CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-253

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NEW DRUG APPLICATION *SUPPLEMENT* *CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW*			
NDA:	21-253	**Drug:** **[Sponsor's Code / Generic / Brand]**	Olanzapine for Injection Zyprexa® Intramuscular
Code:	AZ – Major Amendment – Multiple Disciplines (Oct 31) BM – Minor Amendment-Medical (Mar 27) Amendment to Response to Approvable Letter of April 19, 2001		
Correspondence Date:	October 31, 2003 March 27, 2003	**Sponsor:**	Lilly Indianapolis, IN

1 EXECUTIVE SUMMARY

1.1 Contents of Submission

The present submission is an amendment to the sponsor's response to the approvable letter of April 19, 2001. A section of the present submission contains study reports for three clinical pharmacology studies, which were conducted as part of the development program for the Japanese NDA and which were not previously submitted to the US NDA. These studies are listed in Table 1.

Table 1 Clinical Pharmacology Studies Included in Present Submission

Study Code	Study Title
FID-JE-HGJM	A Single-Dose Study to Examine the Safety of Rapid Acting Intramuscular Olanzapine in Healthy Subjects
FID-FW-LOBI	A Single Dose Study to Assess the Pharmacokinetics and Pharmacodynamics of Rapid Acting Intramuscular Olanzapine in Asian and Caucasian Subjects
FID-JE-LOBJ	A Single Dose Study to Assess the Pharmacokinetics and Pharmacodynamics of Rapid Acting Intramuscular Olanzapine in Healthy Subjects

All three studies are of similar design and examine the pharmacokinetics and pharmacodynamics of olanzapine after a single IM dose to healthy male volunteers at doses of 1, 2, and 4 mg. The studies primarily differ with respect to the ethnicity of the subjects in each of the 3 studies with Caucasian and Chinese subjects examined in protocol LOBI and Japanese subjects examined in studies HGJM and LOBJ.

1.2 Sponsor's Conclusion:

According to the sponsor:

"Lilly has reviewed the updated information enclosed in this submission and concluded that it does not alter any of the previous conclusions regarding the safety and efficacy of Zyprexa IntraMuscular, nor warrant changes to the previously agreed upon Zyprexa IntraMusuclar labeling text (submitted 30 January 2002 in electronic format):"

The previously agreed to labeling comments with regard to race follow:

Race–[ ]

[ ]

Dosage modifications for race are, therefore, not recommended.

1.3 Reviewer's Conclusion:

Exposure to olanzapine as indicated by Cmax and AUC∞ is greater (~33%) in Japanese and Chinese subjects as compared with Caucasians. This is not nearly as great as previously reported, (i.e. 2x greater in Asians). However, the differences in Cmax and AUC in the present study disappear when corrected for body weight.

After IM olanzapine, the maximum response of the digit symbol substitution test, a surrogate marker for CNS effect, is similar in Japanese and Chinese subjects, however the response is much less in Caucasian subjects. This indicates that there is a different pharmacokinetic/pharmacodynamic relationship in Caucasians. However, it's not possible from these clinical pharmacology studies to tell whether this translates into differences in safety or efficacy by ethnicity.

1.4 Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA 21-253 BZ submitted March 27, 2003 and October 31, 2003, and makes the following recommendations:

- Changes in dosage and administration by ethnicity are not recommended at the present time.
- It is recommended that the clinical pharmacology section of the labeling describe the observed differences in the concentration effect relationship of olanzapine by ethnicity.

1.5 Comments to Medical Review Team

The medical review team is requested to evaluate if additional information should be submitted, additional studies should be performed, or additional safety or efficacy analyses by ethnicity are warranted to determine if there is a difference in safety or efficacy by ethnicity and if there is a need to recommend additional changes to labeling.

The medical review team is requested to evaluate if changes to the proposed labeling are needed at present and if additional studies or safety or efficacy analyses by ethnicity are warranted or not.

Possible changes to the labeling for consideration follow:

Additions to the current labeling proposal are indicated by the <u>underlined text</u>.

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

2 REVIEW

2.1 Pharmacokinetics

At each dose level Cmax and AUC vary by ethnicity with Asians having higher exposures than Caucasians. Among Asians Chinese generally have higher exposures than Japanese.

When exposures are normalized to dose and weight, Chinese subjects continue to have the higher exposures than Caucasians (115%), with Japanese subjects having slightly lower exposures than Caucasians (90%). However, the variability is so great that the differences are unlikely statistically significant (statistical analysis not performed). Most of the differences in exposure by ethnicity thus appear to be due to differences in weight. Thus Caucasians have the lowest exposures at each dose level primarily because they weigh the most. Summary statistics of pharmacokinetic metrics by dose and ethnicity may be found in Appendix 1, Table 3. Mean pharmacodynamic and pharmacokinetic metrics as well as comparative ratios between Asians and Caucasians may be found in Table 2.

2.2 Pharmacodynamics

Figure 1 shows the time course of changes in level of consciousness (LOC), digit symbol substitution test (DSST), and olanzapine concentration over time in a typical subject. This figure demonstrates the lag between changes in concentration and changes in effect as well as the relative insensitivity of LOC to measure pharmacodynamic effects and to quantify pharmacokinetic/pharmacodynamic relationships.

Figure 1 **Olanzapine Concentration and Effect vs. Time Profiles in a Typical Subject Receiving IM Olanzapine**

