Human Metabolism

Process

- Primary
  - Glucuronidation (10-N, 4'-N)
  - 4'-N-demethylation
    (Olanzapine metabolism decreased in non-smokers, females, geriatric population)
  - 2-methyl-hydroxylation
    (Olanzapine metabolism not different in 2D6 deficient subjects)
  - 4'-N-oxidation

Enzyme System

- CYP-P450-1A2
  - 36μM
- CYP-P450-2D6
  - 89μM
- FMO system

Note: No significant in vitro affinity for CYP-P450-2C9, CYP-P450-2C19, CYP-P450-3A

*In vivo drug interaction studies demonstrate no influence of olanzapine on drugs metabolized through these systems
Human Metabolism (continued)

- Secondary Oxidation of 2-hydroxymethyl metabolite
- Further glucuronidation

Olanzapine
Human Metabolites

- 10-N-glucuronide\textsuperscript{a,b}: Major plasma and urinary metabolite
- Olanzapine\textsuperscript{a,b}: 28\% of plasma radioactivity at $T_{\text{max}}$
- 4'-N-desmethylolanzapine\textsuperscript{a,b}: in plasma, 44\% of parent
- 2-hydroxymethylolanzapine\textsuperscript{a}
- Olanzapine-4'-N-oxide\textsuperscript{a,b}
- 4'-N-glucuronide\textsuperscript{b}: Major urinary metabolite
- 2-carboxyolanzapine\textsuperscript{b}
- 2-carboxyglucuronide\textsuperscript{b}
- 2-carboxyolanzapine-4'-N-oxide\textsuperscript{b}
- 2-carboxy-4'-N-desmethylolanzapine\textsuperscript{b}

Note: 4'-N-desmethylolanzapine and 2-hydroxymethylolanzapine have some affinity for $D_2$, $D_1$, 5-HT\textsubscript{2A} receptors; no metabolite studied to date active in vivo

\textsuperscript{a}Detectable in plasma
\textsuperscript{b}Detectable in urine; account for 60\% urinary radiocarbon recovery (54\% total radiocarbon), 3 additional urinary peaks
OLANZAPINE CLINICAL DEVELOPMENT:

Molecule To Drug Candidate
Development Milestones

Synthesis: 4/29/82

IND filed: 7/24/86

First human dose: 9/10/86

First open-label clinical dose: 12/9/88

First double-blind, placebo-controlled efficacy dose: 11/21/91

Completion of core studies: 2/14/95

World wide regulatory submission filed: 9/21/95

Olanzapine
<table>
<thead>
<tr>
<th>Human Exposure (2/14/95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Dose: 3,139</td>
</tr>
<tr>
<td>≥ 1 Month: 1,962</td>
</tr>
<tr>
<td>≥ 6 Months: &gt; 876</td>
</tr>
<tr>
<td>≥ 1 Year: &gt; 301</td>
</tr>
</tbody>
</table>

Olanzapine
Core Studies (All Double-Blind)

- Study 1 (S1)
  - N=152
  - Schizophrenia, inpatient, BPRS_{0-6} ≥ 24
  - 6 weeks
  - Placebo, olanzapine 1 mg/day, olanzapine 10 mg/day

- Study 2 (S2)
  - N=335
  - Schizophrenia, inpatient, BPRS_{0-6} ≥ 24
  - 6 weeks, extension
  - Placebo, olanzapine 2.5 - 7.5 mg/day, olanzapine 7.5 - 12.5 mg/day, olanzapine 12.5 - 17.5 mg/day, haloperidol 10 - 20 mg/day
Core Studies (All Double-Blind)

- **Study 3 (S3)**
  - N=431
  - Schizophrenia, inpatient, BPRS \( 0-6 \geq 24 \)
  - 6 weeks, extension
  - Olanzapine 1 mg/day, olanzapine 2.5 - 7.5 mg/day, olanzapine 7.5 - 12.5 mg/day, olanzapine 12.5 - 17.5 mg day, haloperidol 10 - 20 mg/day

- **Study 4 (S4)**
  - N=1,996 (randomization - 2 olanzapine:1 haloperidol)
  - Schizophrenia/schizophreniform disorder/schizoaffective disorder, in-/outpatient, BPRS \( 0-6 \geq 18 \), or intolerant of current therapy
  - 6 weeks, extension
  - Olanzapine 5 - 20 mg/day, haloperidol 5 - 20 mg/day
Efficacy: BPRS - Total Score (Mean change, LOCF)

