

Review and Evaluation of Clinical Data
NDA #21-253

Sponsor:	Eli Lilly and Company
Drug:	Zyprexa IntraMuscular
Proposed Indication:	Acute Agitation
Material Submitted:	Response to 1-19-01 Request for Information
Correspondence Dates:	March 15, 2001 and March 23, 2001
Dates Received:	March 16, 2001 and March 26, 2001

I. Background

On 6-15-00, the sponsor submitted this NDA for the approval of an intramuscular formulation of olanzapine in the treatment of acute agitation. The development program consisted of a total of 11 completed Phase 1, 2, and 3 studies that involved a total of 848 patients and healthy volunteers.

The safety review of this NDA revealed two cardiovascular findings which had not been recognized in association with oral formulations of olanzapine: 1) simultaneous hypotension and bradycardia, observed mostly in healthy volunteers or non-agitated psychiatric patients, and 2) sinus pauses, which were documented on telemetry in three healthy volunteers.[1] These findings were not deemed to constitute safety issues that would preclude the approval of this NDA mainly because they were self-limited and not observed to any appreciable extent in the target population.

Nonetheless, a survey of the total safety experience with oral olanzapine for similar findings was thought to be prudent. Therefore, we requested such an assessment in a 1-19-01 FAX to the sponsor. These submissions contain Lilly's response to our request.

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[1] Please see the 3-10-01 clinical review of this NDA for further details.

II. Clinical Data

A. Data Sources and Methodology

Lilly analyzed clinical data from Phase 1-4 studies conducted with oral formulations of olanzapine, including capsules, tablets, rapidly disintegrating tablets, and fine granules. The safety data cutoff was 1-19-01.

Due to significant differences in study design, Phase 1 results were not pooled with Phase 2-4 data. Additionally, because of incompatibility between the Japanese and global (non-Japanese) databases, data from Japanese trials are reported separately.[2]

Essentially, the approach used to evaluate these data was two-fold:

1) to assess the incidence of simultaneous hypotension and bradycardia, utilizing the criteria described in Appendix 1 to this review.

2) to assess the incidence of clinical adverse events that might be associated with significant hypotension and bradycardia or sinus pauses, namely events coded as the COSTART terms "heart arrest," "shock," "syncope," or "dizziness."[3]

ECG telemetry was not conducted in the oral olanzapine studies.[4] Hence, definitive information about sinus pauses cannot be derived from these analyses.

B. Results

Non-Japanese Phase 1 Studies

The proportions of healthy volunteers who met criteria for simultaneous hypotension and bradycardia by treatment group in non-Japanese Phase 1 trials are displayed in Table 1

---

[2] All Phase 2-4 and non-Japanese Phase 1 data are contained in the 3-15-01 submission. Japanese Phase 1 data are contained in the 3-23-01 submission. All these data are encompassed in this single clinical review.

[3] Adverse events in the Japanese Phase 1 studies were not coded to COSTART terminology; verbatim terms were used in this dataset.

[4] This was verified by the sponsor at the 2-14-01 PDAC meeting for this NDA.

below. The difference between olanzapine and placebo is not significant (p=0.387).[5] Among the 13 olanzapine-treated subjects with simultaneous hypotension and bradycardia, none experienced syncope or fatal outcome.

TABLE 1
NON-JAPANESE PHASE 1 STUDIES
PROPORTION OF SUBJECTS WITH SIMULTANEOUS HYPOTENSION AND BRADYCARDIA[6]

Treatment Group	n	N	% (n/N × 100%)
Olanzapine	13	533	2.4%
Placebo	0	76	0.0%
Other Active	0	112	0.0%

There were no reports of events coded as heart arrest or shock in this study pool.

Syncope was reported in 3.9% (21/545) of olanzapine subjects and 0% (0/76) of placebo patients (p=0.095).

Dizziness was reported significantly more frequently in the olanzapine versus placebo subjects (23.7% vs. 6.6%; p= 0.001; Yates-corrected Chi-Square).

Japanese Phase 1 Studies

The proportions of healthy volunteers who met criteria for simultaneous hypotension and bradycardia by treatment group in Japanese Phase 1 trials are displayed in Table 2 below. The difference between olanzapine and placebo is not significant (p=1.000). Among the two olanzapine-treated subjects with simultaneous hypotension and bradycardia, neither experienced syncope or fatal outcome.

[5] Unless otherwise noted, p-values are based on a 2-tailed Fisher's Exact Test.
[6] n = number of subjects meeting criteria for simultaneous hypotension and bradycardia; N = total number of subjects with evaluable data for this analysis.

TABLE 2 JAPANESE PHASE 1 STUDIES PROPORTION OF SUBJECTS WITH SIMULTANEOUS HYPOTENSION AND BRADYCARDIA			
Treatment Group	n	N	% (n/N × 100%)
Olanzapine	2	100	2.0%
Placebo	0	23	0.0%

There were no reports of treatment-emergent heart arrest, shock, or syncope in this study pool.

Dizziness was reported significantly more frequently in the olanzapine versus placebo subjects (83.0% vs. 30.4%; p= 0.000; Yates-corrected Chi-Square). The sponsor explains the very high incidence of dizziness in this database as most likely due to increased ascertainment: a broader set of verbatim adverse event terms were included in this computation instead of the specific COSTART terms that were used for the other datasets.

