CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020592Orig1s040s041

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DRUGS: ZYPREXA, PROZAC **PRIMARY REVIEWER**: Andre Jackson

ZYPREXA

(b) (4)

NDA 20-592/SE8-039 Submission date : 2-4-08
NDA 21-086/SE8-021 Submission date : 2-4-08

NDA 20-592/SE5-040 Submission date : 2-5-08
NDA 20-592/SE5-041 Submission date : 2-5-08

(b) (4)

SYMBYAX (Zyprexa/Prozac)
NDA 21-520/SE1-012 Submission date : 2-1-08
(b) (4)

PROZAC
NDA 18-936/SE8-077 Submission date : 2-4-08
NDA 18-936/SLR-075 Submission date : 3-21-07

Applicant : Eli Lilly

FORMULATIONS: Zyprexa (Tablet,Intramuscular,ODT), Fluoxetine (Capsules), Zyprexa/Prozac) Capsules

Review of a CBE Labeling Supplement

Background:

The firm has submitted a detailed list of outstanding Label revisions for Zyprexa NDA 20-592, Zyprexa Zydis NDA 21086 and Zyprexa Intramuscular NDA 21-253 and Prozac NDA 18-936, Symbyax NDA 21520.

Only those supplement items with relevant concerns for OCP will be listed.

Table of contents:

A. Supplements for Zyprexa tablets NDA 20-592

(b) (4)

o S-039 (PAS for use of Zyprexa and Prozac in combination to treat treatment-resistant depression)
o S-040 (PAS: adolescent use in bipolar disorder [acute manic or mixed episodes])
o S-041 (PAS: adolescent use in schizophrenia)

FIRM'S PROPOSED LABEL FOR ZYPREXA

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Andre Jackson
7/15/2008 10:50:49 AM
BIOPHARMACEUTICS

Raman Baweja
7/15/2008 03:25:37 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review
BPCA Summary Review

PRODUCT (Generic Name):	Olanzapine
PRODUCT (Brand Name):	Zyprexa
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	2.5, 5,7.5, 10 and 20 mg
NDA:	20-592/040,041(SE5)
NDA TYPE:	Supplement for **Schizophrenia** and Bipolar disorder in adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	October 30, 2006
SPONSOR:	Eli Lilly
OND DIVISION:	HFD

EXECUTIVE SUMMARY

Olanzapine is currently indicated in the treatment of schizophrenia or bipolar I in adults. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose. This sNDA provides information on the clearance of olanzapine in adolescents age 13-17 years with varying doses of 2.5 to 20 mg/day.

This sNDA includes a population pharmacokinetic study done in adolescents using flexible doses between 2.5mg/day to 20 mg/day.

The population pharmacokinetic study was done in 105 patients (Study F1D-MC-HGMF) . Study duration was 4 and ½ weeks and the study population consisted of 64 males and 41 females .

The overall conclusions from the pharmacokinetic study in adolescents were:

- The exposure at steady-state in adolescents was 30-63% higher than in adults.
- Clearance in female adolescents was found to be 28% lower than in male adolescents.

RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested by the reviewer.

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/s/

Raman Baweja
4/2/2007 11:37:34 AM

Office of Clinical Pharmacology and Biopharmaceutics/ Pharmacometrics Review

NDA:	20-592-SE5/040, 041
Compound:	Olanzapine
Submission Dates:	October 30, 2006
Sponsor:	Eli Lilly
Reviewer:	Andre Jackson

Executive Summary

A study was done combining data from several centers in adolescents ages 13-17 to determine if the pharmacokinetics were similar or different from that previously observed in adults. The study data from 4 study sites were analyzed by mixed effects modeling to identify any important covariates which impacted Olanzapine pharmacokinetics in adolescents. The study results indicated that weight and gender were the significant covariates which influenced the clearance of Olanzapine in the subject population. Clearance/F in females was found to be 13.6 L/hr whereas that for males was 17.5 L/hr. Exposure in adolescents was higher due to their lower average body weights.

Introduction

Study F1D-MC-HGMF (Study HGMF) was performed to address the request by the United States (US) Food and Drug Administration (FDA) to provide pharmacokinetic information in a population of adolescent patients with schizophrenia or bipolar I disorder. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose (Studies F1D-MC-HGCS, F1D-MCHGGC).

In this report, the pharmacokinetic data from Study HGMF was combined with other existing adolescent pharmacokinetic data (Studies F1D-MC-HGCS, F1D-MCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY) to characterize olanzapine pharmacokinetics in adolescents and to address pharmacokinetic aspects of the FDA Pediatric Written Request for olanzapine.

Summary

The goal of this study was to collect data for Olanzapine in a pediatric population to determine if the levels were similar or different from those observed in adult schizophrenia or bipolar I disorder subjects. Previous studies in adults showed that the CL/F was 13.6 L/hr with smoking and gender being important covariates. In the current analysis the sponsor has used a 1 compartment model similar to that used in adults and analyzed the data obtained following a 4.5 week study in adolescents ages 13-17 following the administration of doses ranging from 2.5 to 20 mg/day. Body weight and gender were identified as important covariates. The label claim from this analysis was that (b) (4) However this was not accepted by OCP since the result was not consistent with the experimental data.

COMMENTS TO MEDICAL REVIEWER

OCP has revised the following portion of the label based upon the completed Pediatric Written Request:

The firm had a statement saying that (b) (4) This statement was deleted.
The firm also wanted to include a statement that (b) (4) .
However due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used.

OCP REVISED LABEL
Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients.

Objective of the analysis

The primary objective of this study was to characterize olanzapine pharmacokinetics (CL/F and V/F); the inter- and intra-subject variabilities of olanzapine pharmacokinetics; and the potential influence of patient factors such as age, weight, gender, ethnic origin, and smoking status on olanzapine pharmacokinetics in adolescents 13 to 17 years of age that have been diagnosed with schizophrenia or bipolar I disorder.

Methods

Design

Study#1:

Study HGMF was a multicenter, openlabel, single arm trial in adolescent patients (13 to 17 years) meeting diagnostic criteria for schizophrenia or bipolar I disorder as defined by the DSM-IV-TR . The study design consisted of two study periods:
Study Period I was a 2- to 14-day Screening and Washout Period, and Study Period II was a 4 and ½ -week Open-Label Treatment Period. In order to protect patient well-being, this study employed as short a washout period as practical and was consistent with washout periods typical of real-world clinical practice. Since the elimination half-life of most orally administered antipsychotics ranges from 20 to 40 hours and the half-life of decanoate depot preparations (for example, fluphenazine) ranges from 7 to 10 days , the washout period was appropriate for this patient population. Patients already taking olanzapine continued on their previous dosage (between 2.5 to 20 mg/day) unless a dose adjustment was deemed necessary by the investigator, while patients new to olanzapine therapy started on an initial dose of 2.5 to 5.0 mg/day, as determined by the investigator.

