



Eli Lilly & Company  
Health Economics Research

**HEALTH ECONOMICS**  
**OLANZAPINE OVERALL PLANS**

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#### References

#### Olanzapine HE Meeting and Publication Plan

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## Health Economics Olanzapine Plan - Brief (one pager)

Goal: Provide key customers with the necessary olanzapine data on long-term economic gains and improved quality of life to support reimbursement, pricing, formulary review and marketing.

- Cost of Illness Studies in a few countries
- Quality of Life data (phase II and phase III vs haloperidol) global
- Resource Utilization data from HGAJ=Cost-Effectiveness Analysis (received dataset 11/95)
- Comparative data vs risperidone
- Treatment Resistant data Austria and Spain
- Many data points from above feeds the Schizophrenia Treatment Clinical Decision Model
- Core Economic Evaluation Package (Pricing Dossier) available to affiliates 9/96
- European Epidemiology study
- Treatment Resistant data (final)
- Quality of Life study for Japan
- Research on new quality of life scales
- Schizophrenia Care and Assessment Program (Patient Registry) for US, export methodologies

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## Health Economics Olanzapine Plan - Executive Summary

**Goal:** Provide key customers with the necessary olanzapine data on long-term economic gains, improved quality of life, and disease prevention and management interventions to support reimbursement, pricing, formulary review and marketing; ultimately supporting optimal care.

- Objectives:**
- ✦ Increase awareness regarding the prevalence, prognosis and related costs of schizophrenia
  - ✦ Differentiate olanzapine Vs. haloperidol, and other comparators in terms of long-term economic gains and improved QOL to support reimbursement, pricing and marketing. Document VALUE
  - ✦ Publish and present data on new comprehensive outcome measurements and economic evaluation; co-ordinate data dissemination with overall communication plans
  - ✦ Educate health providers, regulators, and international health organizations in the practice of health economics for schizophrenia.

### Approaches:

#### Collect and publish cost of illness data where appropriate

- Multiple cost of illness studies are ongoing (Belgium, Spain, France, Germany)
- Review of previously published literature available

#### Analyze and publish QOL and resource utilization data

- Quality of life reports included in submission  
Abstracts being submitted to various congresses - Manuscripts to follow
- Resource-utilization data being analyzed for a cost-effectiveness analysis; start Nov 1995
- Patient targeted resource utilization data analysis

#### Analyze global risperidone study data

Interim analysis (8 week + some 6 month data) 5/96  
Summary report of clinical and HE to be included in economic evaluation dossier

#### Schizophrenia Treatment Clinical Decision Model

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- Model will estimate the cost-effectiveness of olanzapine compared to haloperidol and risperidone. Literature, cost of illness study, clinical trial and expert opinion data to be fed into the model.
- Core-model to be developed first, then country adaptations. International advisory group is helping MEDTAP with development of core-model (Core-model complete: Feb 96, computer model: Mar 96, country adaptations: Feb 96 onwards)

**Provide affiliates with core olanzapine economic evaluation dossier**

- Package will include epidemiology and cost of illness data, clinical safety and efficacy summary, quality of life, resource utilization, clinical economics (including results of cost-effectiveness analysis) and conclusions
- Affiliates will use this information for different purposes (e.g. pricing negotiations, formularies) and core package will have to be customized locally
- Work with affiliates to develop a dissemination plan

**Continued research to further document the value of olanzapine by collecting further data on new outcomes measurements**

- European Epidemiology Cohort (includes patients' assessment needs for services)
- Family Burden study in Italy and/or Germany; Start Q3/96
- Treatment-resistant patient studies in Spain and Austria
- Risperidone studies in Australia and Canada
- Pilot study of the Quality of Life Index-Mental Health in the US, Austria
- Pilot study of the QLS in Japan

**Assist Health Care Solutions Team with disease prevention and management intervention strategies for schizophrenia**

- Develop patient registry for schizophrenia to collect data within outcome domains and overall. Outcomes data help determine which medical practices for which patients produce the best care at the best price. US pilot project; export methodology to Europe

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## BACKGROUND INFORMATION on SCHIZOPHRENIA and RELATED PSYCHOTIC DISORDERS

