

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-086**

**CLINICAL PHARMACOLOGY and**  
**BIOPHARMACEUTICS REVIEW(S)**

DEC 7 1999

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

NDA: 21-086 Submission Dates: 3/1/99, 5/5/99

Generic Name: Olanzapine  
 Brand Name: Zyprexa™ Zydys™  
 Strengths: 5 mg, 10 mg, 15 mg and 20 mg Tablets  
 Formulation: Orally Rapid Disintegrating Tablets (RDT)  
 Indication of Drug: Psychotic Disorders  
 Sponsor: Eli Lilly and Company  
 Type of Submission: NDA (New Dosage Form)  
 Reviewer: Hong Zhao, Ph.D

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**SYNOPSIS (Question-Based)**

**What is the active moiety?**

Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine class.

**What are the dosage form, strengths and dosing regimen?**

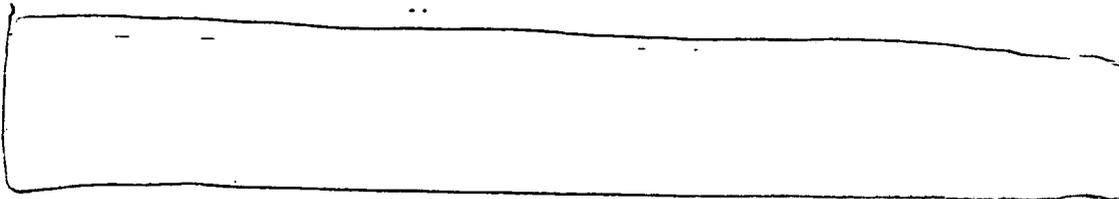
The dosage form is a rapidly disintegrating tablet available as 5-, 10-, 15- and 20-mg tablets, dosing at 5 to 20 mg once-a-day.

**Will this dosage form be marketed for pediatric population?**

No. Safety and effectiveness of the drug in pediatric patients have not been established.

**What are the basic pharmacokinetic characteristics of olanzapine?**

Pharmacokinetics of olanzapine described here is from the current labeling for Zyprexa IR tablets. Olanzapine is well absorbed and reaches peak concentrations in 3-5 hours following an oral dose. It is eliminated extensively by first pass metabolism, with ~ 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Olanzapine displays linear kinetics over the clinical dosing range. Its half-life is 30 hours (21 to 54 hours) and apparent plasma clearance is 25 L/hr (12 to 47 L/hr). Olanzapine is extensively distributed throughout the body, with a volume of distribution of ~ 1000 L. It is 93% bound to plasma proteins, binding primarily to albumin and alpha 1-acid glycoprotein.



**What are the metabolic pathways?**

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. 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.

**Is the major metabolite active?**

No. Both metabolites lack pharmacological activity at the concentrations observed in humans.

**Is there any dosage adjustment for olanzapine in special populations?**

No. However, the lower starting dose (5-mg) is recommended for patients with the combination of the following factors (nonsmoking female patients with age >65 years) since these factors may result in slower metabolism.

*Age:* The mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly (<65 years).

*Gender:* Clearance of olanzapine is approximately 30% lower in women than in men.

*Smoking:* Olanzapine clearance is about 40% higher in smokers than in non-smokers, although dosage modifications are not routinely recommended.

**Are there any clinical studies in this NDA?**

No. Three bioequivalence studies have been conducted to support the approval of this new dosage form (RDT).

**What is the reference product?**

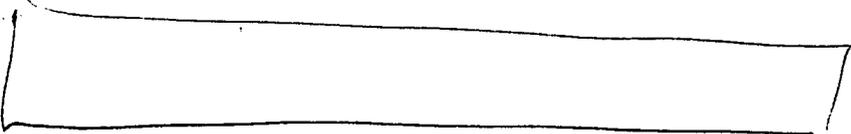
Olanzapine was approved (NDA 20-592) in a solid oral dosage form (IR tablet) as Zyprexa™ on September 30, 1996 for the treatment of the manifestations of psychotic disorders.