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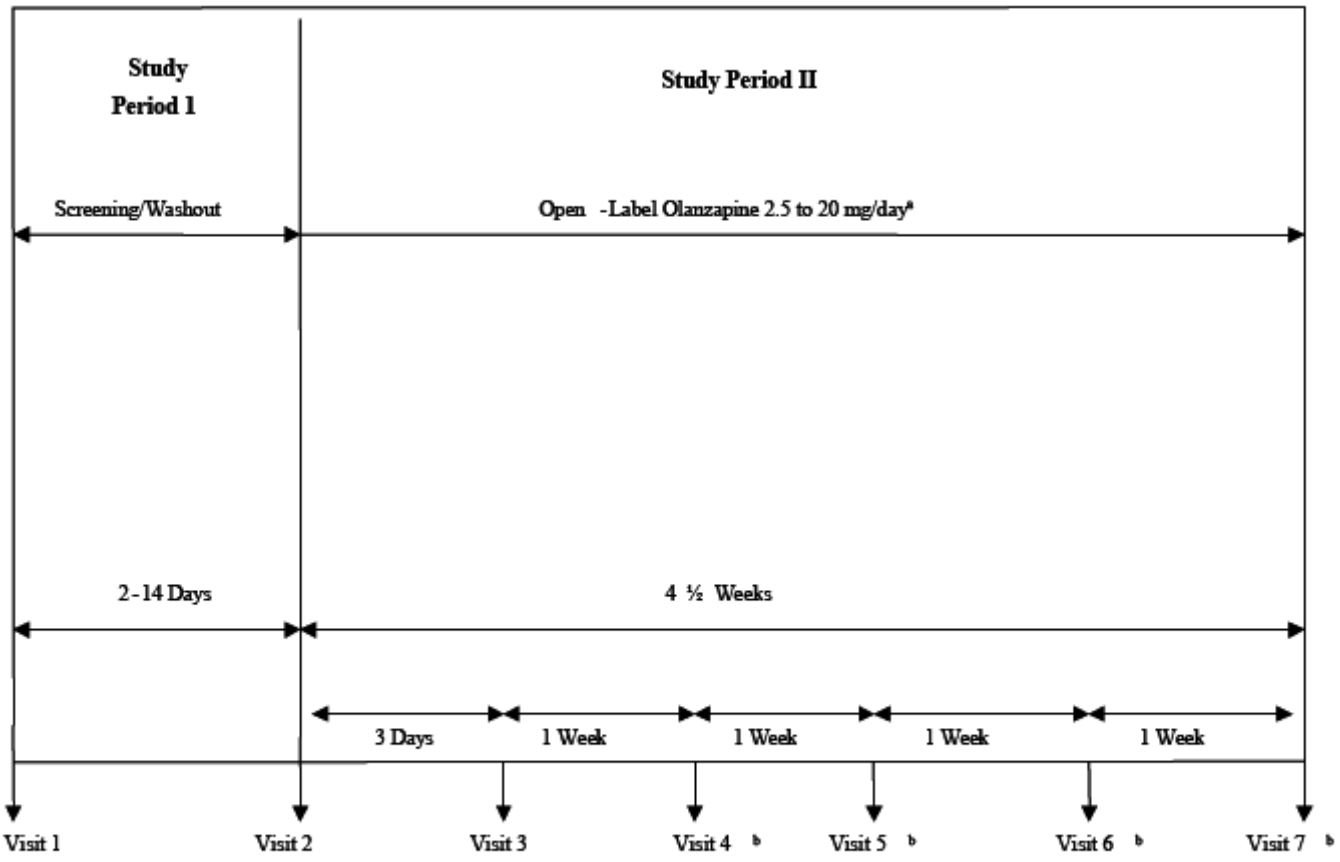

[a]The starting dose for olanzapine-naïve patients was 2.5 to 5 mg/day. For patients entering the study already on olanzapine treatment, the maximum initial dose was 20 mg/day.
[b]PK sampling at Visits 4, 5, 6, and 7.

Table 1. Summary of Olanzapine Studies Included in the Adolescent Population Pharmacokinetic Evaluation

Study	Patient Population	Dose (mg) [a]	Sample Collection [b]	Patients and Observations
HGMF	• 80-100 adolescents • 13-17 years old • Diagnosed with schizophrenia or bipolar I disorder	• 2.5 - 20	• 4 blood samples per patient	• To be determined after database lock
LOAY	• 88 adolescents and young adults • 12-20 years old • Diagnosed with schizophrenia, shizoaffective or schizophreniform disorders	• 5 - 20	• 1 to 8 blood samples per patient	• 80 adolescents • 293 observations
HGCR/S	• 9 children and adolescents • 10-18 years old • Diagnosed with schizophrenia	• 2.5 - 20	• 9 to 15 blood samples per patient	• 6 adolescents • 84 observations
HGGC	• 23 children and adolescents • 5-14 years old • Diagnosed with bipolar disorder	• 2.5 - 20	• 1 to 4 blood samples per patient	• 5 adolescents • 15 observations

[a] Olanzapine was administered as a once-daily (QD) oral dose
[b] All samples were collected at steady-state. Steady-state is defined as a patient being on a fixed olanzapine dose for at least 5 consecutive days.

Analytical

Assay Validation - Zyprexa

Parameter	Zyprexa
Method	Olanzapine was assayed by liquid chromatography with electrochemical detection (LCEC), using extracts based on its acid-base behavior.
Extract Stability	6 days
Number of Freeze-thaw	2 Cycles QC's 80, 40, and 0.64 ng/ml Diff=0.1%, -0.4% and --2.8%

Benchtop Stability at RT	4 hrs
Long term at –20° C -60C -80C	378 days 1017 days 8.5 months
Extraction Recovery	79% @ 80 ng/ml 72% @ 40 ng/ml 80% @ 0.64 ng/ml Internal standard 69%

All samples stored at -80C

1.F1D-MC-HGGC

Date of first sample analysis: 13 April 1999

Date of last sample analysis: 20 April 1999

Date for 1st sample draw 2/27/98
Total storage time= 425 days

Table 2 **Back Calculated Calibration Standard Concentration Data for HPLC Assay for Olanzapine in Human Plasma**

Summary Statistics:

	Concentration (ng/mL)								
Nominal	100	50.0	25.0	10.0	5.00	2.50	1.00	0.500	0.250
Average	99.7	50.8	24.8	9.87	4.81	2.44	1.02	0.521	0.252
% Error	-0.3	1.7	-0.9	-1.3	-3.8	-2.5	2.1	4.2	0.8
N	2	2	2	2	2	2	2	2	2

Individual Results:

Batch	
S031	(b) (4)
S041	

Table 3 **Control Results from the HPLC Assay for Olanzapine in Human Plasma**

Summary Statistics:

	Concentration (ng/mL)				
Nominal	80.0	40.0	0.640	80.0	(DFAC of 6.67)
Average	84.9	42.9	0.703	82.4	
Std. Dev.	1.80	1.17	0.0343		
Precision (%)	2.1	2.7	4.9		
% Error	6.2	7.3	9.9		
N	4	4	4	2	

Individual Results:

2.F1D-MC-HGCS

Date of First Sample Analysis: 18/11/96 (d/m/y)

Date of Last Sample Analysis: 23/04/97 (d/m/y)

Date for 1st sample draw 10/25/95
Total storage time= 545 days

Table 2 **Back-Calculated Calibration Standard Concentrations**

	nominal olanzapine concentration (ng/mL)								
batch	**100**	**50.0**	**25.0**	**10.0**	**5.00**	**2.50**	**1.00**	**0.500**	**0.250**
O00F									(b) (4)
O01F									
O02F									
O03F									
O04F									
n	5	5	5	5	5	5	5	4	4
mean	99.9	50.5	25.0	9.52	5.17	2.48	1.00	0.500	0.253
std dev	0.943	0.793	1.08	0.724	0.538	0.126	0.0140	0.0491	0.0245
%rsd	0.9%	1.6%	4.3%	7.6%	10.4%	5.1%	1.4%	9.8%	9.7%
% error	-0.1%	0.9%	0.0%	-4.8%	3.4%	-0.7%	0.3%	0.1%	1.1%

Table 4 **Assay Accuracy Data - QC Samples**

	nominal Olanzapine concentration (ng/mL)					
batch	80.0	80.0	40.0	40.0	0.640	0.640
O00F	[redacted] (b) (4)					
O01F						
O02F						
O03F						
O04f						
n	10		10		9	
mean	82.7		39.9		0.638	
std dev	2.53		1.92		0.0971	
% rsd	3.1%		4.8%		15.2%	
% error	3.3%		-0.2%		-0.3%	

3.F1D-MC-HGMF

Date for 1st sample draw 6/1/05
Total storage time=

Analytical Performance: Back-Calculated Concentrations (ng/mL) of LY170053 Calibration Standard in (Human) (Plasma - hep) in (Protocol 0062-05167)

Assay Date	Analytical Run Number	STD 0.250 0.250 ng/mL	STD 0.500 0.500 ng/mL	STD 1.00 1.00 ng/mL	STD 2.50 2.50 ng/mL	STD 5.00 5.00 ng/mL	STD 10.0 10.0 ng/mL	STD 25.0 25.0 ng/mL	STD 50.0 50.0 ng/mL	STD 100 100 ng/mL
11-Jan-2006	1	[redacted] (b) (4)								
12-Jan-2006	2									
26-Jan-2006	4									
07-Mar-2006	5									
15-Mar-2006	6									
22-Mar-2006	7									
27-Mar-2006	8									
Mean		0.252	0.523	1.01	2.41	5.04	9.88	24.2	50.8	100
S.D.		0.0202	0.0301	0.0565	0.119	0.189	0.36	0.829	1.59	2.11
%CV		8	5.8	5.6	4.9	3.8	3.6	3.4	3.1	2.1
%Bias		0.8	4.6	1	-3.6	0.8	-1.2	-3.2	1.6	0
n		12	13	13	14	14	14	14	14	14