### SUMMARY OF KEY POINTS

- Schizophrenia is a very expensive disease and accounts for 3% of US direct medical expenditure
- In the absence of comprehensive community-based and disease management programs, the move away from institutionalization may not in itself reduce costs
- Schizophrenia care may increasingly become the burden of communities as governments seek to reduce their health care budgets
- Given the proper combination of pharmacotherapy, psychotherapy, psychoeducation, and psychosocial retraining, many patients with schizophrenia are able to reintegrate back into society
- Outcome metrics in schizophrenia are difficult to define and quantify, and there are no universally validated and accepted measures
- Quality of life is very important to patients and caregivers, but tools for assessment are limited

### Definition

There is international agreement that the presence of delusions and hallucinations are integral to the definition and classification of psychosis. These symptoms, along with functional deterioration and signs of disturbance for 6 months, define that subgroup of psychotic conditions known as schizophrenia. Specifically, schizophrenia is a disturbance with at least 1 month active phase with 2 or more of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms.

The course of schizophrenia is highly variable and can be divided into specifiers when 1 year has elapsed after onset of acute symptoms. Specifiers include episodic with interepisode residual symptoms \*, episodic with no interepisode residual symptoms, continuous \*, single episode in partial remission \*, single episode in full remission, and other or unspecified pattern. (\* denotes that prominent negative symptoms can be added to this specifier) In addition, there are five types of schizophrenia: catatonic, disorganized, paranoid, undifferentiated, and residual (1). It should be noted, that in general there is not widespread agreement on the definition of schizophrenia and the definition provided here is for reference only. The terms schizophreniform and

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schizoaffective refer to syndromes which are closely related to schizophrenia but lie outside the strict definition. These syndromes are often included in many discussions of schizophrenia, however, and all are grouped as schizophrenic disorders.

## Epidemiology

The one-year prevalence rate of schizophrenia from the Epidemiologic Catchment Area study in the US is 0.9% and the lifetime prevalence is 1.3% with a remission rate of 33% (2). The prevalence rates are fairly constant over time, even with changes in diagnostic criteria, and are very similar throughout the world. The one-year incidence rate varies from 0.2 to 0.6 per 1,000 person-years. Studies conducted by the World Health Organization (WHO) found symptoms to be similar in all cultures and countries studied (3). However, patients in developing countries have a more acute onset, fewer affective symptoms, and a better outcome than patients in the industrialized world. Patients who initially respond to standard neuroleptics and later relapse comprise 20-30% of the patient population. The prevalence of treatment-resistant schizophrenia, including those who fail to respond or develop severe side effects to standard anti-psychotics is estimated to be 5-30% of the total group. About half of the treatment-resistant group will respond to clozapine (4).

In men, the onset is typically between ages 17-30 and in women between 20-40 (5). There are three phases of illness which occur during the course schizophrenia: prodromal, active, and residual. The onset of positive symptoms (delusions and hallucinations) signals the acute stage and usually requires hospitalization. Negative symptoms (blunted affect, low motivation, etc.) are more prominent in the residual phase. Common co-morbidities include depression, alcoholism, and substance abuse. The course of schizophrenia varies and does not typically include progressive deterioration. About 5 to 15% will suffer severe continuous psychosis.

A National Institute of Mental Health (NIMH) longitudinal study showed that from the period of index hospitalization to follow-up assessment (2-12 years) 78% of patients with chronic schizophrenia experienced relapse, 38% attempted suicide, and 24% had episodes of major affective illness (6). The outcome of patients with schizophrenia is complex and is heavily dependent on the subtype (paranoid, catatonic, affective, etc.). There are also significant gender differences in outcome. Men tend to suffer a more chronic course with a less favorable outcome than women. Social functioning, occupational role, hospital utilization, and symptoms at the time of diagnosis are the best predictors for long-term outcome, but these variables are only slightly correlated to one another. All must be considered independently and yet linked together for practical applications (7). Unfortunately, no single unit of measurement which incorporates all the relevant outcome domains has been well established. It is incomplete to classify outcome with only measurements such as the reduction of

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hospital days or a reduction in BPRS score. Until a comprehensive single measurement unit is established, many separate measures will have to be used.

### **Mental Health Services**

Treatment of schizophrenia varies around the world. Most treated patients enter the specialty mental health sector where psychiatrists and other professionals play a major role and most care occurs in the outpatient setting. There has been a major shift in care from the institutions to the family and to community settings. This concept has generally been embraced, but communities are not prepared, or in some cases willing, to provide support for work sheltered programs or group homes. Still, there is a disproportionate amount of hospital beds (US) occupied by patients with schizophrenia. Many people with schizophrenia do not receive medical care in any context. For example, it is estimated that 1/3 of the homeless in the US are schizophrenic and most likely not linked into any health care system.

