

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-253

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Reviewer Name: Lois M. Freed, Ph.D.

Division Name: Neuropharmacological Drug Products

HFD#120

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NDA number: 21-253

Submission date: 6/16/00

Information to sponsor: Y

Sponsor (or agent): Eli Lilly and Co.

Lilly Corporate Center

Indianapolis, IN 46285

Manufacturer for drug substance: Eli Lilly and Co., Indianapolis, IN

Drug: olanzapine for injection

Code Name: LY170053

Generic Name: olanzapine

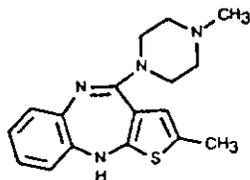
Trade Name: Zyprexa

Chemical Name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1.5]benzodiazepine

CAS Registry Number: n/s

Molecular Formula/ Molecular Weight: 312.44

Structure:



Relevant INDs/NDAs/DMFs: IND 55,342 (Zyprexa), NDA 20-592 (Zyprexa tablets for psychotic disorders), NDA 20-592(S006) (Zyprexa for acute manic episodes associated with bipolar I disorder), NDA 21-086 (Zyprexa ZYDIS for psychotic disorders and acute manic episodes associated with bipolar I disorder).

Drug Class: selective monoaminergic antagonist

Indication: agitation

Clinical formulation: 10 mg of lyophilized powder to be reconstituted with sterile water for injection or sponsor's supplied Olanzapine Diluent (0.33% NaCl solution)

Route of administration: i.m.

Studies reviewed within this submission: none

Studies previously reviewed:

PK/ADME (Beagle dog, cynomolgus monkey)

1-mo i.m. subchronic toxicity study (with TK) in Beagle dog

in vitro muscle irritation of i.m. formulation of olanzapine and haloperidol

acute i.m. irritation study in rabbit

Studies not reviewed within this submission: none.

PHARMACOLOGY

The sponsor cross-referenced NDA 20-592 for pharmacology data.

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PHARMACOKINETICS/TOXICOKINETICS

The sponsor cross-referenced NDA 20-592 for PK/ADME data. In addition, the sponsor submitted a summary of additional PK/ADME data in Beagle dog and cynomolgus monkey to IND 55,342 [cf. Review and Evaluation of Pharmacology and Toxicology Data, Lois M. Freed, Ph.D., 4/6/98]. No new data were submitted to the NDA for Zyprexa —

The PK data in female dog (3/grp) and female cynomolgus monkey (3/grp) are summarized in the following table:

SPECIES	DOSE (mg/kg)	OLANZAPINE				TOTAL PLASMA RADIOACTIVITY			
		T _{max} (hr)	C _{max} (ng/mL)	AUC (ng•hr/mL)	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng-eq/mL)	AUC (ng-eq•hr/mL)	t _{1/2} (hr)
Beagle dog	5 i.m.	0.7	744 ± 353	3818 ± 832	10.7 ± 1.47	0.8-1	1156 ± 422	19493 ± 7044	7.4, 16.3, 73.5*
	5 p.o.	3.25	172	1923	9.2	1	949	13405	30
	5 i.v.	0.08	871 ± 139	2633	6	0.39 ± 0.31	1145 ± 113	18813	32
cynomolgus monkey	0.1 i.m.	0.17 ± 0	176.7 ± 70.5	132.8 ± 34.9	2.16 ± 0.30				
	0.3 i.m.	0.17 ± 0	461.7 ± 185.2	216.7 ± 41.3	2.58 ± 0.40				
	1.0 i.m.	0.39 ± 0.11	409.4 ± 53.7	542.9 ± 111.0	2.45 ± 0.28				
	1.0 p.o.	1.67 ± 0.33	40.4 ± 7.1	168.1 ± 36.6	2.46 ± 0.27				
	2.0 p.o.	2.00 ± 0	67.0 ± 12.7	346 ± 80.3	2.65 ± 0.34				
	4.0 p.o.	3.0 ± 1.53	154.5 ± 23.1	1192.2	3.06				

