Zyprexa - A Major Step Toward A Health Care Solution For Psychosis

GDT/dle

July 20, 1995
Olanzapine Core Impact Team

GTD/dle

July 20, 1995
Presentation Outline

I. Overview Module

II. Concept of the HWT "Lifecycle" and a "Deliverables Matrix"

III. Phased Deliverables by HWT Components

IV. HWT Learning Points

V. Resource Requirements

VI. Issues

VII. Conclusions

VIII. Question Wrap-Up

GDT/dle

July 20, 1995
Presentation Objectives

- The customer
- Recognition of the strategic importance of Zyprex to Lilly shareholders
- Road to major market submissions
- From submission to launch (and beyond)
- HWT approach enhanced both quality and speed; efficiency, and employee satisfaction/ownership

[approved for 2 category one credits by the ZMA]

July 20, 1995
Schizophrenia

“In schizophrenia, all of the normal mental processes - sensation, perception, language, emotion, interpersonal relationships - appear to go complete awry. People with the disorder lose touch with the real world. They hear voices that are not there, speak a language that does not exist, laugh for no reason, or sit motionless for hours on end. The entire human personality is laid waste, and the psychological and social building blocks of every day life are crushed, often beyond recognition.”


GDT/dje

July 20, 1995
Schizophrenia

I. Background

• **worldwide prevalence** - 1 percent
• **neurochemistry** - disturbance of select regional 5-HT and/or DA activity - $1^0$ or $2^0$??
• **pathophysiology** - “intrinsic wiring abnormality”
• **onset** - mid-teens to young adulthood
• **course** - chronic in more than half of victims
Schizophrenia

• Assessing the burden
  – 370,000 years of lost productivity for U.S. men
  – accounts for nearly 3% of total health care expenditure
    » ex. half the cost of MI annually despite 1/12th as common
  – per patient costs - exceed $20,000 per year
  – approximately 10% of the totally and permanently disabled in the U.S. are people with schizophrenia

GDT/dle

July 20, 1995
Schizophrenia

II. Symptomatic Presentation

Positive
- delusions
- hallucinations
- disorganized speech
- catatonia

Negative
- affective flattening
- alogia
- avolition
- anhedonia

Social/occupational dysfunction
- work
- interpersonal relationships
- self-care

July 20, 1995
The Neuroleptic Market

$1406
WW USD Sales (millions)
1993 WW USD Growth = 5%

2665 DOT (millions)
1993 WW Growth = 4%

July 20, 1995
Market Opportunity: The Patient’s Perspective

- Superior efficacy for negative symptoms
- A lower incidence of adverse events eg, EPSE, hematoxicity
- Reversal of poor compliance leading to relapse, rehospitalization, and “downward drift”
Market Opportunity: The Analyst’s View

GDT/dle

July 20, 1995
A Major New Market Opportunity

- The market for schizophrenia drugs appears to be underserved and highly dissatisfied with existing drugs.
- Currently a one billion dollar market but the potential to be an estimated $3.5 billion market by 2000.
- Abbott Labs, Eli Lilly, Pfizer and Zeneca appear to be in a close race to introduce the next major drug. “We believe that Eli Lilly’s olanzapine is the best overall new drug on the horizon.”

1994
Richard R. Vietor, CFA          Nigel J. G. Barnes
First Vice President U.S.A.     First Vice President U.K.

Merrill Lynch & Co.
Global Securities Research & Economics Group
Global Fundamental Equity Research Department

GDT/dle                           July 20, 1995
Stover Haley Burns, Inc.    June 26, 1995

Investment Recommendation: Strong Buy

“We continue to believe that olanzapine will be a drug of major importance for Lilly and likely will emerge as the antipsychotic drug of choice. It could do for the treatment of schizophrenia what Prozac has done for depression.”
Olanzapine Global Forecast

GDT/dle

July 20, 1995
Forecastsed Sales ($mil) in Year 5 (2000)