Optimal medical care is supplemented by psychosocial and rehabilitation support. Case managers organize services, although case loads are often so heavy that little time can be spent on any one case. Services a patient may receive include: occupation skills development, supervised shelters, social training, education on good health practices and other functional rehabilitation. The psychosocial and rehabilitation support services that a patient receives varies by country. For example, in Italy caregiving rests mostly with the family due to laws that restrict institutionalization. In contrast, there may be financial incentives to encourage long term hospitalization in Belgium.

Pharmaceuticals play a major role in treatment of schizophrenia. Typical neuroleptics relieve positive symptoms but produce severe side effects such as tardive dyskinesia, akathisia, rigidity, tremors and dystonia. Negative symptoms are usually not responsive to typical neuroleptics. Since there is no cure for schizophrenia the goal of treatment is to eliminate or reduce symptoms without producing too many side effects and to prevent relapse. Risperidone and clozapine (for treatment resistant schizophrenia only) are 2 new entries to the market after a 20-30 years of no new pharmacologic treatments. Side effects and patient's perceptions of medication contributes to low compliance rates with the typical neuroleptics, resulting in use of depot formulations in many countries. It is estimated that the current relapse rate is 3 times higher than it needs to be in schizophrenics and that this could be improved by a series of psychoeducational sessions for patients and monitoring of doctor's relapse prevention measures (8).

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## Economics of Schizophrenia

The cost of schizophrenia in the US in 1990 has been estimated to be [REDACTED] (9) via a prevalence-based approach. In the UK, a 1987 study estimated the total cost to be [REDACTED] an estimate which is about half that in the US on a capitated basis (10). The difference may be related to differences in study methodology and perhaps differences in the patterns of practice within the NHS system. Of the [REDACTED] in the US, just over half of the costs [REDACTED] represents the direct treatment and support costs, and 10 % reflects the costs of caregiver and other related services. Almost half of the direct costs are for care in specialty institutions, including hospitals, freestanding mental health facilities, and correctional institutions. This compares with the estimated 1.2% of amount spent on schizophrenia for prescription drugs. The cost of hospitalizing patients with schizophrenia remains one of the easiest identifiable and largest source of financial burden for governments concerned about cost containment to document. The direct costs of schizophrenia account for approximately 3% of personal health care spending for all illnesses in the US in 1985 (11). In the UK study, the most severe cases of schizophrenia (41%) consume 97% of the direct costs (10).

For the non-institutionalized population, the indirect costs of schizophrenia are also important to consider. Most people with schizophrenia are able to work at some time in their lives. At any given time, however, approximately 43% of patients are employed, compared with 56% of the total population, and there are longer periods of unemployment (2). Thus the costs of disability and reduced productivity may be very real for those employers who provide disability benefits for employees with schizophrenia. Furthermore, schizophrenia frequently interrupts the opportunity to complete the final levels of formal education, further reducing productivity. Public financial assistance plays a major role in the life of patients with schizophrenia, especially welfare and disability benefits.

## Cost-Effectiveness

The cost-effectiveness of the treatment of schizophrenia has not been extensively studied. Most of the work has been produced to define the effects of clozapine on payers, and the studies share certain limitations. All of the analyses are retrospective, do not consider the costs associated with psychosocial and rehabilitative support which might be associated with successful treatment, and are confined to the most costly, treatment-resistant group.

Specific cost studies for psychotropic drugs are slowly emerging. Revicki compared the costs of mental health services associated with clozapine and the costs associated with standard neuroleptic therapy in a sample of treatment resistant patients (12). The study showed that net savings to be approximately [REDACTED] per patient favoring clozapine after 2 years of treatment. There are design issues because patient sampling

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were from different sources and the patients who discontinued early were not followed. In another study by Meltzer, the before and after costs of mental health associated with 2-year clozapine treatment, demonstrated an  decrease per year per patient (13). There was no control group in this study.

Davies' analysis of the UK situation is more properly a cost-effectiveness analysis because it defines an effectiveness measure, expressed as symptom free time. This measure may have intuitive appeal for analyses of chronic mental illnesses such as schizophrenia, but has not been validated or widely accepted. Still, this analysis suggests that, on average, patients will benefit from about 5.9 additional symptom free years and spend  less if they take clozapine than if they do not (14).