*α, β, γ, respectively

Following i.m. dosing in dog, radioactivity was extensively distributed into cellular elements [AUC = 34,769 ± 12,578 and 19,493 ± 7044 ng-eq•hr/mL for whole blood and plasma, respectively]. With p.o. dosing, whole blood and plasma levels were fairly similar. Following i.m. dosing, total radioactivity was eliminated to a similar extent in urine and feces [46.1 ± 16.7 and 42.2 ± 7.12%, respectively]. Following p.o. dosing, elimination was primarily via the feces [38.4 ± 2.57 and 45.6 ± 5.41% in urine and feces, respectively]. The parent compound accounted for 20% of total plasma radioactivity following i.m. dosing, but only 14% of total radioactivity after p.o. and i.v. dosing. These data indicate extensive metabolism of olanzapine regardless of route.

In both dog and monkey, T_{max} was more rapid and C_{max} and AUC were greater following i.m. dosing as compared to p.o. dosing at the same dose level.

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TOXICOLOGY

The sponsor cross-referenced NDA 20-592 for toxicity data. In addition, the sponsor submitted a 1-mo i.m. toxicity study in Beagle dog, *in vitro* muscle irritation study, and an acute i.m. irritation study in rabbit to IND 55, 342. These studies have been previously reviewed [Review and Evaluation of Pharmacology and Toxicology Data, Lois M. Freed, Ph.D., 4/6/98]. No new data were submitted to the NDA for Zyprexa —

CARCINOGENICITY

The sponsor cross-referenced NDA 20-592 for carcinogenicity data. Due to the short duration of dosing, no carcinogenicity testing is required for the i.m. formulation.

REPRODUCTIVE TOXICOLOGY

The sponsor cross-referenced NDA 20-592 for reproductive toxicity data.

GENETIC TOXICOLOGY

The sponsor cross-referenced NDA 20-592 for genotoxicity data.

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OVERALL SUMMARY AND EVALUATION

In the original IND submission for olanzapine i.m. (IND 55,342), the sponsor provided a summary of the PK/ADME data (including results of two i.m. studies) and study reports for a 1-mo i.m. toxicity study in Beagle dog and two special toxicity studies to assess local irritation [*in vitro* rat muscle irritation, acute i.m. irritation in rabbit]. No i.m. studies were conducted in rat. At the pre-NDA meeting (1/6/00), the need for a 1-mo i.m. study in rat was discussed with the sponsor. The sponsor was informed that either a 1-mo study in rat should be conducted or justification should be provided that such a study would not be necessary. Specifically, the sponsor was asked to submit a table summarizing PK/TK data in rat and human so that it could be determined whether or not the oral toxicity studies in rat provided sufficient coverage of the expected systemic exposure in humans with the i.m. formulation. The sponsor submitted the requested information to IND 55,342 in Amendment N-035. These data and the toxicity study reports have been previously reviewed [cf. Review and Evaluation of Pharmacology and Toxicology Data (4/6/98), Pharmacology/Toxicology Memorandum to IND 55,342 (3/22/00)]. No additional data were submitted to the NDA.

PK/ADME

A comparison of PK/ADME following i.m. and p.o. dosing was conducted in Beagle dog and cynomolgus monkey, but not in rat. The monkey was not used for toxicological evaluation of olanzapine.

In the dog, the absolute i.m. bioavailability of olanzapine was >100% (based on the AUC values provided) and absorption was complete. The absolute oral bioavailability of olanzapine was 73%. Peak plasma levels of olanzapine were reached more rapidly following i.m. than following p.o. [0.7 and 3.25 hrs respectively]. The $t_{1/2}$ for olanzapine was \approx 10 hrs after i.m. and p.o. dosing. Olanzapine was extensively metabolized when administered by p.o., i.m., and i.v. routes, with the parent compound accounting for \approx 14-20% of total plasma radioactivity via the three routes.

The metabolic profile after i.m. and p.o. dosing was compared only in humans. The sponsor stated that the metabolic profile was qualitatively similar in humans after p.o. and i.m. dosing. In addition, the C_{max} and AUC estimates at the maximum recommended clinical p.o. and i.m. doses were stated to be similar. [This is discussed further in the Toxicology section.]