Non-Japanese Phase 2-4 Studies[7]

Non-Japanese Placebo-Controlled Studies
In the pool of placebo-controlled Phase 2, 3, and 4 studies, there were no cases of simultaneous hypotension and bradycardia among olanzapine-treated patients (846 patients with evaluable data). There was one such occurrence in a placebo-treated patient.

One olanzapine-treated patient (HGFV/019-1802) experienced an adverse event coded as "heart arrest" (1/882 = 0.1% or 5.1 per 1,000 PEY's). This occurred in an 84 year old female with a recent history of urosepsis and possibly some degree of congestive heart failure who had received olanzapine for about 16 days. There was no autopsy.

There were no cases of events coded as shock.

[7] The sponsor also provided analyses from subsets of the non-Japanese Phase 2-4 study pool by active comparator (i.e., haloperidol, risperidone, and clozapine). Examination of these analyses revealed findings consistent with those from the analyses presented in this review. For this reason, these analyses are not specifically presented.

There was no significant difference between olanzapine and placebo in the proportion of patients who experienced syncope (0.7% for olanzapine vs. 0.6% for placebo). Incidence of syncope per 1,000 PEY's was higher for placebo (30.4 for olanzapine vs. 51.8 for placebo).

The incidence of dizziness was significantly higher among olanzapine-treated patients: 7.0% (62/882) vs. 3.9% (20/517); p=0.018.

Non-Japanese Overall Phase 2-4 Study Database
In the overall Phase 2-4 database, 0.1% (5/5419) of olanzapine-treated patients had documented simultaneous hypotension and bradycardia, yielding an incidence of 1.7 per 1,000 PEY's. None had syncope or a fatal outcome associated with this finding.

A total of 7 olanzapine patients in the overall Phase 2-4 database experienced adverse events coded as "heart arrest" (7/5622 = 0.1% or 2.4 per 1,000 PEY's). A review of the case summaries for these patients suggested that none were reasonably attributable to olanzapine therapy.[8]

No patient experienced an event coded as shock.

The incidence of syncope was 0.9% (50/5622) or 16.8 per 1,000 PEY's.

Dizziness was reported in 5.7% (321/5622) of patients.

Japanese Phase 2-4 Studies

Among olanzapine-treated patients in Phase 2, 3, and 4 studies conducted in Japan, none met criteria for simultaneous hypotension and bradycardia (492 patients with evaluable data).

There were no reports of heart arrest or shock.

The incidence of syncope was 0.5% (3/580) or 10.6 per 1,000 PEY's.

Dizziness was reported in 7.2% (42/580) of these patients.

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[8] These patients were: HGFV/019-1802, HGAJ/035-0206, HGAP/005-1215, HGGV/008-1351, HGBT/241-2403, HGCY/011-2010, and HGEU/015-1533.

III. Conclusions and Recommendations

The data from the oral olanzapine studies are consistent with data from the intramuscular olanzapine studies in this NDA with respect to simultaneous hypotension and bradycardia and adverse events that might be associated with this vital sign abnormality. Specifically, concurrent hypotension and bradycardia were observed at low but appreciable frequencies in healthy volunteers (2% with oral olanzapine and 8% with intramuscular olanzapine) and at frequencies about 10-fold lower in psychiatric patients. These events appear to be self-limited.

Since telemetry was not performed in any studies with oral olanzapine, the occurrence of sinus pauses with oral formulations cannot be ruled out. However, the incidence of adverse experiences that might be secondary to pauses in sinus rhythm (heart arrest, shock, syncope, and dizziness) do not seem excessive and mitigate against a substantial risk of sinus pause with oral olanzapine.

In conclusion, these data provide no solid evidence of an important cardiovascular hazard associated with oral olanzapine related to hypotension with bradycardia or sinus pauses.

Gregory M. Dubitsky, M.D.
May 3, 2001

cc: NDA #21-253
NDA #20-592
NDA #21-086
HFD-120 (Div. File)
HFD-120/GDubitsky
/PAndreason
/TLaughren
/SHardeman

APPENDIX 1

CRITERIA FOR ABNORMALLY LOW VITAL SIGNS AND ECG HEART RATE	
Parameter	**Criterion**
Supine systolic BP (mmHg)	≤90 and decrease ≥20
Standing systolic BP (mmHg)	≤90 and decrease ≥20
Supine diastolic BP (mmHg)	≤50 and decrease ≥15
Standing diastolic BP (mmHg)	≤50 and decrease ≥15
Supine pulse (bpm)	<50 and decrease ≥15
Standing pulse (bpm)	<50 and decrease ≥15
Orthostatic hypotension (mmHg)	≥30 mmHg decrease in SBP
ECG heart rate (bpm)	≤40

SIMULTANEOUS HYPOTENSION AND BRADYCARDIA

Subjects could fulfill the criteria for simultaneous hypotension and bradycardia by any of the following combinations of findings, as defined above, at the same timepoint:

- supine bradycardia + supine systolic hypotension.
- supine bradycardia + supine diastolic hypotension.
- supine ECG bradycardia + supine systolic hypotension.
- supine ECG bradycardia + supine diastolic hypotension.
- standing bradycardia + standing systolic hypotension.
- standing bradycardia + standing diastolic hypotension.
- standing bradycardia + orthostatic hypotension.

For the Japanese Phase 1 studies, the following combinations of findings were also considered as criteria for simultaneous hypotension and bradycardia:

- sitting bradycardia + sitting systolic hypotension.
- sitting bradycardia + sitting diastolic hypotension.