Baseline

33.4
41.8
41.7
37.1

Mean Change

S4
S3
S2
S1

Placebo ■ Olanzapine ■ Haloperidol

* p ≤ 0.05 vs placebo
** p ≤ 0.01 vs placebo
*** p ≤ 0.001 vs haloperidol

Olanzapine
Efficacy: BPRS - Positive Score
(Mean change, LOCF)

Baseline

0 12.6 13.3 13.0 10.3
Mean Change

S1 S2 S3 S4

*p ≤ .050 vs placebo
**p ≤ .010 vs placebo

Placebo  Olanzapine  Haloperidol

Olanzapine

Lilly
Efficacy: Negative Symptom Scales (Mean change [%], LOCF)

Baseline (% Max) vs Mean Change [%]

- Placebo
- Olanzapine
- Haloperidol

* p ≤ 0.10 vs placebo
** p ≤ 0.01 vs placebo
*** p ≤ 0.05 vs haloperidol
Acute EPS: Simpson-Angus Scale
(Mean change, LOCF)

Baseline

<table>
<thead>
<tr>
<th></th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change</td>
<td>2.21</td>
<td>1.89</td>
<td>2.54</td>
<td>2.78</td>
</tr>
</tbody>
</table>

!p ≤ .050 vs haloperidol
!!p ≤ .001 vs haloperidol

Legend:
- Placebo
- Olanzapine
- Haloperidol

Olanzapine

Lilly
Acute EPS: Barnes Akathisia Scale
(Mean change, LOCF)
Long-Term Treatment Emergent Dyskinesia

- Methods
  - Double-blind extensions of HGAD, E003, HGAD
    - Median exposure: OLZ - 237 days, HAL - 203 days (range 6 wk - 3+ yr.)
  - Definition: Cross-sectional RDC criteria for TD assessed by items 1-7 of AIMS
    - 1+ item ≥ 3, or 2+ items ≥ 2
  - No historical or secondary condition of TD and failure to meet cross-sectional RDC criteria at baseline

Olanzapine

Lilly
Long-Term Treatment Emergent Dyskinesia
(continued)

- Results

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine (N=707)</th>
<th>Haloperidol (N=197)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal persistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any postbaseline assessment</td>
<td>50 (7.1%)</td>
<td>32 (16.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Final AIMS assessment</td>
<td>16 (2.3%)</td>
<td>15 (7.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Final 2 AIMS assessment</td>
<td>7 (1.0%)</td>
<td>9 (4.6%)</td>
<td>.003</td>
</tr>
</tbody>
</table>
Adverse Events vs Placebo (p ≤ 0.05 & ≥ 2%)

<table>
<thead>
<tr>
<th>S1</th>
<th>Olanzapine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anorexia</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Delusions</td>
<td>0%</td>
</tr>
</tbody>
</table>
# Adverse Events vs Placebo

\( p \leq 0.05 \& \geq 2\% \)

<table>
<thead>
<tr>
<th></th>
<th>S2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olanzapine</strong></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>39.1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17.4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.5%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10.1%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>16.2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1.5%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>5.9%</td>
</tr>
</tbody>
</table>
# Adverse Events vs Haloperidol

\[(p < .05 \& \geq 2\%)

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>7.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>4.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>6.5%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10.4%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Tremor</td>
<td>3.6%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>3.2%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.7%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>
### Adverse Events vs Haloperidol

\((p < .05 \& \geq 2\%)\) cont.

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal syndrome</td>
<td>2.1%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Increased salivation</td>
<td>2.2%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.0%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Joint disorder</td>
<td>1.9%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>2.3%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.5%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
Vital Signs, Weight, ECG

- No change in resting vital signs
- Slight increase in orthostatic heart rate increase
- No change in orthostatic blood pressure decrease
- Weight gain dose related
- ECG: no change or slight increase in sinus rate with a corresponding decrease in QT interval
Laboratory Analytes

- Transient, possibly dose-related increase in hepatic transaminases
  - No clinical symptoms
  - No discontinuations during acute phase of S4
- No evidence of hematotoxicity
- Mild, transient dose-related increase in prolactin

Olanzapine
Conclusions:

**Efficacy**

- Excellent overall and positive symptom efficacy
- Superior negative symptom efficacy

**Olanzapine**
Conclusions:

Safety

- Mild sedation
- Mild anticholinergic effects
- Minimal subjective dizziness without orthostasis
- Some transient, asymptomatic hepatic transaminase elevations
- Minimal parkinsonism and akathisia with rare dystonias

Olanzapine
Conclusions:

Atypical Profile

- Greater efficacy against negative symptoms than haloperidol

- Rare dystonic reactions and less parkinsonism and akathisia than with haloperidol

- Substantially less prolactin elevation than with haloperidol