Toxicology

Rat: in Amendment N-035, the sponsor demonstrated that the plasma levels of olanzapine achieved in a 6-mo oral special toxicity study in rat were up to 25 times higher than the "adjusted C_{max} and $AUC_{(0-\infty)}$ " in humans (Study FID-EW-LOAR; $C_{max} = 90$ ng/mL, $AUC = 1314$ ng•hr/mL). The TK data from the special toxicity study (conducted to document the extent of systemic exposure) are summarized in the table below (male and female data were pooled).

TIME	DOSE (mg/kg)	C _{max} (ng/mL)	AUC (ng•hr/mL)
Day 0	1	13.4	<LLOQ
	4	73.6	247.2
	8	297.7	1439.2
	16	1123.0	5655.5
Month 2	1	10.7	52.2
	4	173.4	851.2
	8	575.8	5288.7
	16	1754.2	21191.2
Month 6	1	23.6	222.3
	4	241.4	1282.5
	8	801.6	6578.8
	16	2076.3	29109.3

In the definitive 6-mo rat study (doses: 0, 0.25, 1, 4, and 16 mg/kg), 1 mg/kg was identified as a NOEL [cf. Pharmacology Review NDA #20592, Aisar H. Atrakchi, Ph.D., 4/29/96]. Drug-related findings at the higher doses included sedation (hypoactivity), decreased body wt/food consumption (relative to controls), and microscopic findings in adrenal gland, mammary gland, ovaries, and vagina. No deaths were observed at any dose.

In the NDA, the sponsor submitted results of clinical trial, Study F1D-MC-HGJA, conducted in 20 schizophrenic patients given olanzapine i.m. at 3 x 10 mg (i.e., 30 mg/day). The 2nd dose was administered 2-4 hrs after the initial dose; the 3rd dose was administered ≥4 hrs following the 2nd dose. These data were summarized in the following sponsor's table:

Table HGJA.11.2. Pharmacokinetic Parameter Mean and Range Values for Individual Doses F1D-MC-HGJA

Parameter	Dose 1	Dose 2	Dose 3
C _{max} (ng/mL)	27.1	29.5	41.5
AUC ₀₋₄ (ng•hr/mL)	45.2	79.5	115

Abbreviations: C_{max} = maximum plasma concentration, AUC₀₋₄ = Area Under the Curve for the 4 hours following the injection.

Based on these data (and those from the special 6-mo rat study), the plasma exposure achieved rats in the definitive 6-mo study was markedly higher than that achieved in humans at the maximum recommended human dose (i.e., 3 x 10 mg or 30 mg/day). The mean C_{max} in rats at the HD was 50 times the mean C_{max} in humans and ≈20 times higher than the highest C_{max} detected in humans. The mean AUC in rats at the HD was ≈250 times the mean AUC in humans and ≈170 times the highest AUC detected in humans. [At the NOEL in rats, the C_{max} and AUC were 0.6 and 1.9 times, respectively, the mean C_{max} and AUC and 0.2 and 1.3 times the highest C_{max} and AUC in humans at the maximum recommended clinical dose.] The T_{max} in humans, following a 10-mg i.m. dose (Study F1D-EW-LOAR), was reported to be 0.47 (0.17-2.0) and 0.6 (0.2-2.0) hrs on Day 1 and Day 3, respectively. In rats, the T_{max} following multiple oral doses was ≈0.5-8 hrs. Therefore, although T_{max} tended to be later in rats, there was some overlap between the values in rat and those in humans following p.o. and i.m. dosing, respectively.

The sponsor conducted a clinical trial (Study F1D-EW-LOAC) comparing the metabolic fate of olanzapine in urine and plasma when the drug was administered via the i.m. and oral routes. According to the review of these data [cf. Office of Clinical Pharmacology and Biopharmaceutics Review, Hong Zhao, Ph.D.], the urinary metabolic profile was qualitatively similar after oral and i.m. dosing. No data were provided for plasma. However, according to Dr. Zhao, the metabolic profile would be expected to be similar in plasma after p.o. and i.m. dosing, considering the urinary data.