<table>
<thead>
<tr>
<th>Region</th>
<th>Base Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>$621</td>
</tr>
<tr>
<td>Total Europe</td>
<td>$332</td>
</tr>
<tr>
<td>Japan</td>
<td>$69</td>
</tr>
<tr>
<td>R.O.W.</td>
<td>$17</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1,039</strong></td>
</tr>
</tbody>
</table>

July 20, 1995
Competitive Update

I. Marketed Competition - Generic Neuroleptics
   Mechanisms
   • conventional D₂ antagonists of varying potency/specificity
     without A₉:A₁₀ selectivity
   Advantages
   • known to the practitioner
   • cost
   • effective against positive symptoms for some patients
   • multiple formulations
   Drawbacks
   • absent to limited treatment response in 35-50% of patients
   • no demonstrable long term benefit in negative symptoms
   • no effect or exacerbation of comorbid mood symptoms
   • high incidence of EPSE leading to over 50% non-compliance during maintenance therapy
   • 15% tardive dyskinesia

GDT/dle

July 20, 1995
Competitive Update II

2. Marketed Competition - Recent
   a. Clozaril (Sandoz)
      • mechanism - $5-HT_2$, $D_1$, $D_2$, $D_4$, $M_{1.5}$, $\alpha_{1,2}$
      • indication - patients refractory to conventional treatment
      • safety - agranulocytosis (1.3%); orthostasis
        seizure (5.0%); hypersalivation
      • cost - monitoring ex. first year U.S. $10,500
      • annual sales - $148 million
Competitive Update II

b. Risperdal (JNJ/Janssen)
   • mechanism - 5HT₂, D₂
   • advantages -
     may benefit negative symptoms
     lower incidence of EPSE at bottom of the dose range
   • drawbacks
     curvilinear dose: response (2 - 16 mg)
     haloperidol-like ≥ 6 mg
     requires titration
     administered bid.
     inhibitor of CYP450IID6
   • first year sales $149 million (February launch)
# Competitive Update III

## Compounds in Development (N = 80)

### Closest to Market

<table>
<thead>
<tr>
<th>Product</th>
<th>Mechanism</th>
<th>Company</th>
<th>U.S.</th>
<th>O.U.S.</th>
<th>Critical Assessment</th>
</tr>
</thead>
</table>
| Roxindole EMD49980 | D₂, 5-HT1A Agonist                    | E Merck          | ?    | Phase III (early) | • early efficacy (OL) with low response rate  
|                  |                                       |                  |      |             | • possible negative sx. effect (OL)  
|                  |                                       |                  |      |             | • antidepressant effect (OL)  
|                  |                                       |                  |      |             | • nausea/dizziness                                         |
| Zotepine         | “balanced” dopamine agonist           | Fujisawa         | Reported in Phase II/III | Launched Japan | • BPRS - like haloperidol  
|                  |                                       | Licensed to Boots in U.S. |      |             | • SANS - superior to Hal  
|                  |                                       |                  |      |             | • EPSE - superior to Hal  
|                  |                                       |                  |      |             | • ADR - 1LFT  
| Seroquel™ IC1204636 | A weak D² blocker.                   | Zeneca           | Phase III; NDA submission-end of 1995. | Phase III. | • 1 positive placebo study - weak  
|                  |                                       |                  |      |             | • 1 comparable to chlorpromazine  
|                  |                                       |                  |      |             | • insomnia/sedation  
|                  |                                       |                  |      |             | • sinus tachycardia/LFT  
|                  |                                       |                  |      |             | • ?tox above 500 mg/day                                     |
| Sertindole LU23174 | high affinities for D₂, 5HT₂, and  α-1 receptors-antagonist | Lundbeck, Abbott (US), Shionogi (Japan) | III | III (II Japan) | • two high dose studies separating from placebo (20 mg)  
|                  |                                       |                  |      |             | • titration  
|                  |                                       |                  |      |             | • male sexual dysfunction  
|                  |                                       |                  |      |             | • headache/congestion  
|                  |                                       |                  |      |             | • insomnia/somnolence                                       |
| Ziprasidone CP-88059 | 5HT₂, D₂ antagonist                   | Pfizer           | III  | ?           | • conventional D2 occupancy (85%) by PET  
|                  |                                       |                  |      |             | • 5T1/2 4-6 hours  
|                  |                                       |                  |      |             | • hi dose comparable to HAL  
|                  |                                       |                  |      |             | • EPSE at higher doses  
|                  |                                       |                  |      |             | • headache                                                 |
Background Milestones

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound Synthesized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project Team Formed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Human Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Efficacy Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development Initiated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPAC Review</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent Issued</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Decision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HWT Team Formation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GDT/dle

July 20, 1995
Primary Indication

Olanzapine is indicated for the management of the manifestations of psychotic disorders* which consist of both positive and/or negative psychotic signs and symptoms.