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

/s/

Greg Dubitsky
5/3/01 01:23:59 PM
MEDICAL OFFICER

Thomas Laughren
6/7/01 11:10:30 AM
MEDICAL OFFICER
I agree with Dr. Dubitsky's conclusions.--TPL

M E M O R A N D U M

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

DATE: March 13, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Zyprexa (olanzapine IM) for the acute treatment of agitation in schizophrenia, mania

TO: File NDA 21-253
[**Note:** This overview should be filed with the 6-15-00 original submission of the NDA.]

1.0 BACKGROUND

Olanzapine IM is an intramuscular formulation of the antipsychotic drug olanzapine that is being proposed for use in the "rapid control of agitation." Oral olanzapine was approved for the treatment of schizophrenia on 9-30-96 (NDA 20-592) and for mania on 3-17-00 (NDA 20-592/S-006). Zyprexa Zydis, an orally disintegrating formulation of olanzapine, was approved on 4-6-00 (NDA 21-086).

While there are no drugs approved specifically for the treatment of agitation, several antipsychotic drugs are available in intramuscular form and are used in treating agitated patients. Various benzodiazepines and other sedating drugs are also used for treating agitation.

The clinical trials in support of this application were conducted under IND 55,342 which was submitted 3-4-98. We met with the sponsor on 5-14-98 and informed them that, if they wished to persue a claim for agitation, it would be useful to study it in several different disease models. In a followup teleconference on 11-12-98, they proposed a plan to study agitation in three models, i.e., schizophrenia, bipolar mania, [ ], and we agreed with this proposal. During a preNDA meeting with the sponsor on 1-6-00, we informed them of the plan to discuss the issue of agitation as a claim at an upcoming meeting of the PDAC, and noted that the outcome of this meeting may impact on their development plans for this new formulation.

The original NDA for Zyprexa – was submitted 6-15-00. There was no safety update. The clinical review of this application was conducted by Greg Dubitsky, M.D. This application was the subject of a 2-14-01 meeting of the PDAC.

2.0 CHEMISTRY

The chemistry review of this application was conducted by Sherita McLamore. It is my understanding that there may be a CMC deficiency, based on the plant inspection, that may preclude an approvable action on this application. This issue is not resolved at the time of drafting of this memo.

3.0 PHARMACOLOGY

The pharmacology/toxicology review of this application was conducted by Lois Freed. To my knowledge, there are no pharmacology/toxicology issues that would preclude an approvable action on this application.

4.0 BIOPHARMACEUTICS

The biopharmaceutics review of this application was conducted by Hong Zhao, Ph.D., from OCPB. To my knowledge, there are no biopharmaceutics issues that would preclude an approvable action on this application, at least for the vial intended to be reconstituted with sterile water. Given by IM injection, olanzapine has a shorter Tmax (15-45 minutes vs 5-8 hrs for PO) and a higher Cmax (about 4-5 fold higher) than PO olanzapine. The pharmacokinetics for the two formulations are otherwise similar. The plasma concentrations observed after several doses of olanzapine IM are within the range of observed steady state concentrations in patients dosed maximally with oral olanzapine.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor presented the results of 4 controlled trials involving the use of olanzapine IM in the control of agitation in three different populations: schizophrenia (HGHB; HGHV); bipolar mania (HGHW); ——————— . All 4 trials were both placebo and active controlled, and the primary efficacy assessment was the excited component of the PANSS at 2 hours after the first dose. The PANSS was obtained as follows: baseline (immediately before first IM dose), 15, 30, 45, 60, 90, and 120 minutes after the first IM dose. The 5 items comprising the excited component of the PANSS are: poor impulse control; tension; hostility; uncooperativeness; and excitement. Each item was rated on a scale of 0 (absent) to 6 (extreme), yielding a range for total scores from 0 to 30. The nominal duration of each trial was 24 hours, and patients could receive up to 3 doses of IM treatment, with the second dose being given no sooner than 2 hours after the first, and the third dose no sooner than 4 hours after the second (for HGHB & HGHV) or no sooner than 1 hour after the second (for HGHW & ———). Secondary efficacy measures included: the Agitation-Calmness Evaluation Scale (ACES); the Corrigan Agitated Behavior Scale (CABS); and the Cohen-Mansfiled Agitation Inventory (CMAI). For all 4 studies, the inclusion criteria were: (1) "investigator judgement that the patient is clinically agitated and a clinically appropriate candidate for treatment with IM medication," and (2) "PANSS Excited component total score $\geq$ 14 plus a score of $\geq$ 4 (4=moderate) on at least 1 item using the 1-7 scoring system)." [Note: These scores were modified by subtracting 1 for the purposes of analysis.] Analysis was performed using ANOVA, with a focus on change from baseline to 2 hours, LOCF.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study HGHB

This was a randomized, double-blind, parallel group, 51-center, US and European inpatient study comparing olanzapine 10 mg IM, haloperidol 7.5 mg IM, and placebo (2:2:1 randomization), in agitated patients who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

311 patients were randomized, and 285 were considered completers to 24 hours. The mean change from baseline in PANSS excited component at 2 hours, LOCF, favored olanzapine IM over placebo to a highly statistically significant extent ($p<0.001$), and thus, in my view, this study was successful in demonstrating a calming effect for olanzapine IM in agitated schizophrenic patients.