**What is the study design for the three bioequivalence studies?**

They were all single dose, open-label studies with a crossover design and with a washout period of 13 days between treatments.

**What dose strengths were studied in these bioequivalence studies?**

All dose strengths except 15-mg tablet, were used in the BE studies.



**What conclusion can be made from these bioequivalence studies?**

The 90% confidence intervals (CI) for the ratio of mean values of  $C_{max}$ ,  $AUC_{0-4}$  and  $AUC_{0-∞}$  from these three bioequivalence studies were all within the conventional bioequivalence limits of 0.80 to 1.25. Therefore, the conclusion is that (a) the 5-mg RDT is bioequivalent to 5-mg SDT, (b) 20-mg RDT is bioequivalent to 4x5-mg SDT, and (c) 10-mg RDT<sub>x</sub>, and 2x5-mg RDT<sub>A</sub> are bioequivalent to 2x5-mg SDT.

**What is the impact of the presence of amorphous olanzapine in the tablet on the bioavailability?**

An increased amount of amorphous olanzapine in the tablet can occur when critical steps in the manufacturing process take longer to complete. The bioequivalence study (FID-EW-LOAU) demonstrated that the presence of amorphous olanzapine in the RDT formulation does not appear to affect the bioavailability of olanzapine tablet.

**Are the to be marketed tablets (TBM) the same as the tablets in the BE studies?**

Yes.

**How is the 15-mg tablet linked to the other strengths used in the BE studies?**

The approval of the 15-mg tablet, which was not used in the bioequivalence studies, is based on linear kinetics of the drug, compositional proportionality amongst the three tablet strengths (10-, 15- and 20-mg tablets) and similar dissolution performance.

**Is  $f_2$  metric value used to evaluate the similarity of dissolution performance?**

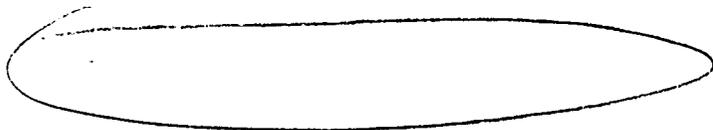
No. Because the RDT tablets of all strengths including 15-mg strength are totally dissolved in 10 minutes.

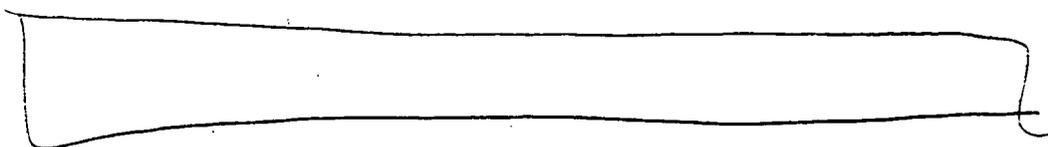
**How is the dissolution medium selected?**

The dissolution medium was selected based on the solubility of the drug substance. The solubility of olanzapine is <0.1 mg/ml in purified water and 20 mg/ml in 0.1N HCL. A comparison of drug release profiles in 0.1N HCL, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and purified water reflects the more limited solubility at neutral pH.

**What is the dissolution method and specification being set?**

The following dissolution methodology and specification are being set for all four strengths of olanzapine Zydis™ tablets:





## RECOMMENDATION

This submission (NDA 21-086) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for meeting OCPB requirements. The sponsor is requested to adopt the dissolution methodology and specification for all four strengths of the olanzapine Zydys™ tablets, as outlined in Comment #3. Also see Labeling Comment (Comment 6) for suggested labeling changes.

## COMMENTS

### Comment 1

The results of three bioequivalence studies show that (a) the 5-mg RDT is bioequivalent to 5-mg SDT, (b) 20-mg RDT is bioequivalent to 4x5-mg SDT, and (c) 10-mg RDT<sub>x</sub>, and 2x5-mg RDT<sub>A</sub> are bioequivalent to 2x5-mg SDT.