*”Schizophrenia and related...” in Europe

GDT/dle

July 20, 1995
Critical Success Factors

- Efficacy with respect to positive symptoms
  - decrease in BPRS > placebo
  - percent responders > haloperidol

- Efficacy with respect to negative symptoms
  - decrease in PANS subscale and SANS statistically significant relative to baseline and > haloperidol

- Safety
  - Incidence of tardive dyskinesia < haloperidol
  - Elevation of liver enzymes transient and non-progressive
  - No “Black Box” or mandatory monitoring requirement
Question

Does a heavyweight team have a half-life that is longer than redacted
The Concept of a HWT’s Life Cycle

Formation

Major Submissions

Major Launches

Successful Commercialization 2/3 World’s Major Markets

Stage I

Stage II

Stage III

You are here at present

GDT/dle

July 20, 1995
Key Component Strategies Vary Over The HWT’s Life Cycle

- Visualize HWT deliverables over time via a matrix plan

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key component strategies are integrated to maximize efficiency and ROI

GDT/dle

July 20, 1995
Deliverables Support the Zyprex Heavyweight Team Strategic Initiatives

- Speed to global markets
- Customer focused product development plan
- Redefine standard of care and position Zyprex as the standard for a cost-effective pharmaceutical solution
- Aim for rapid and broad market penetrations
- Accelerate presence in emerging markets
Preclinical
Olanzapine

- In vitro receptor binding

GDT/dle

July 20, 1995
Preclinical

- In vivo behavioral pharmacology
  - CAR to CAT ratio 4:1
  - increase in punished responding
  - $A_{10}$ mesolimbic selectivity
- Blocks NMDA antagonist neurotoxicity
- Identification/characterization of parent/metabolite profiles

...redacted...

- No behavioral activity from metabolites evident

GDT/dle

July 20, 1995
Stage II
Preclinical Strategy - “Leverage The Neuroscience Explosion”

- Potential blockage of NMDA antagonist-induced neurotoxicity
- Atypical neuroleptics and central amygdaloid membrane properties and synaptic potentials
- Olanzapine in a conflict response model
- In vitro binding profiles across regions/subtypes
- Restoration of PCP-induced deficits in prepulse inhibition (sensorimotor gating)

GDT/dle

July 20, 1995
Stage III

Preclinical Strategy - “Better Living (SOPA) Through Chemistry (and Biology)”

More of a good thing
OLANZAPINE CLINICAL DEVELOPMENT:
Molecule To Drug Candidate

July 20, 1995
Clinical Deliverables

- Execute, analyze, and write up a series of core registration studies designed to illustrate olanzapine’s superior profile (safety, efficacy, functional well being, economics) to both
  - (a) placebo and
  - (b) a representative conventional antipsychotic (haloperidol)
Olanzapine

Human Exposure (2/14/95)

>_1 Dose: 3,100

>_6 Weeks: 1,867

>_6 Months: 880

>_1 Year: 321
Efficacy: BPRS - Total Score
(Mean change, LOCF)

Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Olanzapine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>37.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>41.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3</td>
<td>41.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>33.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

GDT/dle
July 20, 1995
Efficacy: Negative Symptom Scales (Mean change [%], LOCF)

Baseline (% Max)

0 43.2 44.2 49.7 41.1

Y

S1 PANSS S2 SANS S3 PANSS S4 PANSS

Placebo Olanzapine Haloperidol

*p ≤ .010 vs placebo
**p ≤ .001 vs placebo
*p ≤ .050 vs haloperidol

GDT/dl

July 20, 1995
Acute EPSE: Simpson-Angus Scale
(Mean change, LOCF)