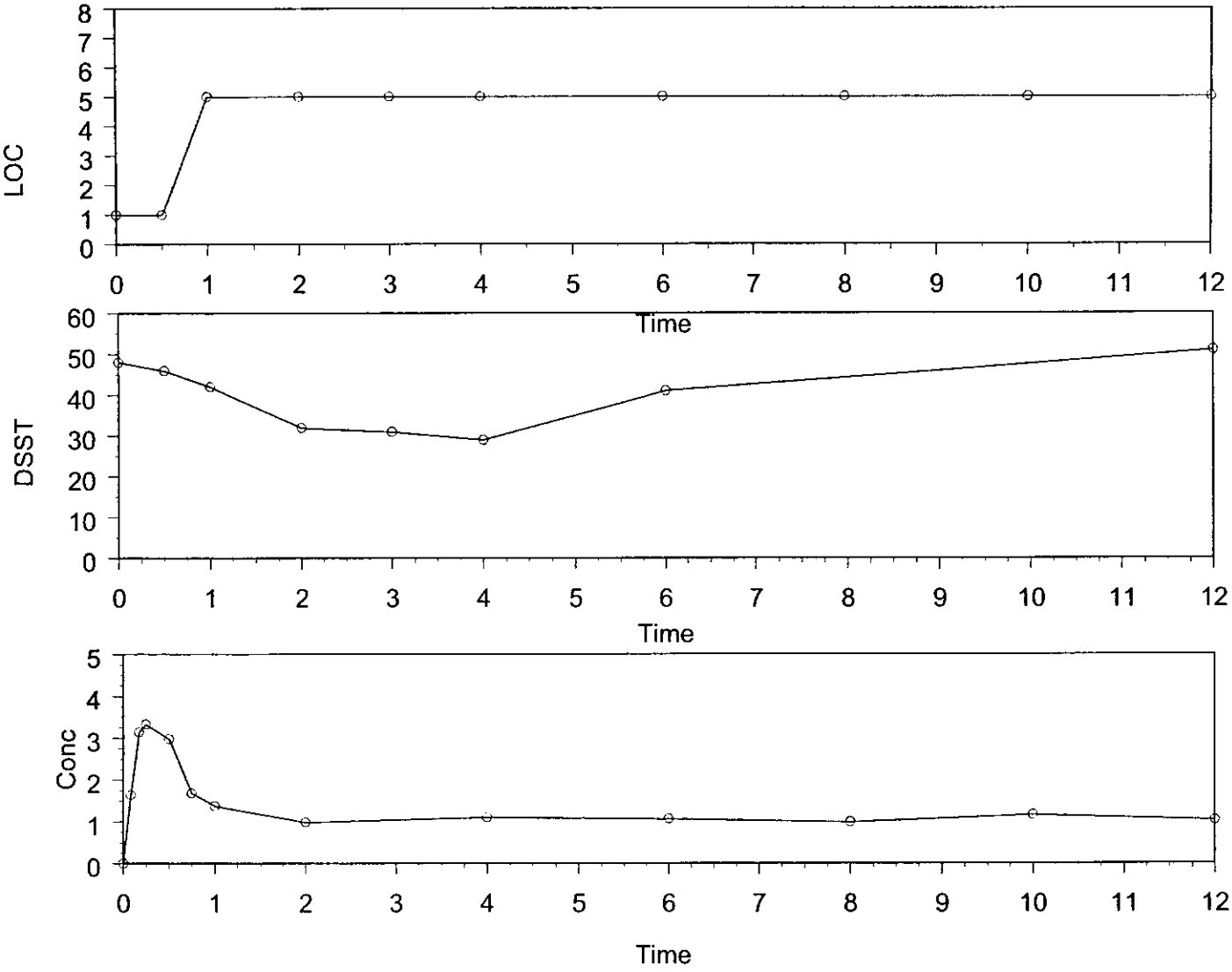


Figure 2 and Figure 3 were provided by the sponsor for study LOBI. Study LOBI examined pharmacokinetics and pharmacodynamics of Olanzapine in Chinese and Caucasian subjects. Figure 2 shows a clear dose response with the digit symbol substitution test (DSST), pharmacodynamic biomarker. Whereas Figure 3 shows that at each dose level the effect is greater in Chinese subjects as compared with Caucasians.

Figure 2 **Mean Changes in DSST over Time by Dose in all Subjects (Chinese and Caucasians) in Study LOBI**

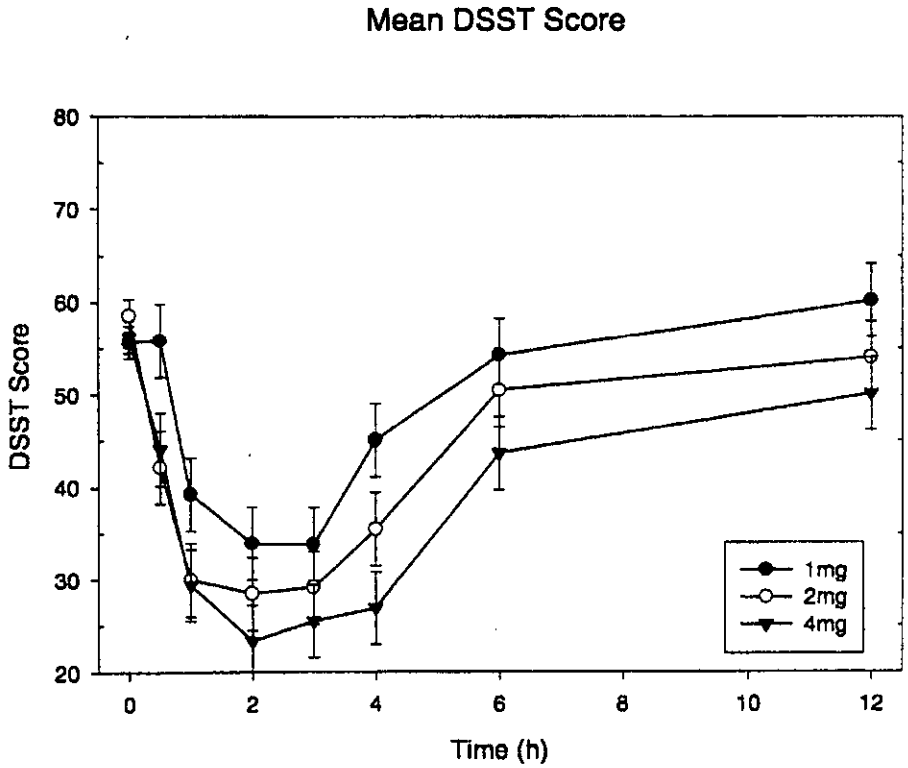
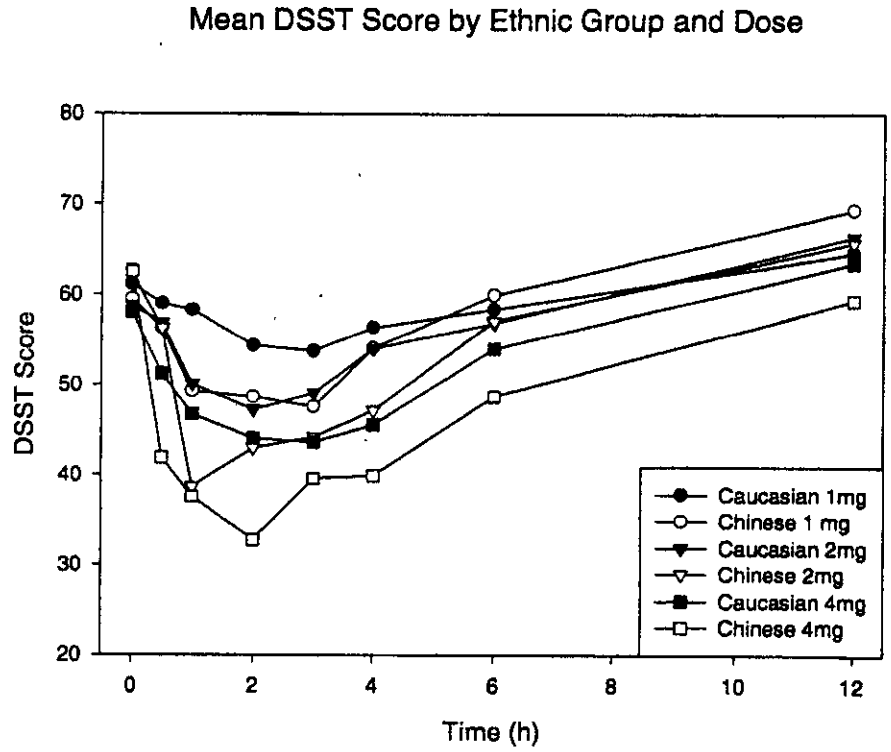
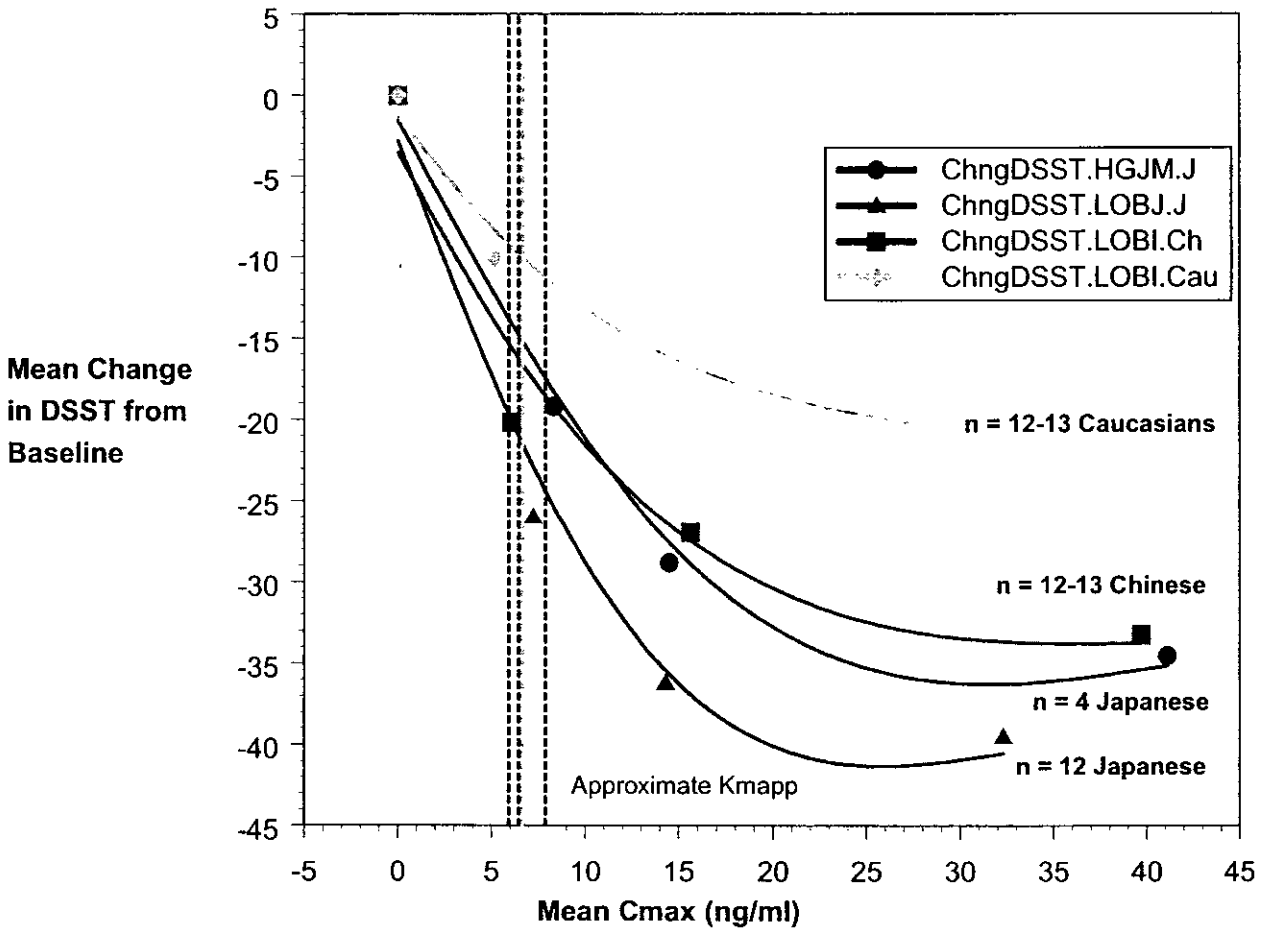