### Comment 2

The approval of the 15-mg Zydys™ tablet which was not used in the bioequivalence studies is based on in vitro dissolution data since the formulations for the 10-, 15-, and 20-mg tablets are proportional in composition. RDT tablets of all strengths including 15-mg strength are totally dissolved in 10 minutes.

### Comment 3

Since dissolution data show that the release from all RDT lots tested are 100% in 10 minutes, the recommended specification is NLT 80% in 10 minutes for all strengths. The sponsor is requested to adopt the following dissolution methodology and specification for all four strengths (5-, 10-, 15- and 20-mg) of olanzapine Zydys™ tablets:



m

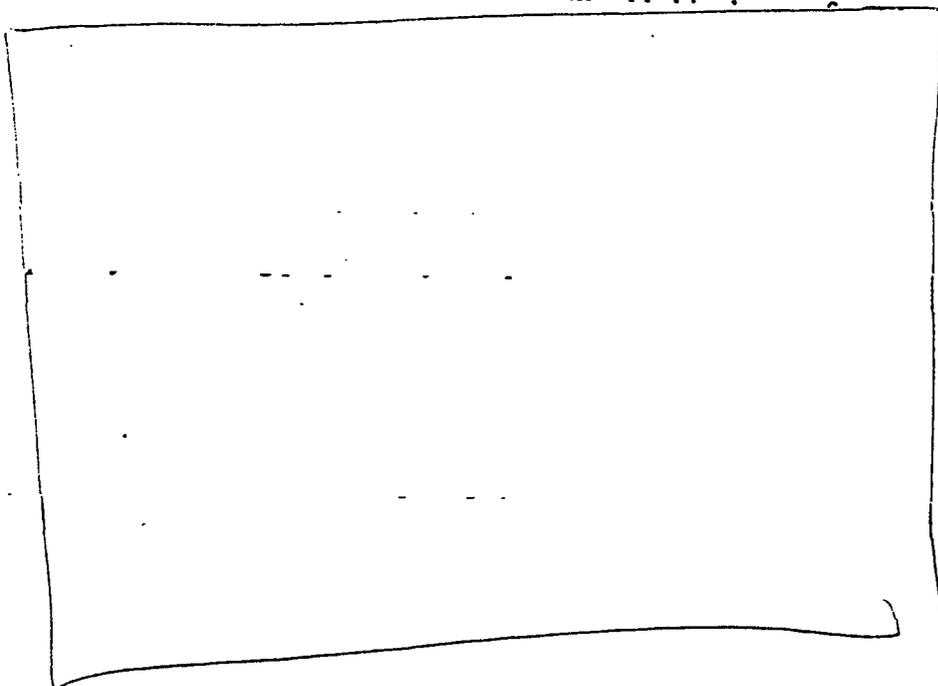
### Comment 4

AUC<sub>0-t</sub> was calculated from measured (observed) concentration values, while the regression line predicted concentration was used instead of observed value for the last measurable plasma sample in AUC<sub>0-∞</sub> calculation. The results of recalculated AUC<sub>0-∞</sub> values using observed C<sub>last</sub> for Study LOAU show that the AUC<sub>0-∞</sub> values are nearly identical to that calculated using extrapolated C<sub>last</sub>.

**Comment 5**

In the three studies included in this NDA, the olanzapine Zydys™ tablet was administered to subjects by placing the tablet on the tongue and allowing it to disperse in the subject's mouth without water. This would be considered the dosing scenario most different from administration of a Zyprexa™ tablet, which is taken with 100 ml of water. Since buccal absorption appears minimal, administration of the olanzapine RDT by placing the tablet on the tongue and allowing it to disperse in the subject's mouth and being swallowed with or without water should not alter the bioequivalence of the olanzapine RDT formulation to the standard oral tablet.