Baseline

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

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

GDT/dle

July 20, 1995
Clinical Safety Summary

- Only three events occurred ≥ 2% which were statistically significantly more common than Haldol
- Early discontinuations due to ADR comparable to placebo
- No change in resting vital signs
- Significantly less tx. emergent T.D. than with Haldol
- Weight gain dose related; early plateau
- ECG: no clinically significant changes

GDT/dle

July 20, 1995
Laboratory Analytes

- Transient, possibly dose-related increase in hepatic transaminases
  - No clinical symptoms
  - No discontinuations during acute phase of S4 (N = 1995)
- No evidence of hematotoxicity
- Mild, transient dose-related increase in prolactin
- Substantially less prolactin elevation than with haloperidol

GDT/dle

July 20, 1995
Conclusions:

Atypical Profile

- Greater efficacy against negative symptoms than haloperidol. Dose range 5-20 mg once daily. Optimal dose 10-15 mg. No titration to an effective dose.

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

- Superior long term compliance during maintenance therapy with significantly fewer re-hospitalizations
Clinical Deliverables
Stage II and III

I. Clinical Plan

- Institute a “second wave” of clinical investigation ('96, '97) for the following purposes:

  goal 1  optimize pricing decisions
  goal 2  prepare for timely launch in selected type II countries
  goal 3  differentiate product attributes of olanzapine from key competitors

GDT/dle

July 20, 1995
Clinical Deliverables
Stages II and III

goal 4 leverage the recent explosion of clinical and neuroscience activity in the schizophrenias to position Olz as the innovator

goal 5 select and implement “new indications” capable of significantly growing the market potential

goal 6 recognizing local market idiosyncrasies, provide funding to engage key opinion leaders in publication

GDT/dle

July 20, 1995
# Clinical Studies Stages II and III

## Examples - 1996 Plan

<table>
<thead>
<tr>
<th>Objective</th>
<th>Locale</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emerging market registration</td>
<td>Hong Kong/China</td>
<td>Lieh-Mak</td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New indication</td>
<td>global</td>
<td>many</td>
</tr>
<tr>
<td>– mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– psychosis in Alzheimer’s</td>
<td>global</td>
<td>many</td>
</tr>
<tr>
<td>Expand the package insert wording</td>
<td>U.S.</td>
<td>Lieberman, et al,</td>
</tr>
<tr>
<td>– relapse prevention</td>
<td>Neth</td>
<td>Kahn</td>
</tr>
<tr>
<td>– refractory</td>
<td>U.S.</td>
<td>Tamminga</td>
</tr>
<tr>
<td>Commercialization -</td>
<td>multistate</td>
<td>many</td>
</tr>
<tr>
<td>Local opinion leader involvement - templates</td>
<td>global</td>
<td>many</td>
</tr>
</tbody>
</table>

GDT/dle

July 20, 1995
Health Economics

Overall Strategy

The overall objectives of the Health Economics global plan are several-fold:

• Create a greater awareness about the prevalence of the disease, its *poor prognosis* in a significant number of patients and the large *medical and societal costs* attributed to the various stages of the disease.
Health Economics

Overall Strategy

• Provide authorities with the necessary health economic data to document olanzapine’s value regarding registration, formulary inclusion, level of reimbursement, and pricing negotiations

• Publications in support of olanzapine’s advantage in patient outcomes

GDT/dle

July 20, 1995
Health Economics

Studies

• Cost of illness
  Spain, Germany, Italy Belgium/Australia/France

• Quality of life (QLS)
  HGAD, E003, HGAJ, amisulpride-France

• Targeted resource utilization
  HGAJ

• Treatment-resistant patients
  US; Austria/Spain

• Family burden
  Italy

GDT/dle

July 20, 1995
Regulatory
Regulatory Strategy - Stage I
(road to initial submissions)

- Simultaneously prepare and submit dossiers in the US, EU, and Canada on October 1, 1995. Remaining Type I submission will take place within a 30-day window (except Japan)