Reason Deactivated
* F Calibration standard deactivated due to unacceptable % deviation

Analytical Performance of LY170053 Quality Control Samples in Human Plasma - hep (Protocol 0062-05167)

Run Date	Curve Number	QC 0.640 0.640 ng/mL	QC 40.0 40.0 ng/mL	QC 80.0 80.0 ng/mL	QC 180 180 ng/mL
11-Jan-2006	1	(b) (4)			
12-Jan-2006	2				
26-Jan-2006	4				
07-Mar-2006	5				
15-Mar-2006	6				
22-Mar-2006	7				
27-Mar-2006	8				
Mean		0.651	39.2	76.5	187
S.D.		0.0665	2.02	2.41	29.2
%CV		10.2	5.2	3.2	15.6
%Theoretical		101.7	98	95.6	103.9
%Bias		1.7	-2	-4.4	3.9
n		14	14	14	12
Overall %CV		8.6			

Data:

Studies:

Pharmacokinetics

No dosing or sampling times were recorded during study LOAY. Each of the ten LOAY study sites provided a window of approximate sampling and dosing times. The firm did an analysis including and excluding the LOAY study however the FDA analysis only verified the analysis without the LOAY data set.

The times from dose for the concentrations were unknown because both actual time of last dose and the actual time of the blood sample were not collected in Study LOAY. Smoking status and ethnic origin information were not documented in Study LOAY.

Smoking status in Study HGMF was determined from the results of the cotinine test. Any concentrations reported as below quantification limit (BQL) were treated as missing values for the analyses.

Pharmacodynamics

N/A.

Data Checking

The data was checked by: perusing entered data to see if it was correct for units and definitions were consistent with entries. Data entry was consistent with the control stream. Scatter plots of the raw data were investigated to determine if the data contained a lot of outliers.

Models

Pharmacokinetics

Structural Model

Base Model Development

Pharmacokinetics of oral olanzapine in an adult population has been previously

characterized by a one compartment model (original NDA submission NDA 20-595, 21 September 1995). Therefore, a one compartment pharmacokinetic model with parameters such as absorption rate constant (Ka), oral clearance (CL/F), and oral volume of distribution (V/F) was initially tested to evaluate the adolescent pharmacokinetic data. The available data in adolescent patients did not allow reliable estimation of Ka, therefore, Ka was fixed to the adult population value. The base model was able to determine the inter-patient variability in CL/F and V/F with covariance using the omega block.

Three inter-patient variability models (Equation 1) were tested: η on CL/F, η on V/F and η on CL/F and V/F with covariance (omega block).

$P = \Theta 1 \bullet \exp(\eta)$ Equation 1

where P is the individual parameter estimate (CL/F or V/F), Θ_1 represents the typical or population value of the parameter and η is a random variable with a mean of zero and variance of ω2.

The difference between model predicted olanzapine plasma concentration and the observed olanzapine concentration was modeled using the residual error model. The two residual error models evaluated were proportional (Equation 2) and combined additive and proportional.

Parameter sensitivity analyses were performed on various base models and a final base model was selected for identification of potential significant covariates.

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥10.828, $p<.001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

Covariate Models

Patient factors such as body weight, age, gender, ethnic origin, smoking status, and dose were tested for their influence on CL/F and V/F. Equations 3 to 5 were applied to test continuous covariates (body weight, age) and equation 6 to test categorical covariates (gender, ethnic origin, smoking status, and dose).

$P = \Theta 1 \cdot [1 + \Theta 2 \cdot (COV - MED)]$ Equation 3

$P = \Theta 1 \cdot EXP[\Theta 2 \cdot (COV - MED)]$ Equation 4

$P = \Theta 1 \cdot (COV/MED)\ \Theta 2$ Equation 5

$P = \Theta 1 \cdot (1 + \Theta 2 \cdot IND)$ Equation 6

where P is the individual parameter estimate, Θ1 represents the typical value of a parameter, Θ2 represents the effect of a covariate, COV is the value of a covariate, and MED is the median value of a covariate. IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (for example, smoker=0 and nonsmoker=1).

Each covariate was individually added to the base model and tested. When the objective function of the base model with a covariate was reduced by 6.635 ($p<0.01$), the covariate was considered to be potentially significant.

Random Variance Models

Two residual error models evaluated were proportional (Equation 7) and combined additive and proportional.

$Cij = IPRED \cdot (1 + ERR)$ Equation 7

where Cij is the predicted jth olanzapine concentration in the ith patient, IPRED is the model predicted olanzapine concentration in the individual and ERR is a random variable with a mean of zero and variance of σ2.

Pharmacodynamics

N/A

Model Selection

Final Model Evaluation

Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examined the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was

performed by fixing the parameter of interest to ±5, 10, 15, 20, 30, 40% of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to ±100%. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis

The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model . Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine concentrations were compared to the observed concentrations for each study.

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

Individual estimates of the pharmacokinetic parameters in adolescent patients were obtained from the final model post-hoc estimates. The pharmacokinetic model for oral olanzapine in adult patients from Study F1D-MC-HGAJ (original NDA 20-592, 21 September 1995) was developed in NONMEM, Version 4 using first order (FO) method of estimation. In an effort to be consistent with the software version and method of estimation used for adolescent pharmacokinetic modeling, the individual pharmacokinetic parameters in the adult patients were obtained by rerunning the final pharmacokinetic model for adult patients in NONMEM, Version V and using FOCE with interaction method.

Initial Model Selection

The basis of rejecting and/or accepting a particular model (e.g.: additive versus proportional, with or without weight, sex, etc.,) should be described. The estimation method and the alpha level of the chi-square test should be included. Further, the type of model selection should also be presented (forward, backward, stepwise, etc.,).