5.1.2.2 Study HGHV

This was a randomized, double-blind, parallel group, 14-center, European and South African inpatient study comparing olanzapine IM at 4 fixed doses (2.5, 5.0, 7.5, and 10.0 mg), haloperidol 7.5 mg IM, and placebo, in agitated patients who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

270 patients were randomized, and 268 were considered completers to 24 hours. The mean change from baseline in PANSS excited component at 2 hours, LOCF, favored olanzapine IM over placebo at 5.0, 7.5, and 10.0 mg to a highly statistically significant extent ($p<0.001$), and thus, in my view, this study was successful in demonstrating a calming effect for olanzapine IM in agitated schizophrenic patients. The 2.5 mg dose was also superior to placebo on the primary outcome, but the effect size was less than for the higher 3 doses, and it was not as consistently superior to placebo on the secondary outcomes as were the higher three doses.

5.1.2.3 Study HGHW

This was a randomized, double-blind, parallel group, 29-center, mostly US inpatient study comparing olanzapine 10 mg IM, lorazepam 2 mg IM, and placebo (2:1:1 randomization), in agitated patients who met DSM-IV criteria for bipolar I disorder with an acute manic or mixed episode.

201 patients were randomized, and 173 were considered completers to 24 hours. The mean change from baseline in PANSS excited component at 2 hours, LOCF, favored olanzapine IM over placebo to a highly statistically significant extent ($p<0.001$), and thus, in my view, this study was successful in demonstrating a calming effect for olanzapine IM in agitated bipolar I patients with manic or mixed episodes.

5.1.3 Comment on Other Important Clinical Issues Regarding Olanzapine IM for the Control of Agitation in Several Different Diagnostic Groups

Evidence Bearing on the Question of Dose/Response for Efficacy

Two of the four studies included fixed dose arms that permit inferences about dose response.
-Study HGHV suggested somewhat stronger efficacy for the higher 3 doses (5, 7.5, and 10) compared to the 2.5 mg dose, in agitation with schizophrenia. The effects for the higher three doses were not clearly distinguishable, either based on changes in the primary outcome, or based on the need for additional doses following the first dose. Thus, 5.0 mg should be the recommended dose, in my view.

Clinical Predictors of Response

The sponsor's subgroup analyses revealed no consistent differences in effectiveness based on factors of age, gender, or race. It should be noted that the patients enrolled in these trials did not represent the most severe end of the agitation spectrum, a likely reflection of the reality of getting subjects who are able and willing to give informed consent. In my view, it is not unreasonable to extrapolate the findings in these studies to populations with greater levels of excitement and agitation, since there would be even greater potential for improvement in the more agitated/excited patients and therefore a better opportunity for demonstrating an effect. However, it is possible that somewhat higher doses might be needed for these more severely agitated patients.

Size of Treatment Effect

The mean change from baseline in the PANSS excited component does not lend itself to any obvious clinical interpretation. However, I think the highly statistically significant results for all 4 studies, given rather modest sample sizes, is persuasive that this is a clinically meaningful outcome. What also helps is the fact that this is not a surprising outcome, given prior knowledge of the sedative effects of olanzapine, and in fact for this class of drugs generally.

Duration of Treatment

All 4 trials focused only on the first dose. A minority of patients needed more than 1 dose, and the maximum number of doses for which there any data is 3, within a 24 hour period. While there was no attempt to look systematically at the efficacy of second and third doses, I do not think it is unreasonable to extrapolate the positive findings from the first dose to second and third doses during the first day. However, given that all of the data, both efficacy and safety, are limited to the first day, I think that labeling needs to restrict IM dosing to this period as well.

5.1.3 Conclusions Regarding Efficacy Data

In my view, the sponsor has demonstrated that olanzapine IM, at doses of 5 to 10 mg in schizophrenic or bipolar manic patients, has a beneficial effect on the control of agitation during the initial day of treatment.

5.2 Safety Data

5.2.1 Safety Database

Safety data were provided for olanzapine IM exposed subjects/patients from 11 clinical trials in this NDA (total n=850 olanzapine IM exposures). The cutoff date was April, 2000 for 9 of the studies, and June, 2000 for the remaining two. The entire pool of exposures was ulitized for deaths, other SAEs, and adverse dropouts. Other safety data (common adverse events, labs, vital signs, and ECGs) were explored in 2 pools of the phase 2/3 studies: the younger patients (HB; HV; HW) and the older patients -- In the younger pool, the mean age of patients was about 38, they were about 60% male, and about 70% white. In the elderly pool, the mean age of patients was about 78, they were about 60% male, and about 92% white.

5.2.2 Overview of Safety Findings

The only events that could be reasonably classified as potentially serious adverse events and reasonably attributed to olanzapine IM administration were cases of hypotension, bradycardia, and sinus pause (in 3 normal volunteers); these events will be discussed under 5.2.3. There were very few dropouts, not surprising given the short-term nature of these trials. The adverse events that emerged from the clinical trials as likely drug-related included somnolence, dizziness, and hypotension, but the rates were quite low and hardly distinguishable from placebo. There was no indication of injection site reactions or EPS. There was no indication of changes in laboratory parameters in association with olanzapine IM treatment. There was a small signal for excess hypotension associated with olanzapine IM compared to placebo, and as noted, some of these cases were associated with bradycardia (see 5.2.3). ECGs were obtained at baseline, 2 hours, and 24 hours in the clinical trials. While there was numerically a 9 msec increase from baseline in QTc for the 5 mg group in the geriatric study, there was a 4 msec decrease for the 2.5 mg group and a 3 msec increase for placebo patients. In the larger pool of younger patients, there was no indication of any dose related effects on the QTc interval. It should be noted that the 2 hour ECGs would have missed the olanzapine Cmax in most patients, and thus, would have missed ECG changes that might have been most prominent at earlier time points. On the other hand, there has been little indication from earlier studies with olanzapine, including the head-to-head comparision of olanzapine (study 54 for ziprasidone), of a potential for QTc prolongation with this drug.