**Comment 6: Labeling Comment**



**APPEARS THIS WAY  
ON ORIGINAL**

## INTRODUCTION

Olanzapine is a selective monoaminergic antagonist with high affinity binding to subtypes of serotonin, dopamine, and other receptors. Olanzapine tablets were approved (NDA 20-592) as Zyprexa™ on September 30, 1996 for the treatment of the manifestations of psychotic disorders.

As a product-line extension, olanzapine Zydis™, an orally rapid disintegrating tablet (RDT) was developed. The olanzapine Zydis™ tablet disperses rapidly when placed on the tongue and is difficult to remove from the mouth after dispersal occurs. The availability of the olanzapine Zydis™ tablet will improve compliance and increase convenience for schizophrenic patients.

Three bioequivalence studies have been conducted and the results are presented in this NDA to support the approval of olanzapine Zydis™ 5-mg, 10-mg, 15-mg, and 20-mg tablets. The sponsor claims that these three studies have shown the olanzapine Zydis™ and Zyprexa™ tablets are bioequivalent in rate and extent of absorption and are, therefore, interchangeable dosage forms. The approval of the 15-mg olanzapine Zydis™ tablet which was not used in the bioequivalence studies will be based on in vitro dissolution data since the formulations for the 10-, 15-, and 20-mg tablets are proportional in composition (see Appendix I).

## SUMMARY OF BIOPHARMACEUTICAL STUDIES

### Review of the Bioequivalence Studies

#### What is the design of these bioequivalence studies?

Three bioequivalence studies were all open-label, crossover in design with a 13-day washout period between treatments. The treatments are listed below:

Study #	Treatment				
	RDT Tablet	Standard Tablet	<sup>1</sup> RDT <sub>A</sub>	<sup>2</sup> RDT <sub>x</sub>	N
-LOAJ	5-mg	5-mg			20 (19, M&F) <sup>3</sup>
-LOAL	20-mg	4x5-mg			23 (20, M)
-LOAU		2x5-mg	2x5-mg	10-mg	24 (20, M)

<sup>1</sup>RDT<sub>A</sub> represents tablet with 24.7% amorphous content; <sup>2</sup>RDT<sub>x</sub> represents tablet with >94.8% crystalline content, which is identical with respect to crystalline content to the tablets in the LOAJ and LOAL studies; M and F represent male and female; the number in the bracket represents the number of subjects who completed these studies. Of the seven subjects who withdrew from these studies, one was for personal reason and the rest were due to adverse events.

**Composition and unit formula for Olanzapine Zydis™ Tablet**

<b>Ingredient</b>	<b>5-mg</b>	<b>10-mg</b>	<b>15-mg</b>	<b>20-mg</b>
	<b>(mg/unit dose) (% of tablet weight)</b>			
<b>Olanzapine</b>	<b>5.00(32.26)</b>	<b>10.00(41.67)</b>	<b>15.00(41.67)</b>	<b>20.00(41.67)</b>
<b>Gelatin</b>				
<b>Mannitol</b>				
<b>Aspartame</b>				
<b>Sodium Methyl Paraben</b>				
<b>Sodium Propyl Paraben</b>				
<b>Total wt (% Wt)</b>				