Final Model Selection

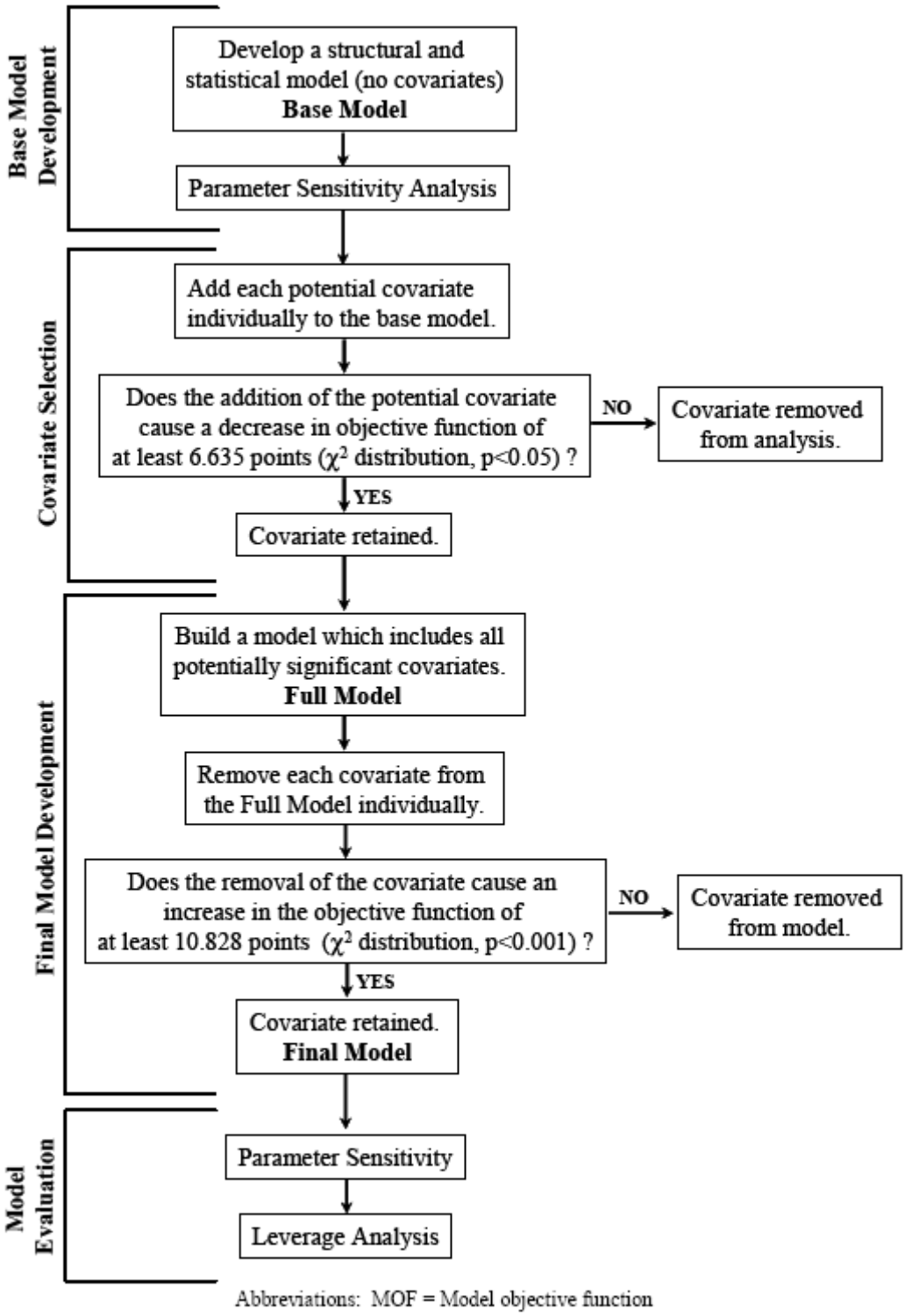

Figure HGMF.5.2. General process for pharmacokinetic model development

Software

The software used for the data formatting, modeling, simulation, graphing, and statistical tests should be included (e.g.; EXCEL, SAS, , S-PLUS, NONMEM version V,,).

Results and Discussion

Design Adequacy

Table HGMF.7.1. Baseline Demographics for Patients Included in the Pharmacokinetic Modeling (Studies HGCS, HGCR, HGGC, HGMF)

Demographic	HGCR	HGCS	HGGC	HGMF	Total
n	9	75	15	363	462
N	1	5	5	105	116
Age (years)					
Mean±SD	16	16.0±1.41	14.3±0.593	16.1±1.37	16.0±1.38
(Min, Max)		(14,17)	(13.3,14.7)	(13.43,17.99)	(13.3,17.99)
Body weight (kg)					
Mean±SD	78.9	65.6±15.8	65.3±10.4	72.9±20.9 [a]	72.3±20.3 [b]
(Min, Max)		(48.2,85.8)	(56.7,77.1)	(41.1,147.7) [a]	(41.1,147.7) [b]
Gender (N)					
Male	1	2	0	64	67
Female	0	3	5	41	49
Smoking status (N)					
Smoker	NA	NA	NA	20	20
Non-smoker	NA	NA	NA	73	73
Origin (N)					
Caucasian	NA	NA	4	90	94
African American	NA	NA	0	8	8
Hispanics	NA	NA	1	7	8

Abbreviations: n = number of observations; N = number of patients; Max = maximum; Min = minimum; SD = standard deviation; NA = not available.

[a] n = 103

[b] n = 114

The number of subjects appears adequate although it may have been better for them to have more subjects at age 13-14 to replace those in study LOAY.

Data Integrity

The data base contained subjects below 13 and above 17 who were excluded.

Model and Model Selection:

Base Model

Model description

Parameter estimation results

Table HGMF.7.3. Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)

	Units	Estimate	%SEE
Pharmacokinetic Model			
Absorption rate constant, K_a	hr^{-1}	0.543 (Fixed)	-
Oral clearance, CL/F	L/hr	16.3	4.61
Oral Volume of Distribution, V/F	L	879	17.1
Interpatient Variability			
CL/F	%	45.9	15.9
V/F	%	68.8	42.3
Covariance between CL/F and V/F	-	0.258	22.5
Residual Error			
Proportional	%	27.0	13.7

Abbreviations: SEE = standard error of the estimate.

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Goodness of fit

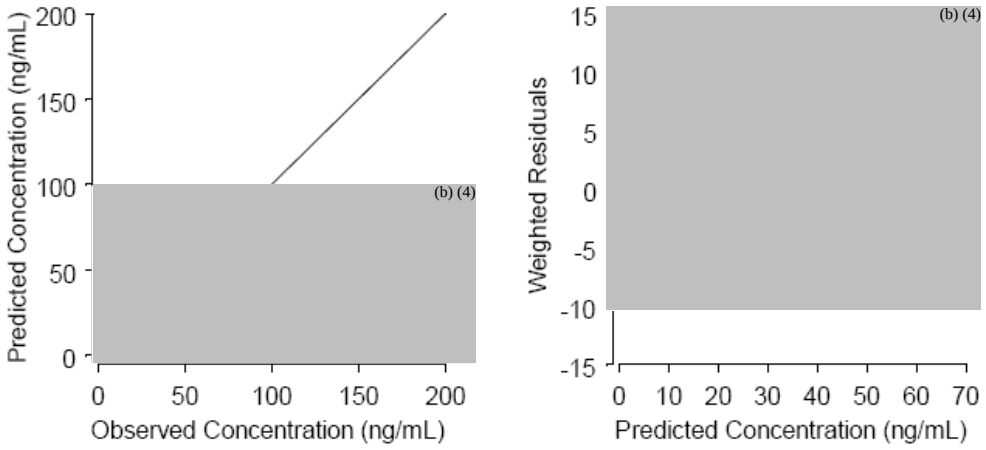

Figure HGMF.7.4. Goodness-of-fit plots for the base pharmacokinetic model. Data from Studies HGCS, HGCR, HGGC and HGMF.