### Perspectives

From the patient's perspective, quality of life (QOL) is an important aspect of care where symptoms, adverse drug effects, social disability, and subjective view impact the overall well-being of the patient. What a patient feels about his or her medication is indicative of compliance in this population (15). Governments stand the most to gain by supporting effective treatment programs which move patients out of the chronic hospital setting. This realization has resulted in the move away from institutionalization, with resulting cost shifts to the community. Because of different cost structures and in many cases lack of rehabilitation, however, it is not always clear if community care saves money. It may only hide the real cost of the disease and put providers and non-governmental payers for health care in conflict with governments. From all perspectives, however, drug therapies that can reduce the number of hospital days (still a very high cost item), encourage compliance, produce minimal adverse events, and relieve enough symptomatology to enable the patient to be trained technically and earn an income.

### Quality of Life

The subjective side of QOL for patients with schizophrenia is a field that needs intensive immediate attention. One scale specifically for the deficit syndrome (a subset of the negative syndrome), the Strauss-Carpenter Quality-of-Life Scale (QLS), has been used and data reports are in the literature (16, 17). Revicki reviews many of the QOL scales such as the Social Adjustment Scale (SAS), the Quality of Life Interview and the Quality of Life Index for Mental Health (18). The few data which exist suggest that the major determinants of the quality of life of schizophrenic patients are the number and frequency of adverse reactions to medications and psychosocial functioning. For a patient with schizophrenia, the ability to function in social situations appears most related to feelings of "inner-harmony" and self-reliance rather than more objective measures such as job status or standard of living.

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## OVERALL OBJECTIVES OF PLAN

1. 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
2. Work with local health economists and regulators on corporate studies and on various country-specific studies to get local input and strengthen relationships
3. Provide authorities with the necessary health economic information to document olanzapine's value regarding registration (*when formally requested*), formulary inclusion, level of reimbursement, and pricing negotiations
4. Develop HE presentations for psychiatric and health services research conferences
5. Publish HE data in scientific journals and lay publications to support pre-, during, and post-launch activities of olanzapine
6. Direct inputs of HE information into Disease Prevention and Management programs.

### **Core Olanzapine Economic Evaluation Package** ("PRICING DOSSIER")

Provide all affiliates with core olanzapine economic evaluation package in September 1996. It is recognized that each affiliate will want to use this information for different purposes (e.g. pricing negotiations, formularies) and that this core package will have to be customized locally.

#### **Outline** (subject to slight changes):

1. Executive Summary - 2 page
2. Epidemiology of Schizophrenia  
Synopsis of literature
3. Cost of Schizophrenia
  - a. Synopsis of published literature
  - b. Synopsis of manuscripts from studies conducted in Spain, Belgium, and France
4. Summary of Pharmacological data
5. Summary of Clinical Efficacy and Safety Results  
Synopsis of the summary from the ISS and ISE  
Synopsis of interim olz/risp 8 week and 6 month data

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6. Summary of Quality of Life Research
  - a. Synopsis of the 1 year data from submission reports
    - I. QLS from HGAD and E003
    - II. QLS and SF-36 from HGAJ
  - b. Synopsis of QLS from ola/risp interim 8 week and 6 month
7. Economic Basis of Submission
  - a. 1-year cost data from HGAJ
    - Type of economic evaluation (justification of method chosen)
    - Description of Population
    - Time Horizons
    - Description of Outcomes
    - Types of Costs
    - Results
  - b. Olz/Risp global trial
    - 6 month - interim report
  - c. Clinical Decision Analysis model
    - core model with olz/hal and olz/risp data, lit, and expert opinion
    - local adaptations
8. Estimate use and Financial Impact  
(required by Australia and may be requested by Canada)
9. Bibliography

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# STUDIES

## 1.0 Cost of Illness Studies

### 1.1 Objectives

- To determine and create awareness regarding the costs to a society or government to treat an illness
- To aid policy decision-makers regarding programs such as rehabilitation and prevention programs
- To raise the interest regarding schizophrenia among the medical society
- To provide a baseline against which new interventions can be assessed

### 1.2 Study Methods

- Collect and analyze all direct and indirect costs spent in one year on the treatment of schizophrenia (retrospective prevalence approach) or
- Collect and analyze all direct and indirect costs for the present and discounted future costs in the year in which the disease first arises (incidence approach)

*Direct costs:* Short-stay hospital days, nursing home days, outpatient psychiatrist visits, outpatient other mental health visits, outpatient other physician visits, prescription drugs, research costs, training costs and other costs

*Indirect costs:* lost work days, lost wages from premature death, familial caregiver's time