- Cultivate key relationships with global affiliates and regulatory agencies to facilitate speed of review

- Electronic plus paper submissions where desired

GDT/dle
July 20, 1995
Regulatory Strategy - Stage II (Submission to Major Launches)

- Prioritize a submission strategy for FSC countries to implement within 60 days of UK approval
- Prepare/submit pricing dossiers
- Rigorous preparation for FDA Advisory Panel meeting
- Anticipate/rapid response to regulatory questions
  - central query database
- High quality 120 day safety update (FDA)
- Prompt printing of labels

GDT/dle

July 20, 1995
Regulatory Strategy - Stage III
Post Marketing

- Liaison with regulatory agencies on new indication, labeling expansion, and line extensions

- Help coordinate safety update
  - DEN
  - PMS

- Work with marketing to optimize promotional materials within local guidelines

GDT/dle

July 20, 1995
Japan

- Early Phase II/Late Phase II results encouraging

- Inadequate resources in ELJKK, earthquake and many competitors have resulted in project delays
  - current NDA target of July ‘97 very doubtful

- Heavyweight Team visits/meetings with opinion leaders being planned for Q4 ‘95

GDT/dle

July 20, 1995
CM&C General Strategy - Stage I

Bulk Drug: 4 step synthesis

Tablets: white, round, globally acceptable
2.5, 5, 7.5, 10 mg

Granules: “Fine Granules” for Japan
Doubles as reconstitutable solid for R.O.W. in 2.5, 7.5, and 10 mg sachets

GDT/dle

July 20, 1995
CM&C Strategy

Sourcing Strategy for Marketed Products at Launch

Tippe & EFC-Ark → Kinsale → Basingstoke → Tablets for all markets except N. America

Steps 1&2 BDS

Steps 3&4 BDS

Puerto Rico → Tablets for N. America

Basingstoke → Granules for all markets

GDT/dle

July 20, 1995
CM&C Key Strategies

• Early site involvement in process and method development
• Early validation of bulk and product
• Generate stability data for submission on validation lots
• Use validation lots to supply CT’s where possible
• Bracket dosage strengths for validation/stability
CM&C Deliverables - Stage I

- Validate BDS at Kinsale
- Validate tablets at Carolina and Basingstoke
- Manufacture granule stability lots at Basingstoke
- Generate stability data
- Complete CM&C packages
  (NDA, dossier, Canadian NDA)

GDT/dle

July 20, 1995
CM&C Deliverables - Stage II

- Validate granules at Basingstoke
- 15 mg tablet NDA amendment strategy based on current formulation
- Assure manufacturing sites prepared for FDA pre-approval inspection and launch
- Participate in formation/action steps of cross-functional launch team, including emerging market strategy
- Investigate cost-benefit of developing 20 mg tablet and alternative smaller 15 mg tablet
- Pursue customer-focused line extension plan
- Support aggressive CT needs for commercialization studies

GDT/dle

July 20, 1995
<table>
<thead>
<tr>
<th>Formulation</th>
<th>Strategic Partner(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zydus rapid-dissolving tablet</td>
<td>Scherer DDS AAI</td>
<td>Agreement signed, Poor performance from Scherer so far</td>
</tr>
<tr>
<td>Short-Acting IM injection</td>
<td>Cook Imaging (AAI?)</td>
<td>Formulation development in progress</td>
</tr>
<tr>
<td>15 mg tablet</td>
<td>-----</td>
<td>Project plan roughed out</td>
</tr>
<tr>
<td>Patch</td>
<td>1. Lohmann Therapie Sys. 2. Cygnus Therapeutics</td>
<td>Feasibility studies to be completed 3Q95. Select strategic partner 4Q95</td>
</tr>
<tr>
<td>Granules</td>
<td>B - L</td>
<td>Stability ongoing validation 4Q95</td>
</tr>
<tr>
<td>15 and 20 mg tabs</td>
<td>?</td>
<td>Business case pending</td>
</tr>
</tbody>
</table>