Model Selection

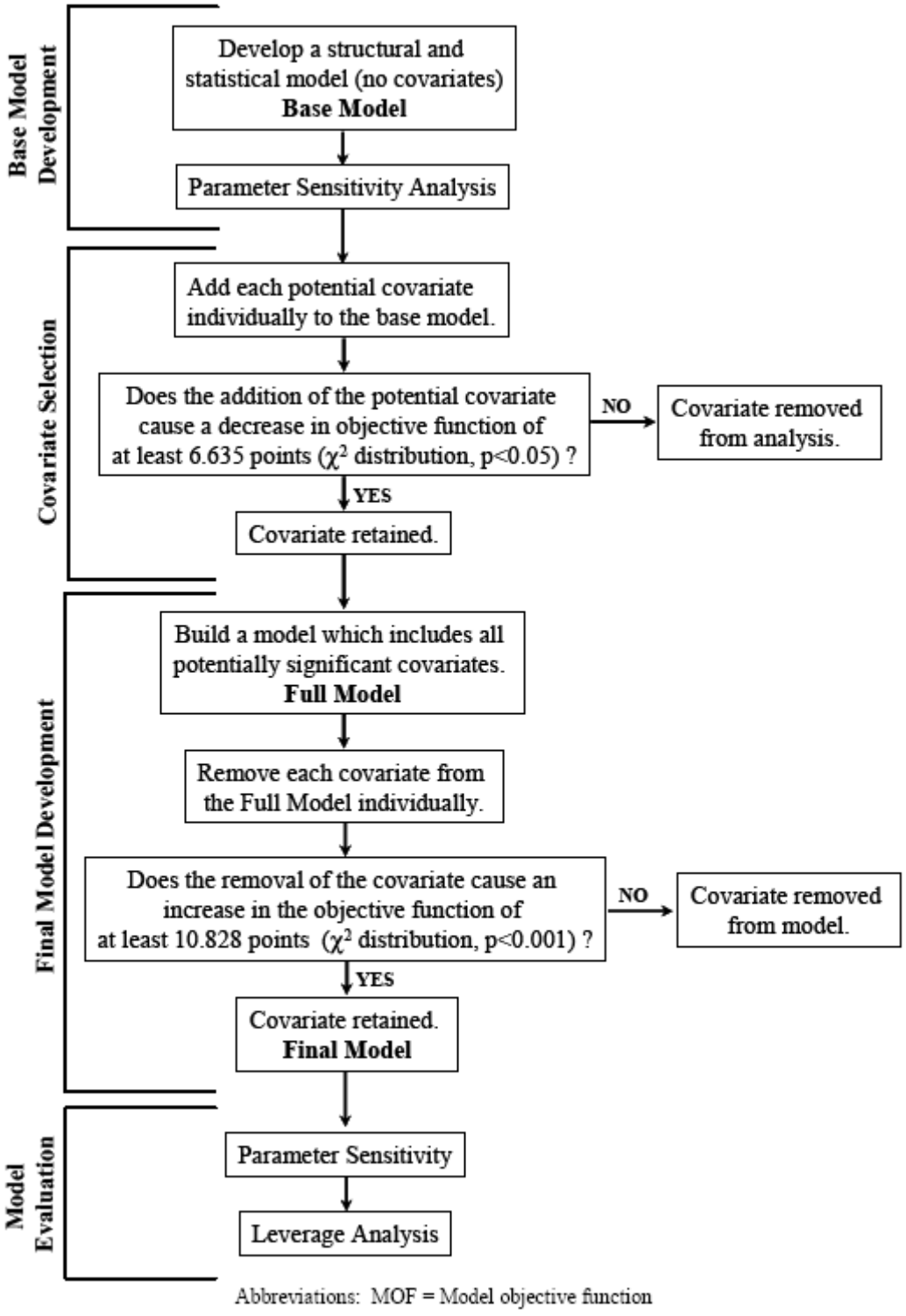

Figure HGMF.5.2. General process for pharmacokinetic model development

Final Model

Model description

Final Model Development

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Final Model Evaluation
Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examines the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was performed by fixing the parameter of interest to ±5, 10, 15, 20, 30, 40% of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to ±100%. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis
The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model (Mandema et al. 1992). Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine

concentrations were compared to the observed concentrations for each study.

Final Pharmacokinetic Model

Two covariates, gender and body weight had a statistically significant influence on olanzapine pharmacokinetics and were retained in the final model. The effects of gender and body weight were on CL/F. Other patient specific factors such as age, race and smoking status did not have a significant influence on olanzapine pharmacokinetics although the Cl/F difference in adolescents due to smoking may have been confounded due to weight..

The following mean concentrations were observed in adolescents.

	Olanzapine Concentration (ng/mL)			
Dose (mg)	**N**	**n**	**Mean ± SD**	**(Minimum, Maximum)**
2.5	20	47	5.11±2.33	(0.290, 9.65)
3.0	1	3	14.5±1.82	(13.11, 16.57)
5.0	47	104	13.8±7.52	(0.890, 70.17)
7.5	28	46	20.6±9.75	(4.41, 52.46)
10.0	47	101	30.9±17.9	(3.18, 101.98)
12.5	10	17	50.3±21.4	(23.86, 118.78)
15.0	26	65	36.6±18.7	(2.56, 97.17)
17.5	7	9	78.2±40.7	(37.14, 145.37)
20.0	16	70	76.5±32.8	(11.36, 160.26)

Abbreviations: N = number of patients, n = number of observations, SD = standard deviation.

Based upon the mean concentrations it appears that dose has no impact on the kinetics of Olanzapine in adolescents. The lack of a dose effect on pharmacokinetics was also observed in adults.

Parameter estimation results Final Model

Table HGMF.7.4. Pharmacokinetic Parameters for the Final Population Model

	Units	Estimate	%SEE	95 % CI
Pharmacokinetic model				
Absorption rate constant, K_a	hr^{-1}	0.543 (Fixed)	-	-
Oral Clearance (CL/F) [a]	L/hr	13.6	6.16	(12.2 – 15.3)
Effect of gender on CL/F (Θ3) [b]	-	0.288	31.1	(0.127 – 0.477)
Effect of weight on CL/F (Θ4) [c,d]	1/kg	0.00585	34.4	(0.00248 – 0.00907)
Oral Volume of Distribution (V/F)	L	899	16.2	(687 – 1150)
Interpatient variability				
CL/F	%	40.5	19.7	-
V/F	%	65.4	47.2	-
Covariance between CL/F and V/F	-	0.232	31.8	-
Residual Error				
Proportional	%	27.1	14.2	-

Abbreviations: CI = confidence interval; SEE = standard error of the estimate.

[a] $CL_{,female} = 13.6$ L/hr.

[b] $CL_{,male} = CL_{,female} \cdot (1+ \Theta 3) = 17.5$ L/hr.

[c] $CL_{,\text{female at weight(n)}} = 13.6 \text{ L/hr} \cdot e^{[\Theta 4(n-70.1)]}$;where 70.1 is the median.

[d] $CL_{,\text{male at weight(n)}} = 17.5 \text{ L/hr} \cdot e^{[\Theta 4(n-70.1)]}$;where 70.1 is the median.

Goodness of fit

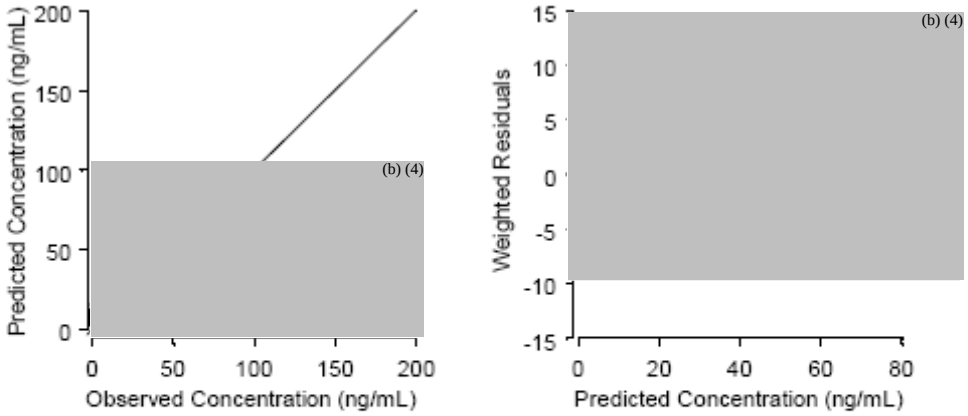
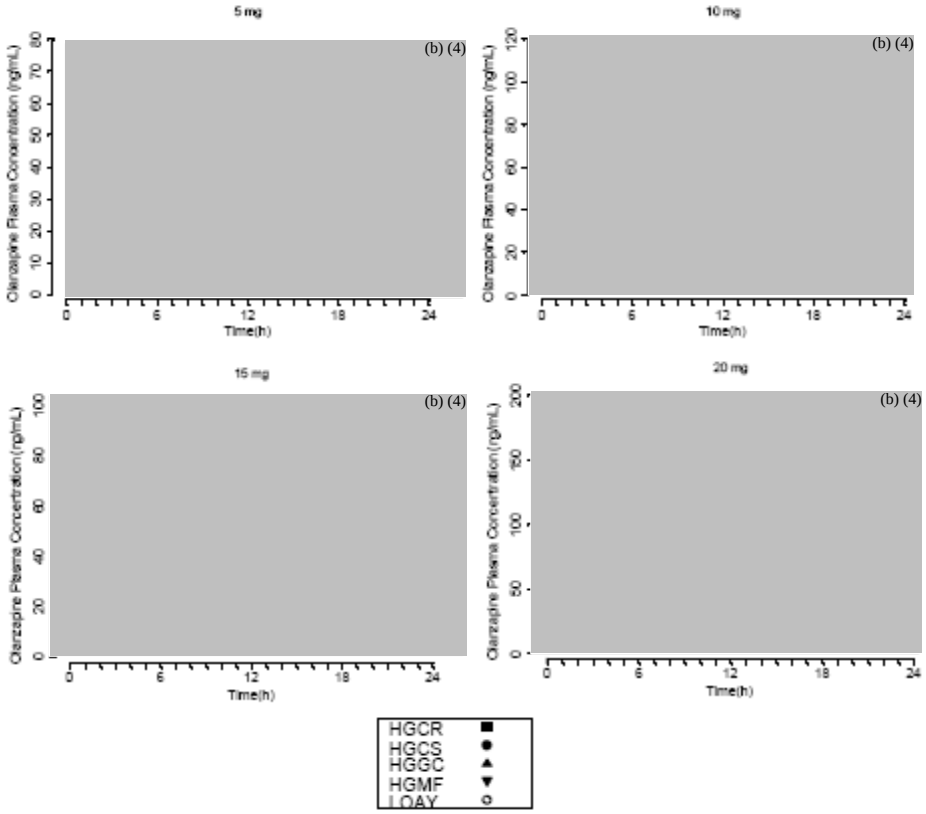


Figure HGMF.7.5. Goodness of fit plots for final model. Data from Studies HGCS, HGCR, HGGC, and HGMF.