### 1.3 Studies and Timeline

1. The total cost of schizophrenia in 2 regions in the north of **Spain**  
Dr. L. Salvador (psychiatrist) and Juan Cabases (economist).  
Incidence based, 90 patients, 3 years retrospective data  
(Scope of project has grown since the Spanish government is sponsoring 2 prevalence studies: a 1 yr retrospective study and 1 yr prospective study)

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Start: 6/94 Stop: 10/95 Manuscript: 7/96 est. Publication:  
3/97

Contact: Sacristan/Martin

Cost: 1994-1996: [Redacted]

2. The total cost of schizophrenia in **Germany**

Prof. Von Der Shulenburg (North German Center for Health Services  
Research)

Retrospective (180 patients - 12 months), prevalence based

Study co-sponsored by Lilly, Janssen and Tropon

Start: 9/94 Stop: 12/96 Manuscript: 4/97 est. Publication:  
10/97

Contact: Oberender/Martin

Cost: 1994-1996: [Redacted]

3. The total cost of schizophrenia in **Belgium**

Prof. Peuskens

Retrospective (150 patients - 12 months), prevalence based

Contact: Gilis/Martin

Cost: 1995-1996: [Redacted]

Start: 12/95 Stop: 7/95 Report: 6/96 Manuscript: 10/96  
est Publication: 6/97

4. The cost of schizophrenia in **France**

Prof. Pellet - Study conducted alongside the European Epidemiology  
Cohort (see Section 10.0)

Prospective (50 patients - 12 months), prevalence based

Contact: Blachier/Martin

Cost: 1994-1996: [Redacted]

Start: 6/94

Stop: 3/96

Interim Report: 7/96

Final Report 12/96

First Manuscript: 12/96

est First Publication: 6/97

1.4 Previous Published Literature Available

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Write review manuscript regarding cost of illness studies that have been completed.

1. US-Dorothy Rice 1990 work
2. UK-Drummond and Davies 1987 work
3. **Australia**-Andrews and Hall 1975 work
4. Other published studies
5. Incorporate results of Sp, Ge, Be, Fr Lilly studies as results available

Start: 5/95    Manuscript: 3/96    est. Publication: 11/96

*Contact:* Genduso/Martin  
*Cost:* none

### 1.5 Outcome

- Background information for economic dossier, country specific
- Lay publication in each targeted country directed towards regulators and health benefits manager informing of high costs of the disease
- Scientific publications in each targeted country and review article multi country impact
- Enhance relationship with local consultants/economists and local government

## 2.0 Olanzapine Vs. Haloperidol Phase II Studies

### 2.1 Objectives

- Compare the Quality of Life Scale for Schizophrenia (QLS) in olanzapine and haloperidol in **US, Europe, S. Africa, Australia, and Israel**

### 2.2 Study Methods

- QLS administered at baseline and in double-blind (db) extension
- MEDTAP (formerly Battelle) is the consultant group assisting in analysis

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## 2.3 Studies

- Completed E003 and HGAD trials with olanzapine, (placebo), and haloperidol

## 2.4 Timeline

Reports (NDA, NDS and EU submission): E003: 8/95, HGAD: 7/95  
Manuscript: 2/96 est. Publications: 11/96

*Contact:* Hamilton/Genduso

*Cost:* Redacted

## 2.5 Outcome

- First impression about QOL improvement alongside clinical improvement
- Provide QOL data for registration package
- QOL publication to support 1st year of launch and pricing
- Multiple market impact

## 3.0 Olanzapine Vs. Haloperidol Phase III Study

### 3.1 Objectives

- Comprehensive collection of global QOL data in large sample size
- One year retro- and prospective resource utilization data collection compared with haloperidol
- Comprehensive collection of global data inputs for core economic model

### 3.2 Study Methods

- HGAJ - retrospective (1 year prior to baseline visit) and prospective resource utilization collections during CT
- QLS (Dutch, English, French, German, Italian and Spanish), SF-36 (English speaking countries only) - endpoint change analyses.