**APPEARS THIS WAY  
ON ORIGINAL**



# F1D-EW-LOAJ

## 5-mg RDT vs. 5-mg SDT

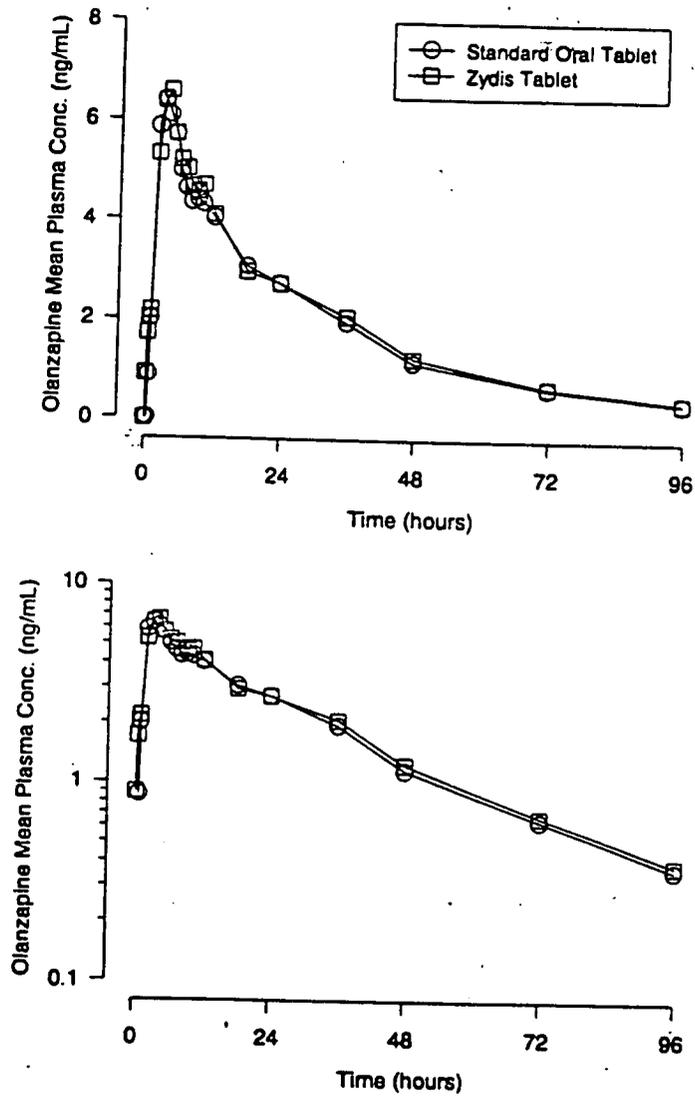


Figure A.

Mean plasma concentrations of olanzapine following a single oral dose of 5 mg olanzapine as a standard oral tablet or as a Zydys™ tablet (n=19 subjects).