Model Qualification

Posterior predictive check allowed for the comparison of the model predicted olanzapine concentrations with the observed olanzapine concentrations for each study. Most of the observed concentrations are within the model predicted concentration range (5th to 95th percentile) (Figure HGMF.7.7).



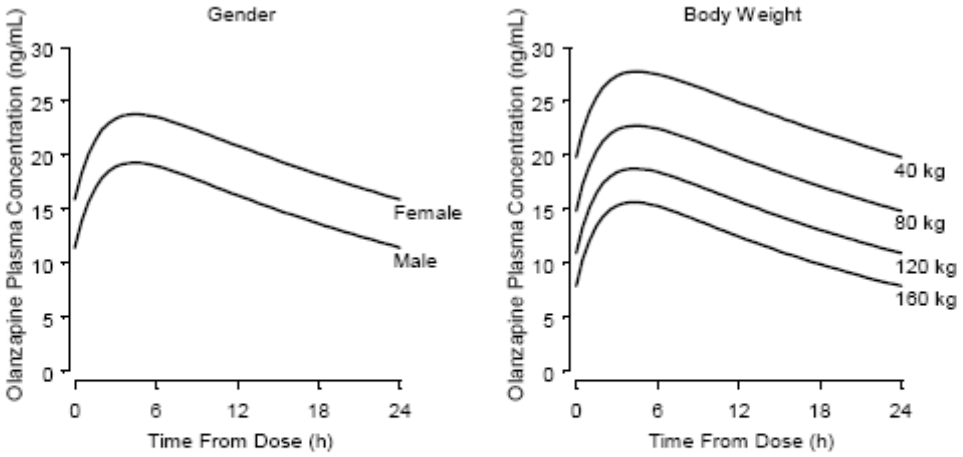
Note: Solid lines represent the 5th, 50th, and 95th percentile of the predicted olanzapine concentration-time profiles obtained simulating 1000 patients. Symbols represent observed olanzapine concentration.

Figure HGMF.7.7. Comparison of model predicted olanzapine concentration and observed olanzapine concentration by dose.

Overall Conclusions

Effects of Gender

Gender had a significant influence on CL/F. Inclusion of gender as a covariate reduced inter-patient variability from 45.9% to 40.5%. The CL/F of olanzapine in male patients is approximately 29% higher as compared with the female patients. Thus, on average, female patients receiving the same olanzapine dose as male patients are predicted to have approximately 29% higher steady state olanzapine concentrations. The predicted effect of gender on olanzapine concentrations for typical population is shown in(Figure HGMF.7.6).



Note: Gender: Predictions shown at the median body weight.
Body weight: Predictions show the effect of body weight on a female patient.

Figure HGMF.7.6. Final population pharmacokinetic model. Predicted effect of covariates on plasma olanzapine concentrations at 10-mg olanzapine dose.

Variability in Olanzapine Pharmacokinetics

Variability in the final population pharmacokinetic model reflects the combination of inter-patient variability in pharmacokinetic parameters and intra-patient variability characterized by residual error. The interpatient variability in CL/F and V/F is 41% and 65%, respectively and the residual error is 27% (Table HGMF.7.4). The model predicted olanzapine concentrations at various doses of olanzapine are summarized in (Table HGMF.7.5). The maximal olanzapine concentration at steady state (Cmax,ss) ranged from 7.81 ng/mL to 146 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg) in the dose range of 5 to 20 mg. The mean time of Cmax,ss was 6.6 hours. The minimal olanzapine concentration at steady state (Cmin,ss) ranged from 5.51 ng/mL to 86.2 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg).

Table HGMF.7.5. Summary of Predicted Steady-state Olanzapine Concentrations Following Simulated Once-Daily Dosing

	C_{maxss} (ng/mL)	C_{minss} (ng/mL)	t_{maxss} (h)
5-mg			
Geometric Mean	16.6	10.8	6.55
Geometric CV%	49.7	43.1	7.38
5th Percentile	7.81	5.51	5.79
50th Percentile	16.7	10.8	6.56
95th Percentile	36.4	21.5	7.37
10-mg			
Geometric Mean	33.3	21.7	6.55
Geometric CV%	49.7	43.1	7.38
5th Percentile	15.6	11.0	5.79
50th Percentile	33.5	21.6	6.56
95th Percentile	72.8	43.1	7.37
15-mg			
Geometric Mean	49.9	32.5	6.55
Geometric CV%	49.7	43.1	7.38
5th Percentile	23.4	16.5	5.79
50th Percentile	50.2	32.4	6.56
95th Percentile	109	64.6	7.37
20-mg			
Geometric Mean	66.6	43.3	6.55
Geometric CV%	49.7	43.1	7.38
5th Percentile	31.2	22.0	5.79
50th Percentile	66.9	43.2	6.56
95th Percentile	146	86.2	7.37

Abbreviations: CV = coefficient of variation

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

(Study HGAJ, 912 patients) which was a study comparing Olanzapine and Haloperidol in the treatment of Schizophrenia.

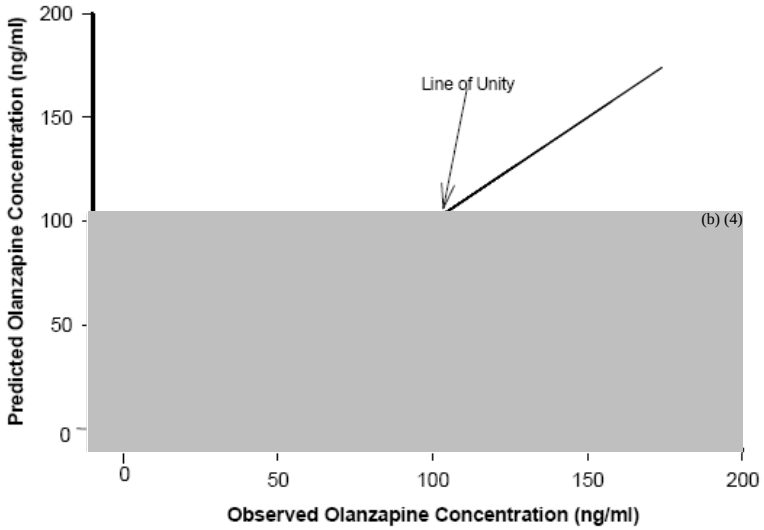
The results from study HGAJ is presented in the following Table: HGMF7.6

Table HGMF 7.6 Population pharmacokinetic parameters and 90% CI from adult study HGAJ

NONMEM Parameter Estimates		
Parameter	Parameter Value	95% Confidence Interval[d]
Cl_1[a] (L/hr)	13.50	12.61 - 14.39
Cl_2_Male_Smoker[b](L/hr)	28.40	27.28 - 29.52
Cl_2_Female_Smoker[b] (L/hr)	23.06	22.15 - 23.97
Cl_2_Male_Nonsmoker[b] (L/hr)	18.01	16.86 - 19.15
Cl_2_Female_Nonsmoker[b] (L/hr)	12.01	11.35 - 12.68
V_Male_Smoker (L)	1360.0	1196.13 - 1523.87
V_Female_Smoker (L)	961.52	792.24 - 1130.80
V_Male_Nonsmoker (L)	918.00	801.92 - 1034.08
V_Female_Nonsmoker (L)	788.80	688.67 - 888.93
P[c]	0.731	0.679 - 0.783

a= Low clearance population
b = High clearance population
c = Fraction of patients in high clearance population
d = Determined from objective function mapping

Predicted vs Observed Olanzapine Concentrations Including The Extreme Outliers In The Final Model (Study HGAJ)



The firm compared the distributions of CL/F and V/F statistically using the Kolmogorov-Smirnov test, a nonparametric method. The test showed that were significantly different in adolescent and adult population ($p<.001$). The common area under the two distributions (adolescent and adult) of Figure HGMF.7.8 represents the proportion of patients having comparable values. Approximately 77% of the adolescent and adult patients had comparable CL/F estimates and approximately 69% of the patients had comparable V/F. The typical values (for example, geometric mean) of CL/F and V/F in adolescent patients are 21% and 17% lower than in adults. It should be noted that in adults, gender and smoking had a significant effect on CL/F and V/F while in

adolescents, gender and body weight had a significant effect. Thus, the effect of body weight on CL/F in adolescent patients and the high proportion of nonsmokers in adolescent patients (78%in adolescents versus 40% in adults) may explain the differences in oral olanzapine pharmacokinetics observed in these populations.