July 20, 1995
## Additional Formulations Approximate Timeline

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Target Submission Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granule</td>
<td>1996</td>
</tr>
<tr>
<td>15 mg Tablet</td>
<td>amend NDA?</td>
</tr>
<tr>
<td>Zydis Tablets</td>
<td>1997</td>
</tr>
<tr>
<td>Short-Acting IM.</td>
<td>1997</td>
</tr>
<tr>
<td>Patch</td>
<td>1998</td>
</tr>
<tr>
<td>Depot Injection</td>
<td>1999</td>
</tr>
</tbody>
</table>

GDT/dle

July 20, 1995
Line Extension Team

- Co-chairs: Tom VanAbeele (DPM) and Paula Franz (PPM)
- Focus: Develop and implement plans to successfully register those line extensions important to our customers
- Team will function much like a project team
- May need additional support from Tippecanoe Development for some line extensions

GDT/dle

July 20, 1995
Global Launch Team

• Co-chairs: Beth Morris (DPM) and Rob Schmid (Marketing)

• Focus: Prepare global readiness and strategies to have product available in minimal time at optimal quantity ASAP after approval
HWT
Commercialization Strategy

• Be next
• Be better
• Be global
Be Next!

<table>
<thead>
<tr>
<th>Eli Lilly</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott/Lundbeck</td>
<td>Sertindole</td>
</tr>
<tr>
<td>Zeneca</td>
<td>Seroquel</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>E Merck</td>
<td>Roxindole</td>
</tr>
</tbody>
</table>

1995

1996

GDT/dle

July 20, 1995
Be Better!
Olanzapine/Schizophrenia Strategy

Goal:
Customers worldwide will recognize Lilly/olanzapine as the company/antipsychotic that delivers optimal therapeutic and economic outcomes.

Strategy:
- Speed to global markets
- Customer focused product development plan
- Redefine standard of care and position olanzapine as the standard of pharmaceutical care
- Aim for rapid and broad market penetrations
- Participate in emerging markets
Be Global!

Develop a global marketing strategy around a consistent brand name and image that is shared by all of our affiliates and recognized by all of our customers
Olanzapine Market Process Timeline

1995

- Emerging Mkt. Study

1996

- Pricing and Reimbursement Study
- Global Branding

1997

- Research Analysis
- Message Testing
- Psychoses Marketplace Library
- Competitor Tracking System
- Global Forecasting

GDT/dle

July 20, 1995
Stage I
Commercialization: Positioning For Rapid and Broad Market Penetration

- Undertake aggressive pre-launch marketing activities
  - energize affiliates to commit resources to implement pre-marketing strategies and programs
  - initiate market research studies
  - craft a product image/branding
  - evaluate opportunities for additional indication
  - develop publication/symposia plan
  - initiate global pricing studies

GDT/dle
July 20, 1995
Stage II
Commercialization: Putting The Strategy Into Place

- Finalize global branding
- Achieve consensus on a global price(s) that optimizes economic return and assures access to as many global patients as possible
- Complete development of preapproved promotional materials
- Finish an emerging market analysis
- Integrate Japanese market planning into the global strategy
Stage III
Achieve Rapid and Broad Market Penetration and Implement an Aggressive Growth Plan

- Implement post-launch marketing strategy to gain broad market access and maximize shareholder benefit
  - do what it takes (i.e., strategic alliances, bundling products/services, risk sharing)
  - manage global brand
  - maximize clinical opportunities through Plan D process
  - introduce line extensions in planned manner
  - ongoing competitive analysis and aggressive strategy

- Manage effective corporate communications plan

GDT/dle

July 20, 1995
Zyprex

- Global branding strategy
- Globally pre-approved materials provided to affiliates
- Pricing
- Packaging
- Market research
- Communication strategies
Making re-integration the standard... ZYPREX Olanzapine - Lilly Antipsychotic power for routine use

GDT/dle

July 20, 1995
Healthcare Solutions
**Lilly Disease Management Offerings**

<table>
<thead>
<tr>
<th>Pharmaceutical Care</th>
<th>Lilly products and interventions/services that pull Lilly products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managed Pharmaceutical Care</td>
<td>Core services, connectivity, and interventions/services and management for total pharmaceutical care</td>
</tr>
<tr>
<td>Medical Management</td>
<td>Delivery of interventions/services and management for the clinical delivery of care to provide specific outcomes</td>
</tr>
</tbody>
</table>