# F1D-EW-LOAL

## 20-mg RDT vs. 4x5-mg SDT

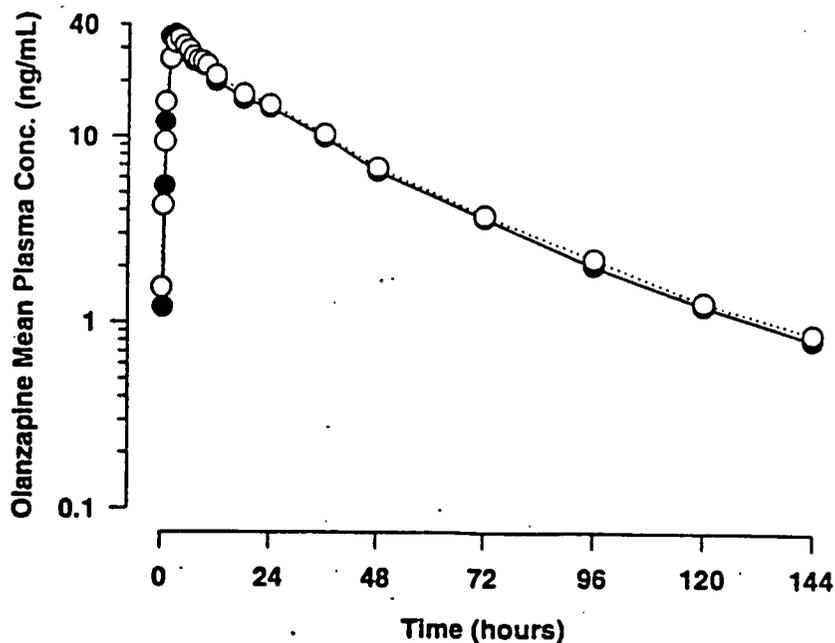
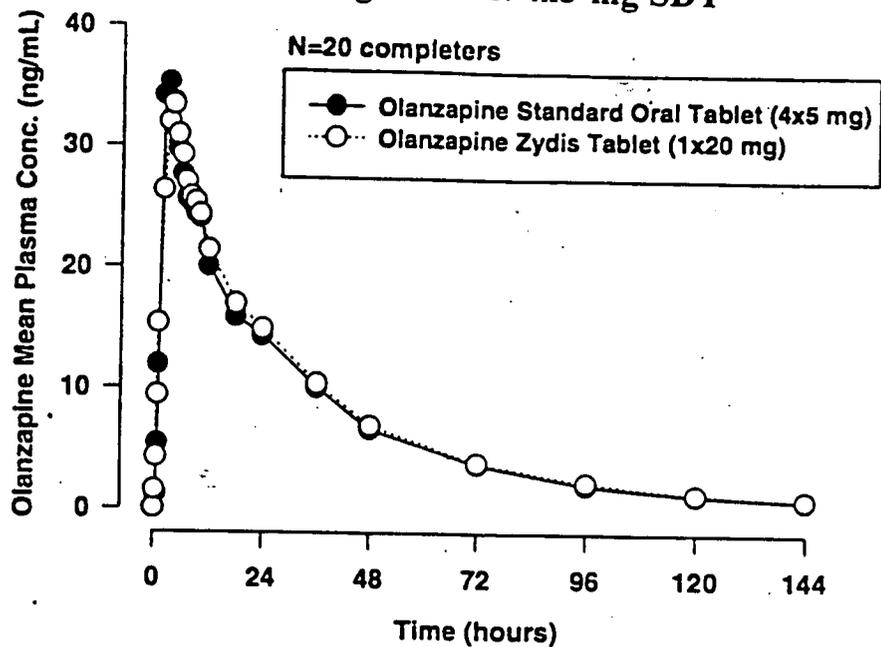


Figure A.

Mean plasma concentrations of olanzapine following a single oral dose of 20 mg olanzapine as a standard oral tablet or as a Zydis™ tablet (N=20 subjects).