Figure 3 **Mean Changes in DSST over Time by Dose and Ethnicity in Study LOBI**



When examined by ethnicity, the mean maximal change in DSST vs. mean Olanzapine Cmax at different dose levels shows an apparent difference in maximal effect with no obvious difference in apparent Km. This more clearly shows that there is a difference in the pharmacokinetic/pharmacodynamic relationship between Asians and Caucasians.

Figure 4 Mean Maximal Change in DSST by Mean Cmax with Olanzapine IM Doses of 1 mg, 2 mg, and 4 mg by Ethnicity (Data from Studies HGJM, LOBJ, and LOBI)



It should be noted that this is a preliminary analysis and more formal population PK/PD modeling is needed to fully explore these differences.

As data was from different studies, the bioanalytic procedures were examined to see if this could explain the observed differences. Examination of the bioanalytic methods revealed that they were sufficiently similar, and performed in the same laboratory within a short time frame such that differences in bioanalysis are unlikely to explain these PK/PD differences, (see Appendix 1, Table 4).

Additional information and analyses would be needed to determine the clinical implications of these findings. Thus it's presently unknown if these differences translate into greater efficacy or more side effects in Asians as compared with Caucasians at similar dosages or exposures.

3 SIGNATURES

/S/

Ronald E. Kavanagh, BS Pharm, PharmD, PhD, OCPB/DPE-1 — Date

/S/

Raman Baweja, Ph.D., Team Leader, OCPB/DPE-1 — Date

CC: NDA 21-253 (orig., 1 copy)
HFD-120 (DubitskyG, LaughrenT, DavidP)
HFD-860 (Baweja, Kavanagh, Mehta)
CDR (B.Murphy)

Appendix 1 Additional Data

Table 2 Mean Pharmacokinetic and Pharmacodynamic Parameters for Single Doses of Olanzapine IM by Dose and Ethnicity

Dose	Study	Ethnicity	N	Body Weight (kg)	Cmax (ng/mL)	Cmax weight dose norm (ng/mL) / (mg/kg)	Ratio of Cmax in Ethnic Group : Caucasians	Ratio of Dose Normalized Cmax in Ethnic Group : Caucasians	AUC(0-∞) (ng.h/mL)	Dose Normalized AUC0-∞	Ratio of AUC0-∞ in Ethnic Group : Caucasians	Ratio of Dose Normalized AUC0-∞ in Ethnic Group : Caucasians	Maximum Change in DSST from Baseline
0 mg	HGJM	Japanese	6	—	—	—	—	—	—	—	—	--	-6.3 ± 5.5 (87.4) 0 - -15 [-5.5]
1 mg RAIM	HGJM	Japanese	4	63.7	8.31	508	1.61	1.28	69.7	4420	1.35	1.10	-19.2
	LOBJ	Japanese	12	62.5	7.22	445	1.40	1.12	59.1	3690	1.13	0.92	-26.0
	LOBI	Chinese	12/13	65.1	6.07	391	1 18	0.98	75.2	4850	1 44	1.21	-20.7
	LOBI	Caucasian	12/13	77.2	5.16	397	1.00	1.00	52.5	4010	1.00	1.00	-10.1
2 mg RAIM	HGJM	Japanese	4	66.5	14.5	471	1.20	1.02	123	4120	1.02	0.89	-28.8
	LOBJ	Japanese	12	62.5	14.3	440	1.18	0.95	131	4070	1.08	0.88	-36.2
	LOBI	Chinese	12/13	65.3	15.6	509	1.29	1.10	161	5220	1.33	1 13	-26.9
	LOBI	Caucasian	13	76.9	12.1	463	1.00	1.00	121	4610	1.00	1.00	-14.6
4 mg RAIM	HGJM	Japanese	4	63.0	41 1	659	1.46	1.23	247	3870	0.95	0.78	-34.5
	LOBJ	Japanese	12	62.4	32.3	496	1.15	0.93	263	4100	1.02	0.83	-39.5
	LOBI	Chinese	13	65.2	39.7	630	1.41	1.18	339	5500	1.31	1.11	-33.2
	LOBI	Caucasian	12/13	76.9	28.1	536	1.00	1.00	259	4950	1.00	1.00	-20.1
Global Mean Ratio Ethnic Group : Caucasians	All Studies	Japanese	—	—	—	—	1.33	1.09	—	—	1.09	0.90	—
		Chinese	—	—	—	—	1.29	1.09	—	—	1.36	1.15	—

Table 3 Pharmacokinetic Parameters after Single IM Doses of Olanzapine in Different Ethnic Groups by Dosage