Based on these data, the sponsor documented (1) adequate systemic exposure to olanzapine in rats in the oral database and (2) that no new metabolites are formed in humans via i.m. dosing (compared to p.o.), thereby eliminating the need for additional toxicity testing in rat.

Dog: the following is a summary of the 1-mo i.m. toxicity study from the review of IND 55, 342:

"In the 1-mo i.m. toxicity study in dog (3/sex/grp), olanzapine was administered daily at doses of 0, 0.5, 1.25, and 2.5 mg/kg. Observations consisted of the following: clinical signs, physical/neurological examination, body wt, food consumption, ophthalmology, ECG (prior to start of dosing, on Days 1, 8, and 27 at 0 and 1 hr postdosing), hematology, clinical chemistry, urinalysis, TK, and terminal studies [gross pathology, organ/tissue wts, histopathology (all animals)].

There were no unscheduled deaths. Drug-related clinical signs, consisting of 'miosis, hypoactivity, ataxia, and head pressing', were noted at all doses in males and females. At higher doses, tremors, squinting eyes, and relaxed nictitating membrane were also noted. Lethargy was observed only at the HD, but in all HD animals. One HDF exhibited a clonic convulsion (1 min) on Day 1, approximately 20 min postdosing. Following the convulsion, the HDF appeared disoriented and ataxic. Pupils were mitotic and menace response was absent..." The plasma C_{max} for olanzapine for this animal (measured on Day 0) was 175 ng/mL; this was somewhat lower than the mean value (289 ng/mL) in HDF on Day 0. It should be noted that, although similar or higher plasma levels were achieved in the 1-yr oral toxicity studies in Beagle dogs, there were no reports of convulsions in these studies.

Body weight was not significantly affected; however, body wts did tend to be higher in dosed females as compared to CF (4-7%). Food consumption was not quantitated, but, according to the sponsor, there were no clear drug-related effects upon visual inspection. The sponsor reported no drug-related effects on ECG parameters; however, heart rate was increased at all doses in both males and females. There were no apparent drug-related effects on ophthalmology, hematology, or urinalysis parameters. Of note, however, was a slight decrease in wbc count in 2/3 HDM (24-34% compared to baseline). On clinical chemistry, the following were noted: (1) decreases in serum P_i in HDM (5%), MDF and HDF (15-16%), (2) decreases in serum cholesterol and TG in HDM (16-50%), and (2) increases in serum Fe in HD animals (70-100%). TK data were collected on Days 0 and 29, and verified systemic exposure. A comparison of the maximum plasma levels of olanzapine achieved in this study with those achieved at the HD in the 6-mo oral toxicity study in rats (16 mg/kg) and in the 1-yr oral toxicity studies in dog (10 mg/kg) is provided in the following table (data: means, means \pm SEM):

STUDY	SPECIES	C _{max} (ng/mL)	AUC (ng•hr/mL)
6-mo oral [*]	Fischer 344 rat	1123 ± 72 - 1754 ± 355	5,656-21,161
1-yr oral ^{**}	Beagle dog	235-286	2539-2864
1-yr oral ^{**}		325-413	3895-4646
1-mo i.m. [†]		289 ± 23 - 356 ± 368	933 ± 177 - 1540 ± 165

^{*}data were collected on Day 0-Month 2. (There was accumulation with multiple dosing.)

^{**}data were collected on Day 0-Month 3. [†]data were collected on Day 0-Day 29.

No clear drug-related effects were detected in terminal studies. Adrenal wt (absolute, relative) was increased in MDM and HDM (19-24%); however, there were no histopathological correlates. Injection site changes (inflammation, regeneration) were evident, but were fairly similar in control and drug-treated grps.

No NOEL was established due to the clinical signs and increases in heart rate observed at all doses; however, the LD could be considered a NOAEL. No target organ for toxicity was determined. Plasma levels of olanzapine associated with the LD were as follows: 55-64 ng/mL [C_{max}] and 144-276 ng•hr/mL [AUC_(0-∞)].”