The observed steady state olanzapine concentrations in adolescent patients were also compared with those observed in adults (Study HGAJ). As noted above, the median steady state olanzapine concentrations in adolescent patients were slightly higher than those in adults at each dose (Figure HGMF.7.9). However, there is considerable overlap in the olanzapine concentration distribution in adolescents and adults. At 20 mg dose, olanzapine concentrations in a few adolescent patients exceeded the maximum concentration observed at 20 mg in adults. Steady state olanzapine concentrations in adolescent patients up to doses of 15 mg were encompassed within the range of olanzapine concentration (10^{th} percentile after 5 mg and 90^{th} percentile after 20 mg) reported in adults.

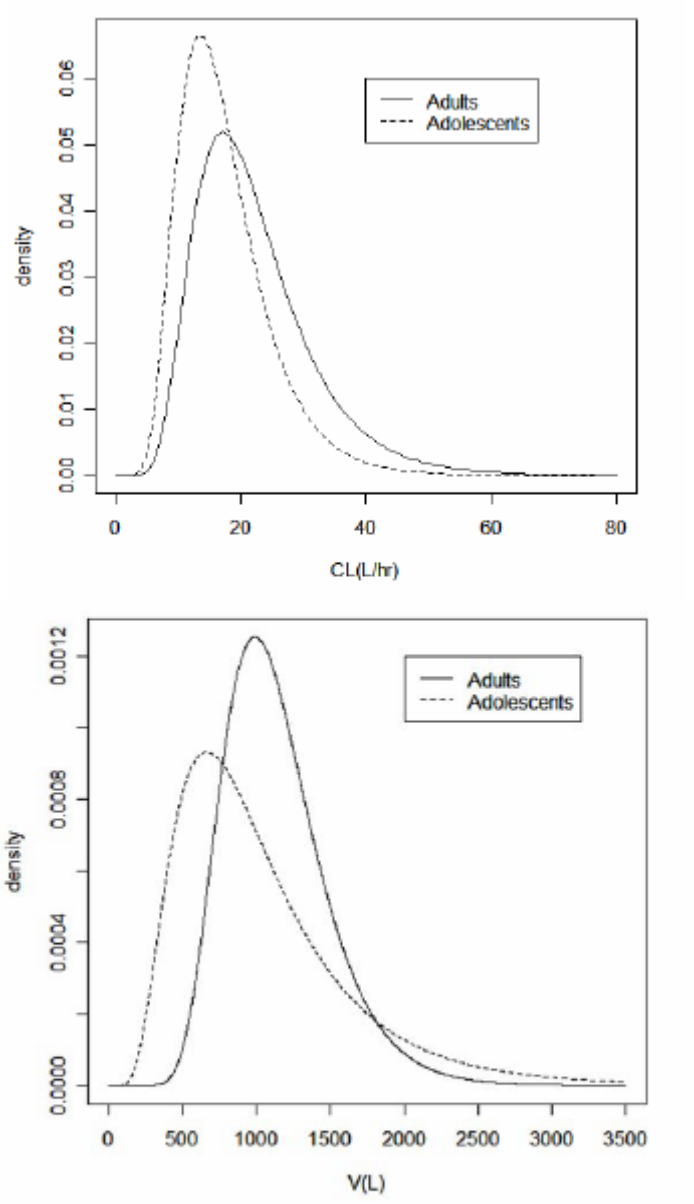
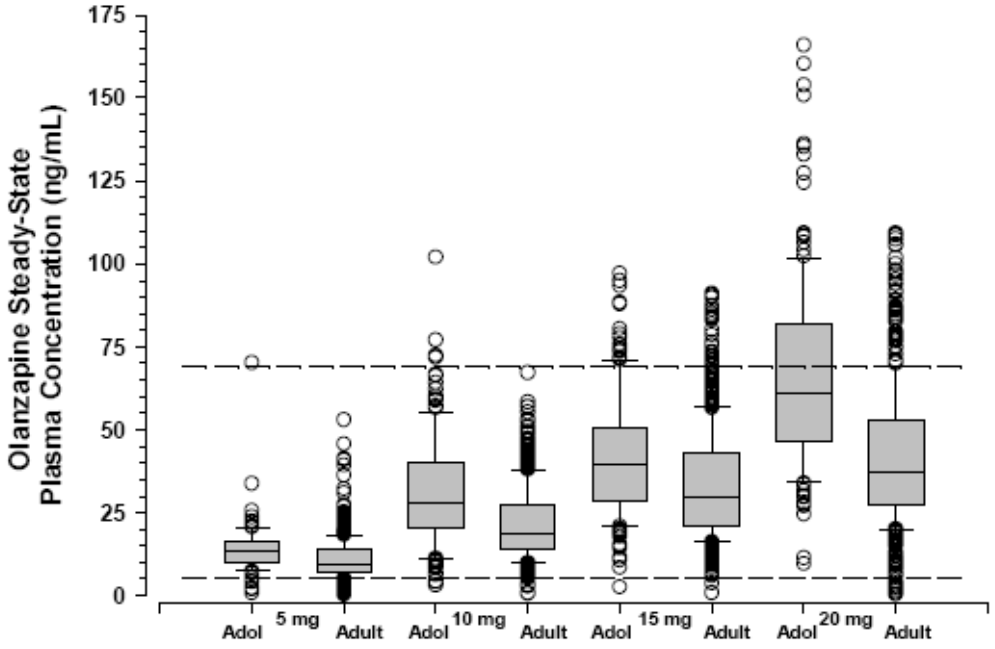


Figure HGMF.7.8. **Distribution of individual olanzapine pharmacokinetic parameters (oral clearance and oral volume of distribution) in adult and adolescent patients.**



Abbreviations: Adol = Adolescent

Note:

The middle line in each box plot represents the median; the top and bottom margins represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points beyond the whiskers represent data in the tails of the distribution.

The dashed lines represent the 10th percentile of olanzapine concentration following 5-mg olanzapine daily and the 90th percentile of olanzapine concentration following oral 20-mg olanzapine daily in adults.

Figure HGMF.7.9. Steady-state olanzapine plasma concentrations in adolescent and adult patients following oral olanzapine administration.