Dose	Study	Ethnicity	N	Body Weight (kg)	Cmax (ng/mL)	Cmax weight dose norm (ng/mL) / (mg/kg)	Tmax (h)	AUC(0-tlast) (ng.h/mL)	AUC(0-∞) (ng.h/mL)	AUC(0-∞) Dose / weight norm (ng.h/mL) / (mg/kg)	AUC(tlast-∞) (%)	λz (h^{-1})	t1/2 (h)	CL/F (L/h)	CL/Fnorm (L/h/kg)	Vz/F (L)	Vz/F norm (L/kg)
1 mg RAIM	HGJM	Japanese	4	63.7 ± 7.53 -11.8 55.4 - 73.5 [62.9]	8.31 ± 4.17 -50.2 3.33 - 12.14 [8.88]	508 ± 224 -44 245 - 747 [520]	NC ± NC (NC) 0.17 - 0.25 [0.250]	56.3 ± 18.9 -33.6 38.4 - 82.2 [52.3]	69.7 ± 19.7 -28.3 51.2 - 94.8 [66.4]	4420 ± 1270 -28.8 3160 - 6090 [4210]	20.0 ± 5.72 -28.6 13.3 - 25.1 [20.8]	0.0281 ± 0.00577 -20.5 0.0207 - 0.0347 [0.0285]	NC ± NC (NC) 20.0 - 33.5 [24.3]	15.2 ± 4.08 -26.8 10.6 - 19.5 [15.4]	0.240 ± 0.0656 -27.3 0.164 - 0.317 [0.240]	539 ± 86.1 -16 475 - 666 [508]	8.47 ± 0.735 -8.68 7.73 - 9.13 [8.51]
	LOBJ	Japanese	12	62.5 ± 5.18 (8.28) 53.8 - 71.8 [61.0]	7.22 ± 2.81 (38.9) 3.50 - 14.1 [7.45]	445 ± 162 (36.3) 246 - 839 [447]	NC ± NC NC 0.25 - 0.75 [0.25]	48.4 ± 14.7 (30.4) 32.4 - 77.4 [43.5]	59.1 ± 17.7 (29.9) 40.4 - 90.7 [52.6]	3690 ± 1150 (31.2) 2460 - 6470 [3360]	18.2 ± 3.70 (20.4) 13.9 - 25.0 [17.4]	0.0325 ± 0.00927 (28.5) 0.0178 - 0.0454 [0.0330]	NC ± NC (NC) 15.3 - 38.9 [21.1]	18.2 ± 4.67 (25.7) 11.0 - 24.8 [19.1]	0.291 ± 0.0740 (25.4) 0.155 - 0.406 [0.298]	567 ± 72.4 (12.8) 461 - 723 [541]	9.09 ± 1.01 (11.2) 7.74 - 10.9 [8.87]
	LOBI	Chinese	12	65.1 ± 8.45 (13.0) 55.5 - 82.6 [62.2]	6.07 ± 2.47 (40.6) 2.43 - 11.9 [5.98]	391 ± 143 (36.7) 145 - 663 [405]	NC ± NC NC 0.170 - 0.750 [0.375]	61.0 ± 11.9 (19.6) 41.2 - 82.6 [63.5]	75.2 ± 10.6 (14.1) 57.7 - 94.9 [75.0]	4850 ± 594 (12.3) 3440 - 5440 [5030]	19.4 ± 6.67 (34.3) 13.0 - 35.1 [17.0]	0.0247 ± 0.00312 (12.6) 0.0203 - 0.0309 [0.0248]	NC ± NC (NC) 22.4 - 34.2 [27.9]	13.5 ± 1.95 (14.4) 10.5 - 17.3 [13.3]	0.210 ± 0.0306 (14.6) 0.184 - 0.291 [0.199]	551 ± 77.4 (14.1) 459 - 746 [540]	8.50 ± 0.874 (10.3) 6.69 - 9.56 [8.66]
	LOBI	Caucasian	12	77.2 ± 8.16 (10.6) 63.0 - 91.6 [80.2]	5.16 ± 2.20 (42.7) 1.71 - 9.15 [4 51]	397 ± 163 (41.0) 108 - 671 [394]	NC ± NC (NC) 0.170 - 0.750 [0.250]	39.9 ± 8.50 (21.3) 28.8 - 56.1 [37 9]	52.5 ± 9.10 (17.3) 40.0 - 70.5 [50.9]	4010 ± 489 (12.2) 3070 - 4770 [3950]	24.2 ± 5.91 (24.4) 17.1 - 34.2 [22.3]	0.0269 ± 0.00451 ± (16.8) 0.0202 - 0.0351 [0.0267]	NC ± NC (NC) 19.8 - 34.4 [26.0]	19.5 ± 3.16 (16.2) 14.2 - 25.0 [19.7]	0.253 ± 0.0320 (12.7) 0.2]0 - 0.326 [0.253]	734 ± 115 (15.6) 544 - 974 [720]	9.52 ± 1.17 (12.3) 7.52 - 11.0 [9.82]
2 mg RAIM	HGJM	Japanese	4	66.5 ± 8.22 (12.4) 58.4 - 76.3 [65 7]	14.5 ± 5.43 (37.4) 7.01 - 19.78 [15.7]	471 ± 156 (33.2) 267 - 605 [506]	NC ± NC (NC) 0.17 - 0.50 [0.250]	111 ± 25.2 (22.7) 85.3 - 145 [107]	123 ± 27.0 (22.0) 93.2 - 159 [120]	4120 ± 1200 (29.1) 2720 - 5560 [4100]		0.0297 ± 0.00358 (12.1) 0.0254 - 0.0327 [0.0303]	NC ± NC (NC) 21.2 - 27.3 [23.0]	16.9 ± 3.63 (21.5) 12.6 - 21.5 [16.7]	0.260 ± 0.0805 (31.0) 0.180 - 0.368 [0.246]	567 ± 79.7 (14.1) 497 - 660 [555]	8.64 ± 1.84 (21.2) 7.10 - 11.3 [8.08]
	LOBJ	Japanese	12	62.5 ± 5.34 (8.54) 53.6 - 72 3 [61.4]	14.3 ± 4.67 (32 7) 8.47 - 25.9 [13.3]	440 ± 127 (28.8) 279 - 767 [407]	NC ± NC (NC) 0.250 - 0.500 [0.250]	117 ± 33.4 (28 6) 78 7 - 190 [101]	131 ± 39.8 (30.5) 90 7 - 220 [112]	4070 ± 1190 (29.2) 2790 - 6360 [3570]	10 3 ± 2.57 (24.9) 6.35 - 13.8 [10.1]	0.0278 ± 0.00717 (25.8) 0.0201 - 0.0401 [0.0249]	NC ± NC (NC) 17.3 - 34.5 [27.9]	16.4 ± 3.97 (24.2) 9.11 - 22.0 [17.9]	0.263 ± 0 0659 (25.0) 0 157 - 0.358 [0.280]	599 ± 120 (20.0) 445 - 856 [559]	9.57 ± 1.62 (16.9) 7.83 - 12.9 [8.97]
	LOBI	Chinese	12	65.3 ± 8.25 (12.6) 55.5 - 82.6 [62.6]	15.6 ± 6.22 (39.8) 9 29 - 32.4 [13.5]	509 ± 206 (40.4) 279 - 1040 [436]	NC ± NC (NC) 0.170 - 0.500 [0.250]	144 ± 18.3 (12.7) 106 - 166 [142]	161 ± 19.9 (12 4) 123 - 189 [155]	5220 ± 674 (12.9) 4290 - 6440 [5260]	10.6 ± 3.26 (30.7) 7.66 - 16 7 [9.40]	0.0240 ± 0.00296 (12.3) 0.0185 - 0.0264 [0.0257]	NC ± NC (NC) 26.2 - 37.6 [27.0]	12.6 ± 1.64 (13.0) 10.6 - 16.2 [12.9]	0 194 ± 0.0252 (13.0) 0.155 - 0.233 [0 190]	530 ± 81.7 (15.4) 426 - 684 [532]	8.15 ± 0.960 (11.8) 6.65 - 9.89 [8.11]
	LOBI	Caucasian	13	76.9 ± 8.21 (10.7) 63.5 - 91.4 [80.7]	12.1 ± 2.44 (20.3) 6.34 - 15.8 [12.8]	463 ± 109 (23.4) 261 - 651 [450]	NC ± NC (NC) 0.170 - 0.500 [0.250]	107 ± 24.9 (23.3) 70.4 - 151 [101]	121 ± 29.1 (24 0) 78.7 - 169 [112]	4610 ± 1040 (22.6) 3300 - 6860 [4500]	11.4 ± 3.16 (27.6) 7.31 - 19.2 [10.5]	0.0264 ± 0.00477 (18.1) 0.0170 - 0.0358 [0.0253]	NC ± NC (NC) 19.4 - 40.9 [27.4]	17 4 ± 4.10 (23.5) 11.8 - 25.4 [17.8]	0.227 ± 0.0478 (21.1) 0.146 - 0.303 [0.222]	661 ± 100 (15.2) 524 - 830 [647]	8.63 ± 1.21 (14.0) 6.47 - 11.1 [8.47]
4 mg RAIM	HGJM	Japanese	4	63.0 ± 5.28 (8.39) 58.2 - 69.2 [62.3]	41.1 ± 13.7 (33.3) 25.30 - 58.41 [40.3]	659 ± 270 (41.0) 373 - 1010 [626]	NC ± NC (NC) 0.17 - 0.50 [0.250]	230 ± 24.4 (10.6) 203 - 262 [227]	247 ± 26.6 (10.8) 224 - 285 [239]	3870 ± 303 (7.84) 3470 - 4200 [3900]	6.89 ± 2.08 (30.1) 5.01 - 9.25 [6.66]	0.0289 ± 0.00220 (7.59) 0.0257 - 0.0304 [0.0299]	NC ± NC (NC) 22.8 - 27.0 [23.2]	16.3 ± 1.63 (10.00) 14.0 - 17.9 [16 7]	0.260 ± 0.0210 (8.08) 0.238 - 0.288 [0.256]	564 ± 18.1 (3.22) 547 - 589 [560]	8.99 ± 0.592 (6.59) 8.49 - 9.69 [8.89]
	LOBJ	Japanese	12	62.4 ± 5.03 (8.06) 54.0 - 71.5 [61.3]	32.3 ± 9.68 (30.0) 19.2 - 50.7 [29.0]	496 ± 128 (25.9) 314 - 750 [454]	NC ± NC NC 0.170 - 0.500 [0.250]	241 ± 47.7 (19.8) 191 - 331 [222]	263 ± 63 9 (24.2) 198 - 395 [237]	4100 ± 1020 (24.8) 3020 - 6400 [3730]	7.84 ± 3.76 (47.9) 3.84 - 16.2 [7.45]	0.0275 ± 0.00594 (21.6) 0.0186 - 0.0407 [0.0263]	NC ± NC (NC) 17.0 - 37.2 [26.3]	15.9 ± 3.25 (20.4) 10.1 - 20.2 [16.9]	0.256 ± 0.0548 (21.4) 0.156 - 0.331 [0.268]	581 ± 70.9 (12.2) 466 - 741 [566]	9.35 ± 1.19 (12.7) 7.52 - 11.3 [9.58]
	LOBI	Chinese	13	65.2 ± 7.81 (12.0) 55.5 - 82.2 [62.3]	39.7 ± 15.2 (38.4) 12.8 - 64.6 [40.1]	630 ± 213 (33.8) 215 - 1010 [608]	NC ± NC (NC) 0.170 - 0.500 [0.250]	306 ± 33.8 (11.1) 246 - 349 [314]	339 ± 39.7 (11 7) 270 - 392 [345]	5500 ± 698 (12.7) 4520 - 6720 [5470]	9.81 ± 1.92 (19.5) 6.06 - 12.9 [9.76]	0.0240 ± 0.00207 (8.61) 0.0212 - 0.0286 [0.0239]	NC ± NC (NC) 24.3 - 32.6 [29.0]	11.9 ± 1.49 (12.5) 10.2 - 14.8 [11.6]	0.184 ± 0.0229 (12.4) 0.149 - 0.221 [0.183]	498 ± 61.1 (12.3) 436 - 626 [481]	7.69 ± 0.823 (10.7) 6.41 - 8.84 [7.62]
	LOBI	Caucasian	12	76.9 ± 8.73 (11.4) 60.4 - 92.4 [78 2]	28.1 ± 9.65 (34.3) 12.8 - 42.1 [27.6]	536 ± 189 (35.3) 269 - 881 [466]	NC ± NC (NC) 0.170 - 0.500 [0.250]	237 ± 30.8 (13.0) 177 - 283 [239]	259 ± 40.0 (15 4) 184 - 323 [256]	4950 ± 773 (15.6) 3740 - 6640 [4850]	8.13 ± 3.08 (37.8) 4.12 - 14.2 [7.41]	0.0264 ± 0.00392 (14.9) 0.0201 - 0.0328 [0.0268]	NC ± NC (NC) 21.2 - 34.4 [25.9]	15.8 ± 2.58 (16.3) 12.4 - 21.7 [15 6]	0.206 ± 0.0314 (15.2) 0.151 - 0.268 [0.206]	600 ± 63.9 (10.7) 506 - 721 [599]	7.85 ± 0.775 (9.88) 7.08 - 9.62 [7.49]