Comparisons of plasma exposure to olanzapine in dog in the 1-mo study and in human are as follows:

- (a) the mean C_{max} in dog at the NOAEL (0.5 mg/kg) was 1.3 and 0.6 times the mean and highest C_{max}, respectively, in humans at the maximum recommended dose. The mean AUC in dog at the NOAEL was 1.6 and 1.1 times the mean and highest AUC, respectively, in humans at the maximum recommended dose.
- (b) the mean C_{max} in dog at the HD (2.5 mg/kg) was 8.5 and 3.8 times the mean and highest C_{max}, respectively, in humans at the maximum recommended dose. The mean AUC in dog at the HD was 12 and 8 times the mean and highest AUC, respectively, in humans at the maximum recommended dose.
- (c) the C_{max} in the one HDF that exhibited convulsions was 4 and 1.8 times the mean and highest C_{max}, respectively, in humans at the maximum recommended dose.

Special toxicity studies: the results of the two irritation studies [acute i.m. irritation study in rabbits, *in vitro* L6 skeletal muscle irritation model] conducted on olanzapine were summarized in the original review of IND 55,342 as follows:

“In both studies, CPK was used to quantitate muscle irritation. In the acute study in rabbits, serum CPK was elevated in all grps, but the increase was greatest in males at 8.4 mg/mL and in females at 4 and 8.4 mg/mL. Histopathology findings at the injection site consisted of degeneration/regeneration, hemorrhage, inflammation, mineralization, and necrosis. Of these, mineralization and necrosis were detected only in treated animals. In males, only mild necrosis was noted at the LD (1/4). In females, degeneration/regeneration, inflammation, and mineralization were observed at all doses; necrosis was noted in only 1/4 HDF.

In the *in vitro* assay, olanzapine produced results consistent with slight irritation at the LC (1.7 mg/mL) and moderate irritation at concentrations of 4.2-8.4 mg/mL.”

Conclusions: the nonclinical data are adequate to support approval. The sponsor documented that plasma exposure to the parent compound in humans at the maximum recommended clinical i.m. dose (i.e., 3 x 10 mg or 30 mg/day) did not exceed to any notable extent that at the maximum recommended clinical p.o. dose. In addition, the metabolic profile of olanzapine in humans following i.m. and p.o. dosing were found to be similar. [Conclusions regarding the human data were based on the review by Dr. Zhao [Office of Clinical Pharmacology and Biopharmaceutics Review.] The one major difference remaining between the i.m. and p.o. routes (in terms of kinetics) is the more rapid increase in plasma drug levels following i.m. dosing. In rat, the range of T_{max} values obtained following p.o. dosing overlapped, albeit to a limited extent, the range of T_{max} values in humans following i.m. dosing. In dog, a comparison of the results from the 1-yr p.o. and 1-mo i.m. studies did not indicate significantly different patterns of toxicity with the two routes. The only exception was convulsions, which was not noted in the oral toxicity studies study [cf. Pharmacology Review NDA #20592, Aisar H. Atrakchi, Ph.D., 4/29/96], but was observed in one HD female in the i.m. [According to Gregory Dubitsky, M.D., medical officer, there was no incidence of convulsions in the i.m. clinical trials of olanzapine.]

The reproductive toxicity and genotoxicity studies included by cross-referenced to NDA 20-293 are adequate to support the olanzapine i.m. Carcinogenicity studies are not necessary due to the limited duration of dosing for the i.m. formulation.

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LABELING

The following sections of labeling should be revised as follows:

Carcinogenesis, Mutagenesis, Impairment of Fertility--

Carcinogenesis--Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m² basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m² basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥ 2 mg/kg/day and in female rats dosed at ≥ 4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (*see Hyperprolactinemia under PRECAUTIONS, General*).

Mutagenesis--No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility--In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m² basis). Diestrus was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² basis); therefore olanzapine may produce a delay in ovulation.

Pregnancy--

Pregnancy Category C--In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed

at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m² basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m² basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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RECOMMENDATIONS

From a pharmacology/toxicology standpoint, there is no objection to the approval of Zyprexa®
— for rapid control of agitation.

[Suggested labeling changes are given in "Labeling" section of review (pgs 10-11).]

Lois M. Freed, Ph.D.