5.2.3 Safety Finding of Particular Interest: Orthostatic Hypotension, Bradycardia, and Sinus Pause

Out of 850 total patients/subjects exposed to olanzapine IM in the development program, 64 experienced bradycardia. Twenty-eight of these cases were among the normal volunteers (i.e., 33% of normal volunteers) and 36 were patients (i.e., 5% of patients). Three of the 28 normal volunteers had sinus pauses, associated with syncope, that remitted spontaneously. Forty of the 64 cases of bradycardia were associated with either resting hypotension or orthostatic hypotension. Only 1 case of syncope was observed in the patient trials. The sponsor argues that this set of findings is consistent with what is known as neurally mediated reflex bradycardia (NMRB), an abnormal reflex that they suggest occurs in 5-10% of the population. Presumably the reflex is triggered by decreases in blood pressure and venous return, and the α_1 antagonism of olanzapine would be expected to facilitate this reflex. They further suggest that normal volunteers would be more likely than agitated patients to experience this reflex, since their heart rates would be lower, they would not have adapted to the α_1 antagonism of antipsychotics, and they might be expected to have higher baseline vagal tone. NMRB is viewed as a relatively benign and self-limited event. The sponsor has accumulated much higher dose animal data that they argue does not support any direct effect of olanzapine on the sinus node. One might expect that older subjects might be more susceptible to a drug that has a direct effect on the sinus node, and such an effect was not seen in this development program. This phenomenon was not observed in any of the patients, including very elderly patients [redacted]

It should be noted that we had obtained a consult from HFD-110 regarding the cases of sinus pause, and received the advice that the drug not be approved until the sponsor is able to explain the effects of olanzapine on the heart. This issue received extensive discussion at the 2-14-01 PDAC meeting, including discussion by both the sponsor's cardiology experts and 2 cardiologists that we had invited as FDA consultants: Jean Barbey, M.D. and Edward Pritchett, M.D. There was virtually unanimous agreement among all experts that the finding can be explained on the basis of the abnormal reflex, did not represent a direct effect on the sinus node, and did not represent a likely risk for most agitated patients. On the other hand, there was also acknowledgment that this event, while self-correcting, is not entirely benign, and that the risk is unknown and might be increased in non-psychiatric patients who might receive this treatment if they presented in a state of agitation. Thus, there was general agreement that the event needs prominent labeling and advice that patients who experience early signs of hypotension and/or bradycardia should remain recumbent.

5.2.4 Conclusions Regarding Safety of Olanzapine IM

Overall, olanzapine IM appeared to be reasonably well tolerated at the doses studied. The potential for hypotension associated with bradycardia and possibly sinus pause, especially in patients not accustomed to taking antipsychotic drugs, will be described in the Precautions section of labeling. One clinical situation not studied in this development program that needs exploration is the use of olanzapine IM in patients already taking olanzapine or another antipsychotic on a regular basis. It would not be uncommon for such patients to need a dose of IM antipsychotic to control agitation,

and there is no experience to address the safety of such use. Labeling can mention this deficiency and the sponsor should be asked to address this question.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

A 2-day meeting of the PDAC was held February 14-15, 2001, with two goals: (1) to discuss generally approaches to developing intramuscular formulations of antipsychotic drugs for treating agitation, and (2) to specifically discuss two applications for such products. Both the general discussion and the specific discussion of the olanzapine application occurred on 2-14-01.

6.1 Background Information for General Discussion

As part of the background information for the general discussion, the committee was provided with an overview of different possible approaches to developing IM antipsychotic products. One approach to gaining approval for parenteral formulations of these newer agents would be to rely on pharmacokinetic (PK) studies characterizing the PK profile for these parenteral formulations, along with sufficient safety data to provide reassurance of the safety of these formulations. The problem with this approach, from FDA's perspective, is that parenteral formulations are almost certainly not going to be bioequivalent with the immediate release formulations, i.e., equivalent regarding both rate and extent of absorption. Thus, relying on this approach would necessitate assuming that either rate or extent of absorption is not pertinent to efficacy, and this is not an assumption the agency has been willing to make for other formulations. For example, sustained release formulations have been proposed for a number of pyschotropic products, and at the current time, the requirements for approval of these formulations include a demonstration of efficacy based on at least one adequate and well-controlled clinical trial. It should be noted that, at the time the parenteral formulations of the older antipsychotics were approved, there was not a requirement for efficacy data to support such approvals.

Thus, as we have been approached by sponsors of more recently approved antipsychotic drug products seeking to develop parenteral formulations for their products, we have had to confront the issue of how best to develop these formulations. In designing a clinical program, the first question to address is what clinical entity to target in the program. Depending on how this question is answered, two alternative approaches for developing parenteral formulations have emerged.