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Ron Kavanagh
3/2/04 04:07:43 PM
BIOPHARMACEUTICS

Raman Baweja
3/2/04 05:05:59 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-253	Submission Dates: 6/15/00, 10/11/00
Generic Name:	Olanzapine	
Brand Name:	Zyprexa™	
Dosage Strength:	10 mg Vials	
Formulation:	Intramuscular Injection	Sponsor: Eli Lilly and Company
Indication of Drug:	Rapid Control of Agitation	Reviewer: Hong Zhao, Ph.D.
Type of Submission:	NDA (New Dosage Form)	Team Leader: Raman Baweja, Ph.D.

TABLE OF CONTENTS

Overall Summary

Olanzapine has a pharmacological profile that supports its actions as an antipsychotic agent. It appears to have a wide therapeutic range. The dosing range for oral olanzapine tablets is 5 to 20 mg administered once daily (NDA 20-592 for Zyprexa® oral tablets and NDA 21-086 for Zyprexa® Zydis® Orally Disintegrating Tablets).

Zyprexa [redacted](olanzapine for injection), a new short-acting intramuscular (IM) formulation of olanzapine, is intended to produce rapid absorption and delivery of the dose to the systemic circulation for rapid control of agitation. This NDA is to support the approval of two product presentations of Zyprexa-[redacted].

(1) a "vial alone" presentation (10 mg) reconstituted using customer supplied water for injection (2.1 ml) to provide a solution containing approximately 5 mg/ml of olanzapine, which is the clinical trial formulation; and

(2) [redacted]

Three 10-mg IM olanzapine doses given 2 hours or 4 hours apart from the initial dose, then 4 hours or longer apart for the third dose within 24-hour interval is the recommended maximum daily dose in the proposed labeling. It is intended that patients switch to oral olanzapine from the IM injection olanzapine as soon as clinically indicated.

Key Findings:

1. Compared to oral administration, IM injection of olanzapine produces 4.5-fold higher C_{max} and much shorter T_{max} (15 to 45 minutes after IM versus 5 to 8 hours after oral administration).
2. When the same dose of olanzapine is administered intramuscularly and orally, it produces a similar AUC and other pharmacokinetic parameters including half-life, plasma clearance, and volume of distribution.
3. As with oral route, C_{max} and AUC after IM injection are proportional to the dose administered.
4. Consistent with oral dosing, one or more IM doses of olanzapine administered daily produced about a 2-fold accumulation in plasma concentrations between Day 1 and Day 3.
5. The metabolic profiles following intramuscular and oral use are qualitatively similar.
6. Sedation occurs more rapidly following IM injection of olanzapine than following oral administration.
7. The total IM daily dose of olanzapine should be administered in divided doses to reduce the substantial difference in maximum plasma concentrations between olanzapine IM injection and olanzapine oral administration given the same total daily dose. The kinetics of the maximum intended 24-hour IM olanzapine (10 mg x 3 over ≥8 hours and ≤20 hours) is consistent with lower doses.
8. The [redacted] water IM formulations of olanzapine were equivalent with respect to AUC. With respect to C_{max}, it was 25% higher for the [redacted] formulation in comparison to the water IM formulation with 90% confidence interval of 103-150%.

9. With respect to AUC, the water IM formulation is equivalent to oral tablet, —

10. When lorazepam was given 1 hour after an IM dose of olanzapine, the pharmacokinetics of either drug was not affected by the other. However, the co-administration resulted in greater (additive) somnolence than was observed with either drug alone.

Comment 1

Comment 2

The results of Study HGIO and Study LOAC show that 5 mg IM olanzapine injection produced C_{max} that was approximately 4.5-fold higher compared to the same oral dose in healthy volunteers (40.3 ng/ml vs. 8.5 ng/ml in Study HGIO, 20.2 ng/ml after 4 mg IM vs. 5.4 ng/ml after 5 mg oral in Study LOAC). The following statement in the proposed labeling "*The peak concentration is about — higher than an equivalent oral dose*" is not accurate. The magnitude of — should be changed to 4.5-fold.

Comment 3

In the Dosage and Administration section of the proposed labeling, the sponsor states that "*The safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials*". Although pharmacokinetics of Olanzapine IM given more frequently than 4-hour apart has not been studied, plasma olanzapine concentrations after various IM doses indicate that the increase of C_{max} when dosing olanzapine IM at 2-hour interval would be small compared to that dosing olanzapine IM at 4-hour interval. This small increase in maximum concentration after second dose is not expected to produce clinical safety concern. Patients has been exposed to higher olanzapine concentrations after the third dose which was given ≥8 hours after the initial dose.

Comment 4

Pharmacokinetics of olanzapine is highly variable and many factors such as smoking status, gender and age affect olanzapine clearance. Even within healthy male non-smoker population, it was observed that there was more than 4-fold inter-subject difference in C_{max} after olanzapine IM injection. Dosing adjustment may be necessary in patients with a combination of factors that may result in largely reduced clearance of olanzapine.

Recommendation

This submission (NDA 21-253) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting the OCPB requirements for Water IM formulation.