FDA RESULTS

BASE MODEL

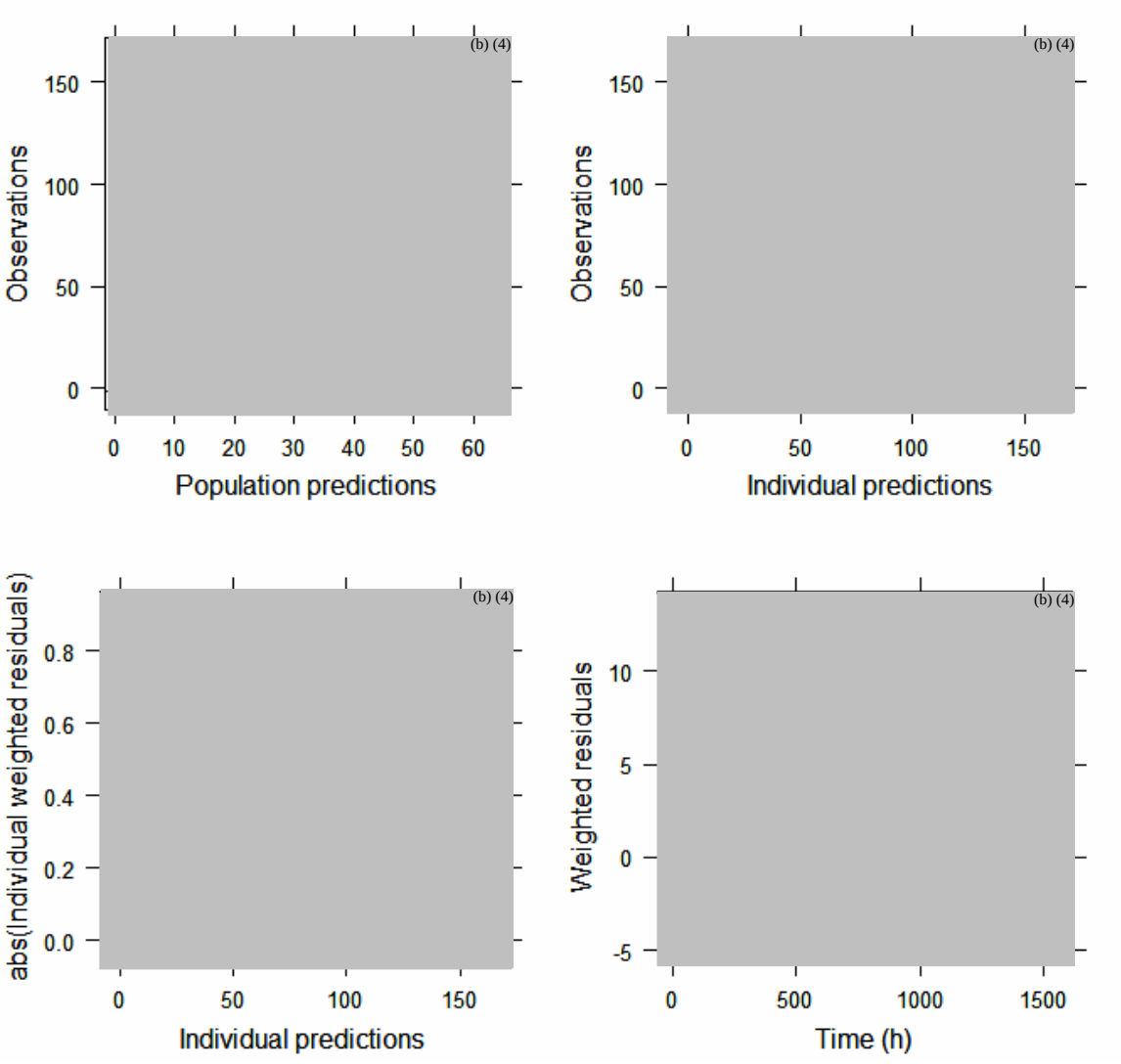


Table Summary of FDA Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)

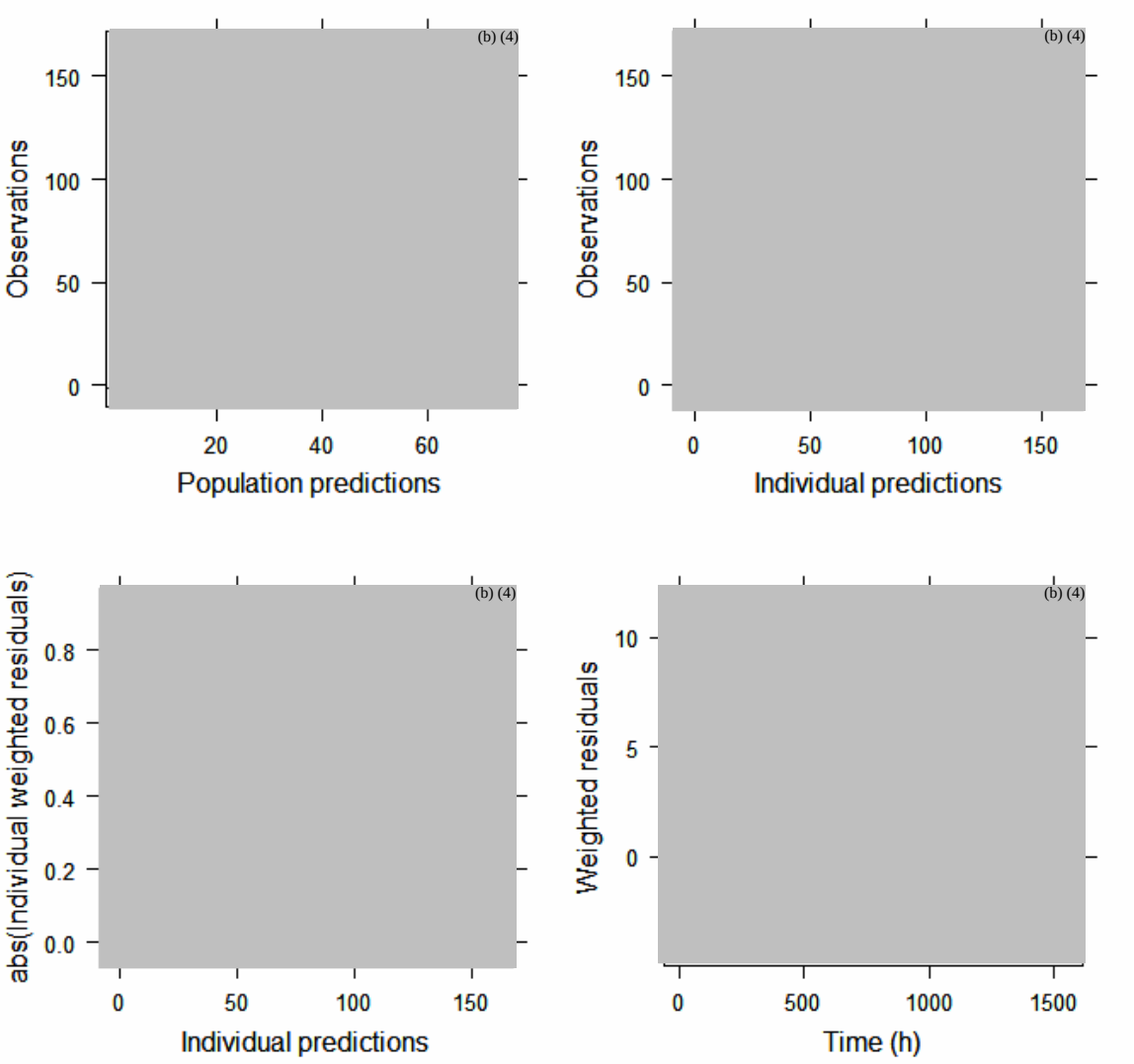
Units Estimate		%SEE
Pharmacokinetic Model		
Absorption rate constant, Ka hr-1	0.543 (Fixed)	-
Oral clearance, CL/F L/hr	16.3	4.61
Oral Volume of Distribution, V/F L	879	17.1
Interpatient Variability		
CL/F %	43.7	15.9
V/F %	62.2	42.3
Covariance between CL/F and V/F -	0.258	22.5
Residual Error		
Proportional %	27.0	13.7

Abbreviations: SEE = standard error of the estimate.

FDA Values all agree with sponsor for the Base model

Table Summary of FDA Pharmacokinetic Parameters for the Final Population Model (Studies HGCS, HGCR, HGGC, HGMF)

Units Estimate		%SEE
Pharmacokinetic Model		
Absorption rate constant, Ka hr-1	0.543 (Fixed)	-
Oral clearance, CL/F L/hr	13.66	456
Effect of Gender on CL/F	0.288	1191
Effect of Weight on CL/F	0.00585	80.7
Oral Volume of Distribution, L	899	993
Interpatient Variability		
CL/F %	38	401
V/F %	60	1291
Covariance between CL/F and V/F -	0.27	
Residual Error		
Proportional %	27	599
Abbreviations: SEE = standard error of the estimate.		



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FDA's PROPOSED LABEL CHANGES

794 12.3 Pharmacokinetics

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents had a lower average body weight compared to adults, resulting in average olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients.

Comments:

1The base model results were consistent with those from the firm, however for the final model only the mean parameter values were in agreement. The variability of the data was much less with the firm's results. When OCP ran the control stream with WINGS OCP obtained a var/cov matrix file but when it was run under NMFE5 it terminated prior to the var/cov step. OCP was informed by the Pharmacometrics Division Director that computational differences were sometimes observed between different compilers and further resolution of the reason for the differences was not necessary.

2.Based upon visual comparison of the observed vs fitted graphs for studies HGAJ in adults and the current study, the graphical results indicate higher olanzapine levels in adolescents than in adults.

SIGNATURES

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 20592, HFD-860(Mehta, Baweja, Jackson)
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References

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Mandema JW, Verotta D, Sheiner LB. 1992. Building population pharmacokineticpharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm 20(5):511-528.

Appendix I

Results from prior Adult Data

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/s/

Andre Jackson
3/27/2007 08:35:38 AM
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Raman Baweja
3/27/2007 12:16:22 PM
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