One approach to targeting a clinical entity is to take the view that the clinical entity being treated with the parenteral formulation is the identical entity for which the antipsycotic drug product has an approved indication, i.e., schizophrenia. In fact, this is consistent with the view of many clinicians who consider the use of parenteral antipsychotic drugs as the only practical way to initiate treatment for some acutely exacerbated schizophrenic patients. Thus, they view the use of an IM antipsychotic agent as the initiation of the treatment of a schizophrenic episode, with the understanding that a switch to oral immediate release medication will occur very quickly. Furthermore, it is understood

that the antipsychotic effect will most likely not be achieved until well after the switch to oral medication is made.

A clinical trial to demonstrate the effectiveness of a strategy of initiating treatment with an IM formulation and then rapidly switching to oral mediation could be done and would simply be a slight modification of a typical short-term antipsychotic trial. The modification would be that, rather than getting oral medication from day 1, patients would get IM medication for some fixed time period, e.g., the first 2 days, and would then be switched to oral medication. Assessments of antipsychotic effect would still focus on the later time points in the trial, since the expected time frame for antipsychotic response would not be changed. However, this does raise the interesting question of whether or not initiation of treatment with IM medication would hasten the antipsychotic response. This question could also be studied, but would involve a more complex design.

An alternative view is that the use of IM antipsychotic medication is not really intended to treat the psychosis per se, but rather, is intended to have a more general calming effect, related to properties of the drug other than its specific antipsychotic effect. The clinical target in this case might be considered to be the "agitation" that is often observed in exacerbated schizophrenic patients. This approach to gaining approval of IM formulations of these products has the advantage of focusing on a clinical target for which a very rapid response could be expected and, thus, an effect would be fairly easy to demonstrate. This approach is also appealing from the standpoint of what the drugs may actually be used for, i.e., initial rapid control of patients, rather than a longer-term antipsychotic effect.

The question then becomes, "What is agitation?" Dorland's Medical Dictionary defines "agitation" as "exceeding restlessness associated with mental distress." It defines "agitated" as "marked by restlessness and increased activity intermingled with anxiety, fear, and tension." DSM-IV defines "psychomotor agitation" as "Excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious and consists of such behavior as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still." These are fairly general definitions that might apply to patients with very different underlying diagnoses. They are consistent with a definition that appeared in a recent paper in the psychiatric literature, i.e., "motor restlessness such as fidgeting and pacing associated with an inner tension..."(Phenomenology and Treatment of Agitation, Alan Schatzberg, J Clin Psychiat, Monograph on "Phenomenology and Treatment of Aggression Across Disease States," Vol 17, Monograph 2, 1999, pp.12-14).

One distinction worth noting is between what might be considered acute agitation and chronic agitation. Acute agitation might be considered the restlessness associated with an acute illness, e.g., exacerbation of schizophrenia. Chronic agitation might be considered a more chronic pattern of behavior associated with a chronic disease state, e.g., Alzheimer's disease. In fact, there was considerable discussion of the concept of "agitation" at a March 9, 2000 meeting of the PDAC focused on behavioral and psychological symptoms associated with various dementias. The chronic agitation associated with an illness like Alzheimer's disease is generally viewed as including a much broader set of behaviors than usually considered to comprise acute agitation.

At the March 9, 2000 meeting of the PDAC, there was no general consensus regarding agitation, either how to define it, or how to think of it in terms of it being either a disease specific entity or a nonspecific symptom. Some members and guests considered agitation of Alzheimer's disease a syndrome distinct to that illness, while others viewed it as an entity that might be considered nonspecific and occurring in a similar form in association with different disease states. In either case, there were widely varying views on how to define the entity. Thus, no agreement was reached at the March 9th meeting on whether or not and how to develop drug treatments for "agitation" in association with Alzheimer's disease.

The committee was reminded that two types of clinical entities are considered appropriate targets for new claims. Specific diseases or syndromes are the usual focus of a drug claim, e.g., congestive heart failure or rheumatoid arthritis. However, nonspecific signs or symptoms not unique to a single disease or syndrome, e.g., pain or fever, may also be the focus for a claim. Antipyretics and analgesics are approved for these nonspecific symptoms on the basis of studies involving different "models" for each such symptom, e.g., headache pain and dental pain as different pain models. The basis for accepting this nonspecific approach to indications is the view that, while the disease states leading to these nonspecific symptoms may differ markedly, the sympoms themselves are: (1) universally defined, in whatever disease context they occur; (2) readily measured, using commonly accepted assessment methods; (3) ideally have a well understood pathophysiologic basis; (4) and respond similarly to drug treatment for that symptom, quite apart from the diverse disease states that may lead to the nonspecific symptom. Of course, we do not understand any psychiatric illnesses at a pathophysiological level, and this would not be an absolute requirement for a nonspecific symptom; however, this is a reasonable goal to strive for in this instance, since an understanding of mechanism may help to establish such a symptom as really independent of the underlying specific disease state in which it happens to occur. Critical to this approach to gaining a new claim is the concept of pseudospecificity. In this context, since the essence of this type of claim is that the symptom is nonspecific, i.e., to any one disease, it is essential that efficacy be demonstrated in several different disease models. To attempt to obtain a claim for a nonspecific symptom in a single disease model would, by definition, be pseudospecific, since such a claim would give the impression that the symptom is specific to that disease.