The OCPB related labeling (Clinical Pharmacology, D-D interaction, Geriatric Use, Dosage and Administration) proposed by the sponsor has two statements that have to be modified:

In Clinical Pharmacology section, the statement of "*The peak concentration is about fold higher than an equivalent oral dose*" is not accurate. The magnitude of should be changed to 4.5-fold.

Please convey the above Comments and Recommendation to Medical Officer.

Hong Zhao, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

cc: NDA 21-253 Zyprexa IM (Olanzapine), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

Summary

Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine class. The dosing range for oral tablets is 5 to 20 mg administered once daily. Three 10-mg IM olanzapine doses given 2 hours or 4 hours apart from the initial dose, then 4 hours or longer apart for the third dose within 24-hour interval is the recommended maximum daily dosing in the proposed labeling for olanzapine IM formulation.

Clinical Pivotal Trials - Four randomized, double-blind, placebo-controlled pivotal clinical studies were conducted in several different patient populations (schizophrenia, bipolar mania, ———— to demonstrate the effectiveness and safety of IM olanzapine in the rapid control of agitation. An active comparator (IM haloperidol or IM lorazepam) was also included in these studies. A total of 552 patients were assigned to receive at least one injection of IM olanzapine. Studies HGHB and HGHV in patients with schizophrenia explored the relationship between dose and response across a dose range of 2.5 to 10 mg IM olanzapine. Studies HGHW ———— in patients with bipolar disorder ———— explored the relationship between dose and response across a dose range of 2.5 to 5.0 mg IM olanzapine. Studies LOAT and HGHB also examined the transition to oral olanzapine therapy, with the oral periods lasting up to 4 days. These studies did not include any pharmacokinetic information.

Pharmacokinetics Studies - There have been seven clinical pharmacology studies, of which five studies characterized the pharmacokinetics of olanzapine after intramuscular injection (Studies LOAC, LOAW, LOAR, LOAT and HGJA); one study (Study HGIO) evaluated bioequivalence between two IM formulations and between oral and IM formulations; and another study (Study LOAV) investigated drug interaction between IM olanzapine and IM lorazepam. The following questions have been raised and answered through review of this NDA:

What are the basic and important characteristics of olanzapine?

Olanzapine, a thienobenzodiazepine derivative, is an antipsychotic agent. Antipsychotic agents of this class have been characterized as exhibiting (1) broader efficacy, especially in the treatment of patients with negative symptoms of schizophrenia, (2) a lower incidence of extrapyramidal symptoms and (3) minimal perturbation of prolactin levels. In vitro studies have shown that olanzapine has high receptor affinities for dopamine (DA) D_1-D_5, $5HT_{2A}$, $5HT_{2C}$, $5HT_3$, $5HT_6$, α_1-adrenergic, and histamine H_1 receptors. Olanzapine is also a potent and subtype-selective muscarinic antagonist in vivo.

Olanzapine is marketed as an oral dosage form. The recommended starting dose is 10 mg/day, administered as a single dose without regard to meals. Daily dose may subsequently be adjusted individually within the range of 5 to 20 mg daily. Pharmacokinetic data have been collected in many studies in which the dose of oral olanzapine ranged from 0.5 to 20 mg in healthy subjects, and 1 to 30 mg in patients with schizophrenia. Pharmacokinetics of olanzapine are linear and dose-proportional within the approved dosage range. The major pharmacokinetic parameters in healthy volunteers are shown below:

Parameter	T_{max} (h)	$t_{1/2}$ (h)	CL/F (L/hr)	V_β/F (L)	Protein Binding (%)
Mean	6.0	33	26	1150	93
Range	[				]

^{14}C-labeled olanzapine studies showed its extensive metabolism to 10-N-glucuronide (largest fraction), 4'-N-desmethyl (CYP1A2), 2-hydroxymethyl (CYP2D6), and 4'-N-oxide (FMO3) metabolites. No pharmacological activity was seen for these metabolites in animal models. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Clearance of olanzapine is about 30% lower in women, 30% lower in elderly, and 40% greater in smokers and after carbamazepine administration. These observations are likely due to differences in CYP1A2 metabolic activity. Food, hepatic or renal impairment has no significant impact on olanzapine pharmacokinetics. Olanzapine has a relative wide therapeutic margin. The response to the drug shows a closer correlation with dosage than with plasma concentrations. The major adverse events are somnolence, dizziness, and hypotension. Safety and effectiveness of olanzapine in pediatric patients have not been established.

What assay methods were used to determine olanzapine plasma concentrations? Were they validated?

Plasma samples were analyzed for olanzapine concentration using an HPLC/ ——————— method over the concentration range — ng/ml to — ng/ml. Coefficients of variation for inter-day accuracy and precision were less than — and stability in matrix at room temperature and freeze/thaw cycles were also tested. The method was fully validated.

Is there any difference in rate and extent of absorption between IM and oral dosage forms?

The results listed below from *Study F1D-EW-LOAC* (12 smokers and 6 nonsmokers) show that C_{max} was greater and occurred more rapidly following IM administration compared to oral administration. With exception of the difference in C_{max} and T_{max}, the values of other pharmacokinetic parameters including $t_{1/2}$, CL, V_d, and the AUC values after dose and weight normalization, were similar for oral and IM administration.

Parameter	2mg IM (N=19)	4mg IM (N=15)	5mg Oral (N=9)	10mg Oral (N=4)
C_{max} (ng/ml)	6.9±2.9	20.2±9.5	5.4±1.4	11.8±2.0
T_{max} (hr)	0.4±0.2	0.3±0.1	6.1±2.7	2.6±1.6
$T_{1/2}$ (hr)	37.6±17.3	33.7±11.5	38.5±9.5	25.4±2.4
CL/F (L/kg/hr)	0.36±0.14	0.36±0.16	0.43±0.14	0.50±0.11
V_d^{ss}/F (L/kg)	15.8±4.1	14.1±3.7	22.1±7.3	18.5±5.1

Parameter	AUC_{0-t} (ng.hr/ml)	Dose and Weight Normalized	$AUC_{0-\infty}$ (ng.hr/ml)	Dose and Weight Normalized
2 mg IM (N=19-22)	66±24	2.31±0.91	91±38	3.18±1.42
4 mg IM (N=12-15)	141±51	2.53±0.99	180±64	3.22±1.26
5 mg Oral (N=9)	163±53	2.28±0.86	190±67	2.65±1.07
10 mg Oral (N=4)	286±62	1.96±0.48	302±54	2.06±0.43

Also, olanzapine pharmacokinetics after two divided doses (5 mg each, 4 hours apart) of IM was compared to a 10 mg oral dose in 24 healthy male volunteers (9 smokers and 15 nonsmokers, *Study F1D-EW-LOAW*):

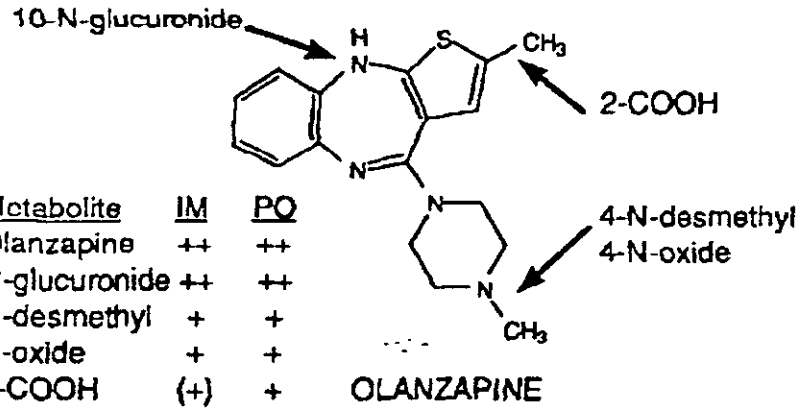
PK Parameter	C_{max} (ng/ml)	AUC_{0-t} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	CL/p (L/hr)
P.O. 1x10mg	15 (7-22)	462 (265-725)	499 (287-838)	3.8 (2-8)	31 (20-44)	22.1 (11.9-34.8)
I.M. 2x5mg[a] (4 hrs apart)	24[b] (13-43)	487 (334-706)	522 (353-792)	3.0[b] (0.3-5)	30 (20-39)	20.2 (12.6-28.3)

[a] Of 24 subjects enrolled, 22 completed the study. [b] The T_{max} data for the IM regimen are from a bimodal distribution. Olanzapine C_{max} and T_{max} typically occurred shortly after the 2nd dose of IM olanzapine, given at 4 hours.