GDT/dle

July 20, 1995
Program Goals

• Improve treatment outcomes
  – Enhance symptom control
  – Manage relapse

• Lower cost of care
  – Minimize re-hospitalizations and LOS

• HRQL outcomes
  – Optimize functional level
  – Enhance social reintegration
  – Decrease caregiver burden
Program Structure

- Comprehensive group of tools and resources
- May be used either independently or as an integrated system
- Accessible to providers, caregivers and consumers
- Flexible
  - Work within all after-care system organizations
    » Mental health care-out/in
      • e.g., Charter hospital
    » STAR/partial hospitalization
    » CMHC/clubhouse
  » Adaptable for international use and with other products

GDT/dle

July 20, 1995
Key HWT Points
Two Aspects of the Heavyweight Team

Team’s Mission

1. Expedite launch in two-thirds of the global major markets

2. Optimize the early commercialization of the product

GDT/dle

July 20, 1995
HWT Innovations/Learning Points

• Product leadership
  – focused accountability
  – vision - creating it/realizing it
  – rapid response to opportunities
  – product champions set the example
    » ex. core team sets priority, gets buy-in, problem solved

• Co-location
  – quicker resolution of issues
    » more ownership of total project
    » more team spirit
    » shared goals
    » enhanced communication
  » Olanzapine database vs. redacted at same time point in life cycle shows improved quality

GDT/dle July 20, 1995
HWT Innovations/Learning Points - cont’d.

- Reallocation
  - apply a resource when and where it is needed
  - one priority, achieving product milestones
    » ex. reallocation of systems analysts to cover a 14 day slip in the creation of the HGAO reporting database

- Decision making
  - delayered
  - concentrated
  - prompt
    » ex. Pharmaco database error; required rerunning 300 reports. No project delay despite initial optimistic view minimum one month delay in re-creating reporting database.

GDT/dle

July 20, 1995
HWT Innovations/Learning Points - cont’d.

- **Efficiency**
  - ability to re-engineer methods in response to unexpected challenges/complications
    - ex. parallel report writing

- **Having Core Team member on each “work group” facilitates getting things done**

- **Work Team “removes layers”**
  - allows upper management to see issues early on and take action
HWT Innovations/Learning Points - cont’d.

• Cross-functional team involvement earlier in process
  – catch issues earlier and save time
    » ex. Canada Study
    In review of an amendment for this study by a cross-functional group, data quality issues became apparent and we averted a possible incomplete database
HWT Innovations/Learning Points - cont’d.

- Quality of the work environment
  - “before some people didn’t even know others on the project”
  - a more relaxed atmosphere
  - “has given everyone an identity they didn’t have back in their functional areas”
  - “more influence/greater responsibility” to the individual
  - individuals have a “better overview of the entire project and a better understanding of what their colleagues are doing”

GDT/dle

July 20, 1995
HWT Innovations/Learning Points - cont’d.

- Launch strategy
  - dedicated global launch team leader instead of having multiple launch teams should provide focus yielding quality and speed to launch planning and execution

- Earlier dedication of resources to commercialization studies than in old paradigm
  - quicker market penetration
  - earlier submission in Type II countries
Process Improvement - Registration Planning

Develop a registration strategy to ensure submission by October 1995 in North America, Europe, Israel, South Africa, and Australia. Submit in Japan by October 1996.

- Hold all non-essential, nonregistration activities until after submission.
- Identify current resources and headcount for registration in all affiliates and compare with the level of resources needed to address critical registration issues. Resource adequately to meet registration milestones.
- Aggressively expedite filling of open requisitions across countries and components and recruit for expertise in the process.
- Utilize routine teleconferences to proactively identify resource issues across countries and components.

GDT/dle

July 20, 1995
Process Improvement - Registration Planning

- Early regulatory summits < info sharing < trouble shooting

- Got approval from FDA to not submit paper CRF’s (reduced submission by 200 volumes or 100 trees saved. Reduced assembly time/quicker review.