In considering new claims, whether for a specific disease/syndrome or a nonspecific sign/symptom, the committee was reminded that similar criteria are used by FDA to evaluate the proposed clinical entity as an appropriate target for a new claim. The proposed clinical entity must be accepted in the relevant clinical/academic community, it must be operationally definable, and it must identify a reasonably homogeneous patient group. The latter two criteria are important to ensure the validity of the clinical trials supporting the claim and to make it possible to inform clinicians in labeling about the use of the proposed treatment.

6.2 Committee Discussion of Specific Questions

Following a presentation of background information, the committee was asked to discuss several questions pertinent to developing parenteral formulations of antipsychotic drugs for IM use.

Following are the questions and a summary of my impression of committee member's views on these issues:

Question: Are effectiveness data needed to support the approval of a parenteral formulation of an antipsychotic for IM use, or is it sufficient to rely on the efficacy data available for the orally administered immediate release formulation?

Response: The committee seemed to be unanimous in the view that efficacy data would be needed to support the approval of any such products.

Question: If effectiveness data are needed, what should be the clinical target that is the focus of the required effectiveness studies?

-In particular, should the focus be on schizophrenia, the approved indication for the oral formulation, or on some other clinical findings present during an acute episode of illness that are deemed to require the use of IM medication?

Response: There was essentially no support among committee members for focusing effectiveness trials for IM antipsychotic products on schizophrenia per se.

Question: If schizophrenia is considered to be the appropriate clinical target for the development of IM formulations of antipsychotic drug products, what study designs would be optimal to support a claim for these products?

Response: As noted, there was agreement that schizophrenia is not an appropriate target for IM antipsychotic product development programs.

Question: Is "agitation" an acceptable clinical target for the development of IM antipsychotic drug products?

-If so, how should "agitation" be defined?
-What outcome measures are optimal for the assessment of "agitation?"
-What study designs are optimal for the study of "agitation?"

Response: There seemed to be general agreement that agitation, however that might be defined, was the appropriate target for these programs.
-There was a fair amount of discussion about what characterizes "agitation," however, no attempt was made to try to define this in a standard way. There was an attempt to try to identify features of agitation that might appropriately lead to the use of IM antipsychotic products, e.g., "threatening behavior," "escalating behavior," "urgently distressing behavior," "self-exhausting behavior that threatened the well-being of a patient," or "behavior that impeded a needed diagnostic assessment of a patient." There seemed to a general view that clinicians "know agitation when they see it."
-There was some discussion of outcome measures, but no consensus on which are optimal.

-There seemed to be general agreement that very short-term trials, i.e., even single dose as was the case for the two development programs to be discussed in this meeting, were appropriate, given the short-term nature of IM treatment.

Question: Is it worthwhile distinguishing between what might be considered "acute agitation" and "chronic agitation?"

Response: There did seem to be agreement that the type of chronic, persistent agitation that might be seen in a patient with dementia can reasonably be distinguished from the acute agitation that occurs in patients with exacerbating illnesses and requires intervention with IM medication.

Question: Is "agitation" a phenomenon that is specific to different disease states or can this be considered a nonspecific symptom that occurs in identical form in association with different disease states?

-If "agitation" can be considered a nonspecific symptom, is it necessary to study it in different disease models in order to gain a claim?
-If so, in what disease models should it be studied?

Response: There was extensive discussion of this issue, and ultimately committee members were asked to individually respond to this question. There was essentially unanimous agreement that these products should not be granted broad claims for "agitation," but rather, that the claims should be tied fairly closely to specific diagnoses. There were several reasons supporting this view, one being a general agreement that we do not yet understand the pathophysiology of agitation. There was particular concern about agitation in psychiatric and non-psychiatric settings, and about the different types of agitation not studied in these programs. These concerns were partly based on possible differences in efficacy, but also on different safety profiles, e.g., the use of these products in patients naive to antipsychotic products. In any case, there was broad agreement that we are not yet ready to consider agitation a nonspecific symptom in the same sense that we consider pain and fever to be nonspecific symptoms.

6.3 Discussion of Olanzapine IM Application

The discussion of this application occurred following the general discussion on the first day of the meeting. After discussion of the application, the committee voted unanimously (9:0) that the efficacy of olanzapine IM in the treatment of agitation associated with the three diagnostic groupings studied had been demonstrated. There was also a unanimous opinion regarding the safety of IM olanzapine.

Considerable time was spent during the olanzapine IM discussion essentially continuing the general discussion about what clinical entity to target for an agitation claim, and these issues are summarized under 6.2. The one issue that received particular attention during the committee discussions of the

olanzapine IM application was the concern about the findings of hypotension, bradycardia, and in normal volunteers, brief sinus pause. I have summarized the discussion of these issues under 5.2.3 (safety).

7.0 LABELING

There are several labeling issues that merit comment:

-Description:

-Description of Clinical Trials: In keeping with the more narrow indication, I have proposed a description of the clinical trials for schizophrenia and related disorder that mentions only the patients with schizophrenia. I have also made it clear that agitation should be viewed in the context of specific diseases, and not as a nonspecific phenomenon.

-Indication: I have again made it clear that agitation should be viewed in the context of specific diseases, and not as a nonspecific phenomenon.

-Precautions: I have modified the statement regarding hypotension, bradycardia, and syncope to include information about the finding of sinus pause in normal volunteers, and to suggest the possibility of somewhat greater risk for this sequence of events in drug naive patients.

-Dosage and Administration: I have again made it clear in this section that agitation should be viewed in the context of specific diseases, and not as a nonspecific phenomenon. I have also modified the dosing recommendations in keeping with my interpretation of the data.