These results again show that C_{max} was greater and occurred more rapidly following IM administration compared to oral administration. AUC values were similar indicating that the bioavailability of 10 mg IM olanzapine given as two 5-mg injections, 4 hours apart was comparable to that of a single 10-mg oral dose.

Is there any difference in metabolic fate of olanzapine between IM and oral dosage forms?

In *Study F1D-EW-LOAC*, plasma samples were analyzed for olanzapine using an HPLC/ ———————— method. Additionally, plasma and urine samples were qualitatively analyzed for olanzapine and its metabolites using mass spectroscopy.



Metabolite	IM	PO
Olanzapine	++	++
N-glucuronide	++	++
N-desmethyl	+	+
N-oxide	+	+
2-COOH	(+)	+

Metabolic profile of olanzapine characterized semi-quantitatively in plasma and urine after oral (PO) and intramuscular (IM) doses of olanzapine (Study LOAC).

The urinary metabolic profiles after oral and IM administration of olanzapine were qualitatively similar.

Is olanzapine PK at the highest IM dose recommended different from that at lower doses?

Three 10-mg IM olanzapine doses given within 24-hour interval (2 or 4 hours apart from the initial dose, then 4 hours or longer apart for the third injection) is the recommended maximum daily dose in the proposed labeling. The PK of 4 hour apart dosage regimen was characterized in a total of 24 non-agitated patients with stable chronic schizophrenia (3 were females and 4 were nonsmokers) who received up to 3 injections (10 mg/injection, 4 hours apart) within 24 hours of IM olanzapine (*Study HGJA*). Of 24 patients, 5 received 2 injections and 1 received 1 injection. The pharmacokinetic results after IM olanzapine 10 mg injections are shown below:

Parameter	Dose 1	Dose 2	Dose 3
C_{max} (ng/ml)	27.1 (4.9-75.1)	29.5 (15.6-52.1)	41.5 (23.1-93.5)
$AUC_{0-4\,h}$ (ng.hr/ml)	45 (13-78)	80 (49-115)	115 (75-174)

Parameter	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L/kg)
Mean (range)	29.5 [ ]	22.9 [ ]	11.2 [ ]
CV%	20%	32%	25%

The kinetics of the maximum intended 24-hour dose of IM olanzapine were demonstrated to be consistent with those observed in earlier single, lower-dose kinetic studies. The sponsor claims that the cumulative 30 mg dose (10 mg x 3 over ≥8 hours and ≤20 hours was safe and well tolerated.

Does this NDA provide information on switching from IM olanzapine to oral olanzapine?

A study (F1D-EW-LOAR) of multiple-dose of IM olanzapine and continued with oral dose was conducted in 26 male patients (24 patients were smokers) with acute non-organic psychosis. Over a period of 3 days, up to 9 injections of IM olanzapine were administered. On the subsequent 2 days, oral doses of olanzapine were administered. The first oral dose was administered 24 hours after the last IM dose. The doses were limited to a single injection from 2.5 mg to 10 mg on the first day, and up to 4 injections (4 hours apart) and a maximum total daily dose of 20 mg per day on each subsequent day. Concomitant administration (rescue medication) of benzodiazepines was also permitted to maintain adequate psychiatric quiescence of the patients. Average pharmacokinetic parameters estimated for study Day 1 and Day 3 are shown below:

Parameter		2.5mg IM	5.0mg IM	7.5 mg IM	10mg IM
N		3-4	6	6-9	10
C_{max} (ng/ml)	Day 1	9.4 (6.6-13.1)	19.9 (6.1-27.4)	23 (10.0-49.3)	33 (9.8-57.9)
	Day 3	17.8 (13.6-25.5)		45 (17-142)	44 (13-68)
	Corrected	9.5 (5.5.-16.7)		30 (8-122)	34 (10-49)
AUC	Day 1	113 (66-169)	190 (79-315)	284 (231-333)	379 (204-727)
(ng.hr/ml)	Day 3	329 (269-365)		916 (584-1284)	860 (349-1659)
	Corrected	141 (93-175)		429 (283-741)	527 (261-1033)

Accumulation factor = $(Dose_{Day\,1} / Dose_{Day\,3}) * (AUC_{Day\,3} / AUC_{Day\,1})$

2.68 (1.36-4.91), Corrected 1.40 (0.90-2.38)

No patients received a 5 mg IM dose of olanzapine on study Day 3. C_{max} was corrected for C_0, C_{max} = Observed C_{max}-C_0exp (-T_{max}*β). AUC_{inf} was corrected for C_0, AUC_{inf} = Observed AUC_{inf} – (C_0/β).

Parameter		2.5mg IM	5.0mg IM	7.5 mg IM	10mg IM
T_{max} (hr)	Day 1	0.29 (0.17-0.50)	0.22 (0.17-0.25)	1.08 (0.25-4.0)	0.47 (0.17-2.0)
	Day 3	0.42 (0.25-0.5)		1.8 (0.2-6.0)	0.6 (0.2-2.0)
$t_{1/2}$ (hr)	Day 1	18 (13-24)	15 (13-18)	18 (12-33)	16 (11-24)
	Day 3	16 (15-17)		23 (16-44)	22 (13-36)
CL/F (L/hr)	Day 1	24.8 (14.8-38.2)	31.5 (15.9-63.2)	26.9 (22.5-32.5)	30.0 (13.8-48.9)
	Day 3	19.1 (14.3-26.9)		19.1 (10.1-26.5)	22.1 (9.7-38.4)

No patients received a 5 mg IM dose of olanzapine on study Day 3.

The results show that administration of one or more IM doses of olanzapine daily produced about a 2-fold accumulation in olanzapine plasma concentrations between Day 1 and Day 3. This degree of accumulation is consistent with the known pharmacokinetics of oral olanzapine and is predictable from the elimination half-life of the drug.

The sponsor claims that smooth transitioning from the parental to oral formulations of olanzapine was observed. In the midst of this transition, a reduction in agitation and overall psychotic symptomatology that had been achieved during Day 1 was maintained and carried on through treatment Days 2-5.

In Study F1D-EW-LOAT, 82 patients were treated with 1 to 4 injections of 2.5 to 12.5 mg IM olanzapine per injection, to a maximum cumulative dose of 20 mg in 24 hours, for 1 to 3 days. Patients were then switched to oral olanzapine treatment, such that each patient received olanzapine (IM/oral) treatment for up to 5 days. Limited PK measurements were made in patients (male and female, smoker and nonsmoker) prior to transfer to oral olanzapine (pooled data):

	IM C_{20min} (ng/ml)			Oral C_{5hrs} (ng/ml)		
Dose	5 mg	7.5 mg	10 mg	10 mg	15 mg	20 mg
	11.2-12.7	34.3±14.3 (16.2-60.9)	31.2±10.9 (16.5-45.8)	42.0±15.6 (19.6-71.1)	50.6±9.4 (32.1-57.3)	41.9
N	2	11	7	15	6	1

Is the proposed shorter IM dosing interval of 2-hour acceptable?

Pharmacokinetics of olanzapine IM given more frequently than 4-hour apart has not been studied. The impact of dosing IM olanzapine using shorter interval between consecutive doses on safety, pharmacodynamics and pharmacokinetics needs to be evaluated. The following table shows olanzapine plasma concentrations between 0-4 hour interval after various IM olanzapine doses:

		Healthy Volunteers *Olanzapine Concentrations (ng/ml)*				Patients	
Time		2 mg	4 mg	5 mg	10 mg (1)	10 mg (2)	10 mg (3)
(h)	*N*	*22*	*15*	*18*	*24*	*24*	*20*
0		0	1.5	0	0	9.4	18.8
0.08		2.6	10.0	16.3			
0.17		5.2	17.7	32.4	14.5	17.8	28.1
0.25		5.6	16.9	36.5	19.6	22.7	29.9
0.5		5.2	11.3	23.9	21.0	24.8	36.0
0.75		3.9	8.3	15.7	15.4	22.9	32.1
1		3.3	7.1	11.6	12.8	22.2	29.7
1.5		2.5	5.6	8.9			
2		**2.3**	**4.8**	**8.0**	**8.9**	**19.0**	**27.3**
3		1.8	4.2	7.1			
4		**1.8**	**4.4**	**6.7**	**9.6**	**18.6**	**28.6**

These concentration data indicate that the increase of C_{max} when dosing olanzapine IM at 2-hour interval would be small compared to that dosing olanzapine IM at 4-hour interval. This small increase in maximum concentration after second dose is not expected to produce clinical safety concern. Patients have been exposed to higher olanzapine concentrations after the third dose that was given ≥8 hours after the initial dose.