# F1D-EW-LOAU

10-mg RDT<sub>x</sub>, 2x5-mg RDT<sub>A</sub> vs. 2x5-mg SDT

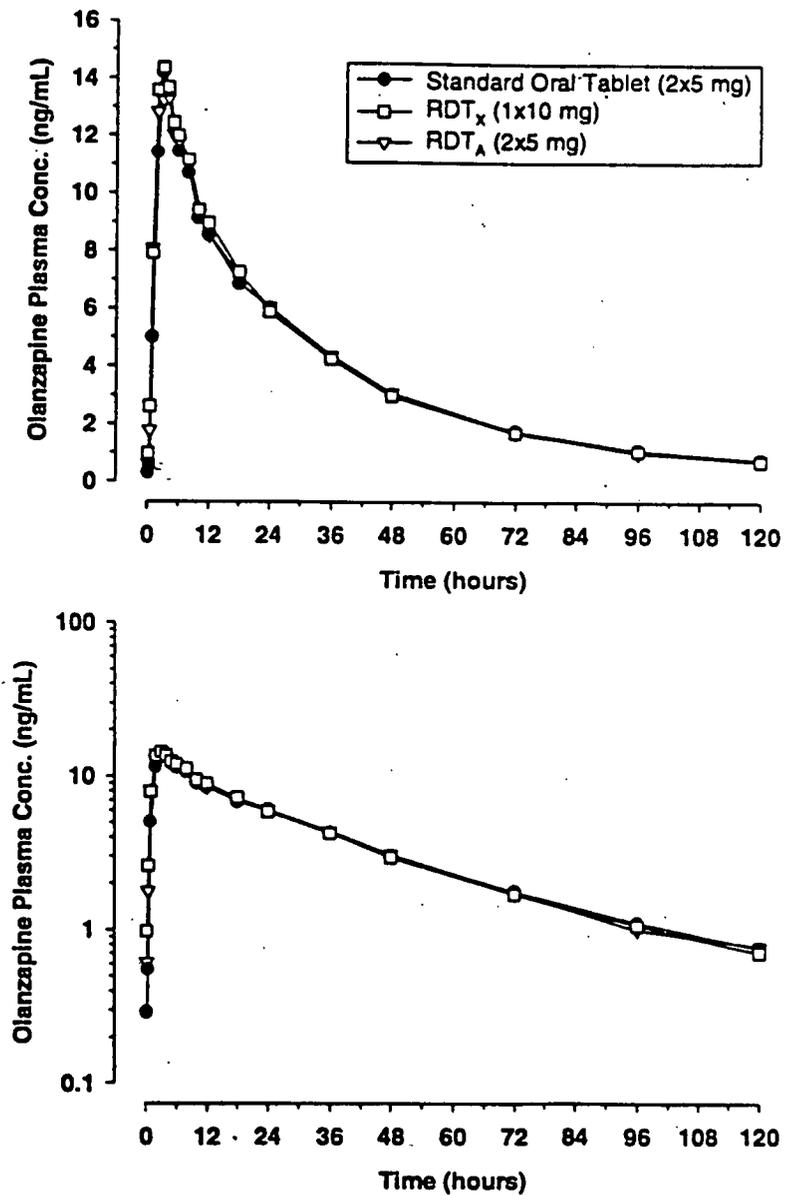


Figure A.

Mean olanzapine plasma concentrations following a single oral dose of 10 mg olanzapine as a standard oral tablet, RDT<sub>x</sub>, or RDT<sub>A</sub> (N=20 subjects).

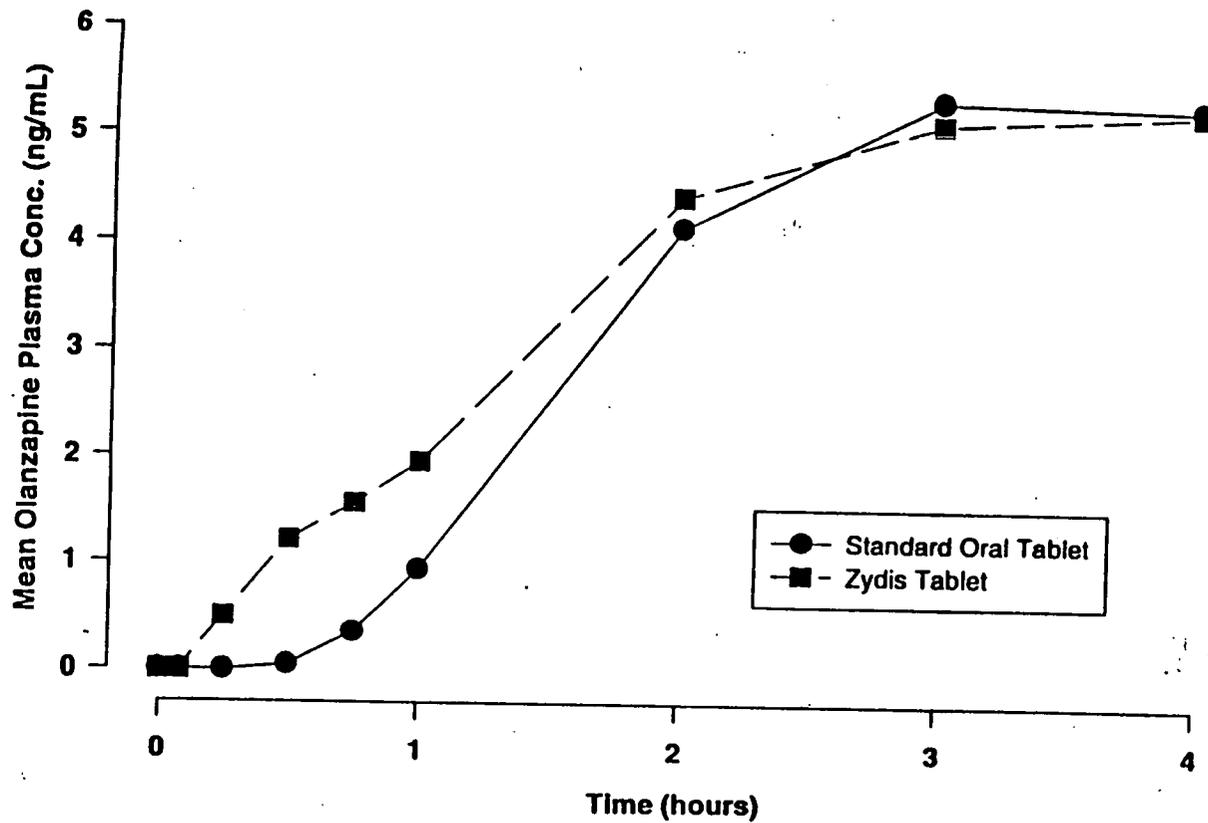
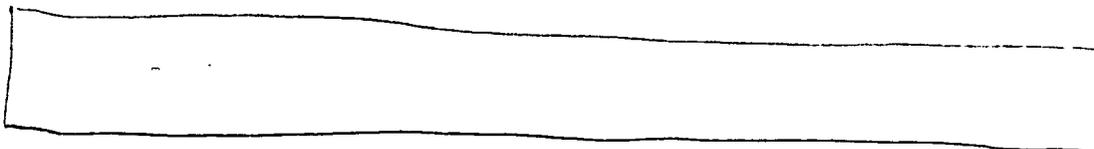