8.0 FOREIGN REGULATORY ACTIONS

To my knowledge, olanzapine IM is not marketed anywhere at this time.

9.0 APPROVABLE LETTER

A draft approvable action letter is included in the package, along with a recommendation for additional work to explore for interactions with olanzapine IM in patients already taking olanzapine or another antipsychotic drug on a regular basis.

10.0 CONCLUSIONS AND RECOMMENDATIONS

In my view, Lilly has submitted sufficient clinical data to support the conclusion that olanzapine IM is approvable for the treatment of acute agitation in patients with schizophrenia, bipolar mania, [redacted] Consequently, assuming the CMC concerns can be satisfactorily resolved, I recommend that we issue the attached approvable letter, for the vial intended to be reconstituted with sterile water, with our proposed labeling.

cc:
Orig NDA 21-253 ([redacted])
HFD-120
HFD-120/TLaughren/RKatz/GDubitsky/SHardeman
DOC: MEMZYPIM.AE1

M E M O R A N D U M

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

DATE: March 18, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approval action for Zyprexa — (olanzapine IM) for the acute treatment of agitation in schizophrenia and mania

TO: File NDA 21-253
[**Note:** This overview should be filed with the 3-27-03 response to our 3-29-01 approvable letter.]

Olanzapine IM is an intramuscular formulation of the antipsychotic drug olanzapine that is being proposed for use in the "rapid control of agitation." Oral olanzapine was approved for the treatment of schizophrenia on 9-30-96 (NDA 20-592) and for mania on 3-17-00 (NDA 20-592/S-006). Zyprexa Zydis, an orally disintegrating formulation of olanzapine, was approved on 4-6-00 (NDA 21-086).

At the present time, there is one other drug approved for the treatment of agitation, i.e., Geodon IM for agitation in schizophrenia. We issued an approvable letter for Zyprexa — for the acute treatment of agitation in schizophrenia, mania, ——— on 3-29-01. However, an approval action was noted to be contingent upon the sponsor's response to certain CMC deficiencies, and we also asked for several additional pieces of information:
-Foreign regulatory update
-World literature update
-Agreement on final labeling.

The sponsor responded to the latter 3 issues in a 4-19-01 amendment. This was reviewed by Dr. Dubitsky, and we reached agreement with the sponsor on labeling by 8-27-01. However, responding to the CMC deficiencies has taken almost 3 years. In anticipation of getting the CMC issues resolved, Lilly amended the application with an update on 3-27-03, and this was followed by a labeling update on 2-13-04. Dr. Dubitsky has reviewed this additional information. Additional reviews were conducted by CMC and OCPB.

Foreign Regulatory Update

-Zyprexa — is approved in the EU, 31 other countries, and is under review in another 18 countries.

Foreign Labeling

-Dr. Dubitsky reviewed labeling for the EU, Australia, and Canada. One difference between these labels and the proposed US label is the maximum daily dose, which is 30 mg in the US label, but 20 mg in the other labels. This issue was already addressed in Dr. Dubitsky's previous review; he feels that the 30 mg total daily dose is supported, and I agree. The other issue was a contraindication for olanzapine in narrow angle glaucoma in other labels, while this is proposed only as a precaution in the US label. This is a theoretical risk, and is addressed with precautionary language for similar products in US labels. Dr. Dubitsky feels this is acceptable, and I agree.

World Literature Update

-Lilly has updated its literature review for olanzapine for the period of 4-10-01 to 3-10-03, and has not identified any new safety information that would impact on labeling or the approvability of this product.

New Biopharm Studies

-Since the original submission, Lilly had conducted 3 similar pk/pd studies in Japan involving single 1, 2, and 4 mg doses of Zyprexa — in healthy subjects of different ethnic background (Caucasian, Chinese, and Japanese). The results of these studies were submitted in the 3-27-03 amendment, and Lilly did not feel that these results merited any mention in labeling. However, Dr. Kavanagh reviewed these data and concluded that these studies revealed a lesser effect of ethnicity on exposure than had been suggested by earlier cross-study comparisons, but also revealed an apparent difference in pharmacodynamic effects for different ethnic groups, based on results of DSST assessments. OCPB had recommended that we add information to labeling noting a greater effect of Zyprexa — on DSST in Chinese and Japanese subjects compared to Caucasian subjects, but an absence of differences in exposure based on within-study comparisons. The sponsor objected to the inclusion in labeling of the DSST data, since they are of unclear relevance to the use of this product in agitated schizophrenic patients, and I agree. However, we have added the new information on exposure. Dr. Dubitsky reviewed the safety data for these trials and did not discover any findings that would impact on an approval action.

CMC

-The manufacturing deficiencies have been adequately addressed as of 11-3-03.

Labeling

—]

— We have reached agreement on final labeling for — as of 3-18-04.

Conclusions and Recommendations

-In my view, Lilly has submitted sufficient data to support the conclusion that olanzapine IM is safe and effective for the treatment of acute agitation in patients with schizophrenia and bipolar mania, and I recommend that we issue an approval letter, with our mutually agreed upon final labeling.

cc:
Orig NDA 21-253 (Zyprexa IM)
HFD-120
HFD-120/TLaughren/RKatz/GDubitsky/SHardeman
DOC: MEMO ZYPREXA AP1.doc

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

/s/

Thomas Laughren
3/18/04 12:21:39 PM
MEDICAL OFFICER