Is there any clinically important PK and/or PD interaction between olanzapine and lorazepam?

Study F1D-LC-LOAV was conducted in 13 healthy male and female volunteers to determine if a pharmacokinetic or pharmacodynamic drug-drug interaction occurred between olanzapine and lorazepam. After receiving a single dose of 2.5 mg IM olanzapine, the subjects were involved in a 3-way randomized crossover periods in which single doses of 5 mg IM olanzapine or 2 mg IM lorazepam were given alone or given in combination. The doses of lorazepam, when given in combination with olanzapine were always administered 1 hour after olanzapine. This design simulated likely clinical usage where it is anticipated that if insufficient tranquilization is achieved from a dose of olanzapine, an IM dose of lorazepam may be administered. The plasma concentrations of olanzapine, lorazepam, total lorazepam, and corresponding pharmacokinetic measurements (see below) revealed that there was no statistically significant pharmacokinetic drug interaction between olanzapine and lorazepam.

Olanzapine

Parameter	C_{max} (ng/ml)	AUC_{0-} (ng.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)	CL_p (L/hr)	V^{ss} (L)
O alone (N=11)	11.5 (44%)*	259 (43%)	0.7 (87%)	33.1 (23%)	23.0 (46%)	951 (28%)
O + L (N=11)	9.3 (41%)	232 (33%)	1.1 (147%)	32.0 (19%)	23.9 (37%)	1028 (25%)

O=Olanzapine, L=Lorazepam, *Coefficient of variation (CV%)

Unconjugated Lorazepam

Parameter	C_{max} (ng/ml)	AUC_{0-} (ng.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)	CL_p (L/hr)	V^{ss} (L)
L alone (N=11)	15.7 (20%)*	448 (39%)	4.3 (41%)	17.1 (25%)	5.1 (35%)	121 (20%)
L + O (N=11)	15.0 (21%)	456 (47%)	4.1 (41%)	17.1 (28%)	5.1 (37%)	122 (18%)

O=Olanzapine, L=Lorazepam, *Coefficient of variation (CV%)

Total Lorazepam

Parameter	C_{max} (ng/ml)	AUC_{0-} (ng.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)	CL_p (L/hr)	V^{ss} (L)
L alone (N=11)	39.6 (12%)*	1476 (22%)	8.4 (34%)	19.3 (38%)	1.4 (24%)	42.6 (18%)
L + O (N=11)	40.8 (15%)	1478 (29%)	8.6 (62%)	18.5 (44%)	1.5 (26%)	41.1 (13%)

O=Olanzapine, L=Lorazepam, *Coefficient of variation (CV%)

Both drugs showed effects on digit symbol substitution test (DSST) and somnolence scales when administered alone. The combination produced more sedation and lower DSST test results than either drug alone. The adverse event profile for IM olanzapine was consistent with events reported after oral olanzapine treatments.

The problem with this drug interaction study design is that the dosing time for lorazepam is not optimal to determine the maximum potential of the interaction because the time to reach C_{max} for both drugs occurred far apart. It was 0.5 hour (7.55 ng/ml) for olanzapine after 5 mg olanzapine IM injection, and was 6 hours and 8 hours for unconjugated lorazepam and total lorazepam, respectively after 2 mg lorazepam IM injection given one

hour after olanzapine. By 6 and 8 hours the plasma concentration of olanzapine had fallen to 4.45 ng/ml and 4.37 ng/ml, respectively.

Is there any difference in rate and extent of absorption between different injection sites (deltoid and gluteus maximus) or different depth of injection?
The clinical trials of olanzapine specified that IM doses of olanzapine were to be administered into the gluteus maximus muscle. Clinical usage of the drug, especially in cases where patients are extremely agitated, might make access to this muscle more difficult. Typical practice in emergency situations might call for injection into other muscles. In *Study HGIO*, Intramuscular formulations were administered in the gluteus in a first group of 12 subjects, and in the deltoid in a second group of 6 subjects. The AUC data are shown below:

AUC (ng.hr/ml) (CV%)	IM (Water)	Oral
Group 1 (Gluteus Block, N=12)	291 (20%)	261 (23%)
Group 2 (Deltoid Block, N=6)	371 (17%)	339 (20%)
Group 2/Group 1	1.28	1.30

The AUC data show that the difference in the mean values of AUC between two groups after IM injection is similar to the difference in the mean values of AUC between two groups after oral administration. This result demonstrates that there does not appear to be any substantial difference that would be clinically important between IM injection of olanzapine into the deltoid or gluteus muscle sites. Also, in *Study LOAV*, 2 subjects were given injections of olanzapine using subcutaneous needles (5/8'') and intramuscular needles (1.5'') and the results show that the depth of IM injection did not appear to make any substantial pharmacokinetic difference.

Sponsor's Labeling with OCPB Suggested Changes

Clinical Pharmacology

DOSAGE AND ADMINISTRATION

Agitation

Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania-- The efficacy of intramuscular olanzapine for injection in controlling agitation was demonstrated in a dose range of 2.5 mg to 10 mg

The safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (see Schizophrenia or Bipolar Mania under DOSAGE AND ADMINISTRATION).

Intramuscular Dosing in Special Populations--A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY; also see Use in Patients with Concomitant Illness and Drug Interactions under PRECAUTIONS).

/s/

Hong Zhao
3/8/01 12:44:24 PM
BIOPHARMACEUTICS

Raman Baweja
3/8/01 01:17:31 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-253	Brand Name	Zyprexa
OCPB Division (I, II, III)	DPE 1	Generic Name	Olanzapine
Medical Division	NeuroPharm, HFD-120	Drug Class	Thienobenzodiazepine
OCPB Reviewer	Hong Zhao	Indication(s)	Rapid Control of Agitation
OCPB Team Leader	Raman Baweja	Dosage Form	Intramuscular Injection
		Dosing Regimen	Maximum 30mg/day, 10mg/dose, 4-hour apart
Date of Submission	6-15-2000	Route of Administration	IM
Estimated Due Date of OCPB Review	4-15-2001	Sponsor	Eli Lilly
PDUFA Due Date	6-15-2001	Priority Classification	3S
Division Due Date	4-1-2001	OCPB Briefing date	3-8-2001

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	4	4	
multiple dose:				
Patients-				
single dose:	x			
multiple dose:	x	3	3	
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1	1	One study on both direction
In-vivo effects of primary drug:	x	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1	1	

Bioequivalence studies -				
traditional design; single / multi dose	x	1	1	Single-dose
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7	7	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable. See Review package
QBR questions (key issues to be considered)	Does this NDA provide information on switching from IM olanzapine to oral olanzapine? Is there any difference in rate and extent of absorption between IM and oral dosage forms? Is there any difference in rate and extent of absorption between different injection sites (deltoid and gluteus maximus)? Is there any clinically important PK and/or PD interaction between olanzapine and lorazepam? Is the to-be-marketed product [redacted] bioequivalent to the clinical trial formulation?	
Other comments or information not included above		
Primary reviewer Signature and Date	Hong Zhao 3/1/01	
Secondary reviewer Signature and Date	Raman Baweja 3/1/01	

CC: NDA 21-253, HFD-850 (Electronic Entry or Lee), HFD-120(CSO), HFD-860(Zhao, Baweja, Mehta), CDR (Biopharm-CDR)

/s/

Hong Zhao
3/8/01 01:21:11 PM
BIOPHARMACEUTICS
This is the NDA review filing and review form.

Raman Baweja
3/8/01 02:45:42 PM
BIOPHARMACEUTICS