Figure 29.

Olanzapine mean plasma concentrations during the absorption phase (0 to 4 hours) for all subjects completing the study (N=19).

***Is the analytical method validated?***



***What conclusions can be made from these BE studies?***

- The results of three bioequivalence studies show that 90% confidence intervals for the ratio of mean values of  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were within the conventional bioequivalence limits of 0.80 to 1.25. Therefore, the conclusion is that (a) the 5-mg RDT is bioequivalent to 5-mg SDT, (b) 20-mg RDT is bioequivalent to 4x5-mg SDT, and (c) 10-mg RDT<sub>x</sub>, and 2x5-mg RDT<sub>A</sub> are bioequivalent to 2x5-mg SDT.
- Other pharmacokinetic parameters ( $T_{max}$ ,  $t_{1/2}$ ,  $V_d$  and  $CL_p$ ) are also comparable between RDT tablets and Standard tablets.
- Intersubject variability for  $C_{max}$  and AUC values \_\_\_\_\_ and intrasubject variability ranged from \_\_\_\_\_.
- The presence of amorphous olanzapine in the RDT formulations does not appear to affect the bioavailability of olanzapine tablet.
- There is no substantial buccal absorption for the olanzapine Zydys™ tablet.
- The clinical acceptance of these formulations was similar, and the adverse events appeared to be olanzapine related rather than formulation related. Female subjects did not tolerate olanzapine as well as male subjects in these studies.

**Review of Dissolution Tests**

***What is the dissolution method?***

The dissolution method uses USP \_\_\_\_\_ maintained at 37°C and first-derivative UV spectroscopy.

***How was the dissolution medium selected?***

The dissolution medium was selected based on the solubility of the drug substance. The solubility of olanzapine is <0.1 mg/ml in purified water and 20 mg/ml in 0.1N HCL. A comparison of drug release profiles in 0.1N HCL, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and purified water reflects the more limited solubility at neutral pH.