- Dialog with FDA to initiate pre-submission early review. Expedite review.

- Data browser (user-friendly review)

- Pre-submission rapporteur discussion with EMA (optimize choice - shorten review/minimize issues

GDT/dle

July 20, 1995
HWT Innovations/Learning Points - Conclusion

In a superior work milieu, a HWT can better employ valuable and finite resources to deliver both quality and speed resulting in a superior EVA to Lilly shareholders
Effects of 6 Month Launch Delay

- October 1995 Submission
- 6 month Delay - Next to Market
- 6 Month Delay - Behind Competitor

GDT/dle

July 20, 1995
Resources

GDT/dle

July 20, 1995
“Formation of a heavyweight team does not need to imply heavy resource commitment...

It is a process where resource intensity should vary during the development cycle.”

W. C. Fields
HWT Resource Requirements

Key - A nucleus of product core competency (experience) must be maintained through the cycle i.e., succession planning

GDT/dle

July 20, 1995
Resourcing: Medical Clinical Grants - $
Clinical Grants - Medical Plans and Data Management Headcount

*Includes CRAs, CRPs, Systems, Statisticians, Secretaries, CIs, CRPs, Secretaries, and Contractors

GDT/dle

July 20, 1995
Resourcing a Customer-focused Product Development Plan

- Oral Solid: 58%
- Liquid: 15%
- Granule: 11%
- Depot: 15%
- IM: 1%

GDT/dle

July 20, 1995
GAP Analysis

- Immediate needs:
  - RA-CMC for Zydis®
  - Analytical development for 15 mg tablet

- Yet undefined additional resources anticipated in 96-98 for other line extensions
GPAC Issues

GDT/dle

July 20, 1995
Issues
What the HWT Would Like from GPAC

- Affiliate accountability/prioritization
  
- Development resources - line extensions in GPAC prioritization exercise

- Japan - mandate that the HWT is empowered/accountable or role clarification

launch readiness opinion leaders cultivated marketing plan

GDT/dle

July 20, 1995
Issues
What the HWT Would Like from GPAC - cont’d.

• Budget
  – a single cross-functional budget to provide flexibility, control, and accountability

• Human resources
  – acknowledgment that registration, commercialization, and speed to launch initiatives are essential/post October 1 the work is not over
  – recognition/protection of current team members’ 2-3 year commitment to the project
  – support a planned, orderly succession strategy when opportunities for team members to assume senior roles as other projects emerge

GDT/dle

July 20, 1995
Conclusion

HWT...  

- Work!
- Represent a process improvement < speed efficiency
- Create a better work environment
- Add economic value
- Require adjustments by us all

GDT/dle

July 20, 1995
If you can’t run with the Big Dogs... stay on the porch!
### Olanzapine HWT 3 Year Plan (Estimate)

<table>
<thead>
<tr>
<th></th>
<th>95 F</th>
<th>1996</th>
<th>1997</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal Grants</td>
<td>21,273</td>
<td>36,834</td>
<td>27,863</td>
<td>16,846</td>
</tr>
<tr>
<td>Subtotal Med HCT</td>
<td>11,643</td>
<td>13,494</td>
<td>11,091</td>
<td>7,751</td>
</tr>
<tr>
<td>CRP/MGMT</td>
<td>750</td>
<td>780</td>
<td>811</td>
<td>844</td>
</tr>
<tr>
<td>Project Coord</td>
<td>360</td>
<td>374</td>
<td>389</td>
<td>405</td>
</tr>
<tr>
<td>PPD</td>
<td>600</td>
<td>624</td>
<td>649</td>
<td>675</td>
</tr>
<tr>
<td>Regulatory</td>
<td>360</td>
<td>374</td>
<td>389</td>
<td>405</td>
</tr>
<tr>
<td>Subtotal Marketing</td>
<td>1,649</td>
<td>5,935</td>
<td>6,707</td>
<td>6,432</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>38,284</td>
<td>64,351</td>
<td>54,607</td>
<td>39,790</td>
</tr>
</tbody>
</table>

GDT/dle

July 20, 1995