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- QLS comparison with efficacy scales (CGI, PGI, PANSS), QLS and SF-36 comparison, assessment of QLS psychometric properties for further validation purposes, deficit and non-deficit syndrome analyses (separate future manuscripts)
- Global data analyzed for QOL; Cost-Effectiveness Analysis (CEA) with US patients due to large sample; not able to do global CEA due methodological difficulties
- Country datasets
- MEDTAP will assist in global analyses

### 3.3 Study

F1D-MC-HGAJ

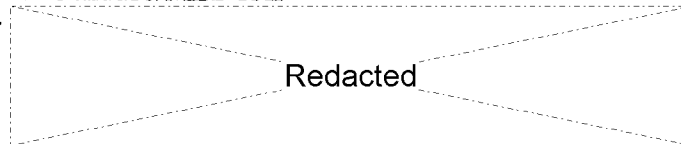
Countries: **Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Italy, Luxembourg, Netherlands, Poland, Portugal, Spain, Sweden, UK, US**

### 3.4 Timeline

Start: 6/93      Stop: indefinite extension  
 Reporting Interval (NDA, NDS and EU submission): 8/95  
 Manuscripts: 3/96      est. Primary Publication: 12/96

Contact: Genduso/MEDTAP

Costs:



### 3.5 Outcome

- Provide QOL data for registration package in all markets
- Economic data to feed economic model (see Section 9.0)
- QOL and economic publications to support launch year and pricing in all markets
- CEA with high impact in US and medium impact in other markets

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### 3.6 Patient Targeted Resource Utilization Data Analysis

- Analysis of subset of patients from HGAJ study. Follow previously discontinued, due to agranulocytosis, clozapine patients for 1 year after starting olanzapine therapy. Compare current episode cost to previous episode costs (case report).
- Timeline
  - Start: 6/96
  - Report: 8/96    Publication: 3/97
  
  - Contact: Genduso/Hamilton*
  - Cost: None*
- Outcome
  - Data for pricing dossier and publication to support olanzapine and possibly shorten regulatory process - may be useful in Canada and Belgium (Precedent with our SSRI, see: Montgomery SA. The Specificity of the Zimelidine Reaction. International Clinical Psychopharmacology. 1989; 4:19-23.)

### 3.7 Additional databases

Looking for outside (non CT) databases to find supplemental data on different long-term treatment outcomes, especially drug utilization including switching, continuity of care, and comorbidities. In US, exploring PCS and looking for one in Europe (Also see Section 15.0 on Pt. registry)

Start: 1/96    Stop: --  
*Contact: Croghan/Genduso/Hylan*  
*Cost: ?*

## 4.0 Global Olanzapine Vs. Risperidone Study

### 4.1 Objective

- Obtain data from important comparator
- Support pricing, marketing and medical needs

### 4.2 Study Methods

- Collect resource use data retrospectively for 6 months and follow all patients for 6 months prospectively.

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- QOL using QLS
- Pool data and disaggregate (economic and possibly QOL) by country if sample size is sufficient. A minimum of 80 patients will be enrolled in the US, 80 patients in France, Belgium and Switzerland together, and 40 patients in Spain.

#### 4.3 Study

- HGBG - double-blind risperidone comparative study

#### 4.4 Timeline

Start: 4/95

Interm Report (8 week and 6 month for clinical and QOL and 6 month for main resource utilization ): 6/96

Final Report: 6/97

Publication: 3/98

Contact: Hamilton/Genduso

Cost: Redacted

#### 4.5 Outcome

- Interm report (clinical safety, efficacy and HE) to be included in the core economic evaluation package with impact on multi markets
- data to feed economic model (see Section 9.0) for multi market impact
- QOL and economic publications to support launch year and pricing for mult market impact

### 5.0 Australian Olanzapine Vs. Risperidone Study

#### 5.1 Objective

- Obtain data from important comparator
- Data to meet the Australian reimbursement **regulations**

#### 5.2 Study Methods

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- QOL (QLS), SF-36, Drug Attitude Inventory (DAI-10), and Caregiver Burden Inventory (CBI)

### 6.3 Study

- P022 - db, randomized, olz, vs hal and risp
- 200 outpatients within first 5 years of illness; 1 year db study
- db followed by an indefinite open-label extension

### 6.4 Timeline

Start: 7/95  
Stop: ?  
Final Report: est. 1Q97  
Publication: 11Q97

*Contact: Wiktorowicz/Genduso*

### 6.5 Outcome

- Information has multi market impact
- Support reimbursement in Canada

## 7.0 Olanzapine Vs. Amisulpride Study (France)

### 7.1 Objective

- Obtain data from important comparator
- Obtain more specific local health economics data

### 7.2 Study Methods

- Collect resource use data retrospectively for 6 months and follow all patients for 6 months prospectively
- QOL using QLS and SDS (Social Disability Scale)

### 7.3 Study

- db olanzapine vs placebo and amisulpride study in schizophrenic deficit patients

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#### 7.4 Timeline

Start: 2/95  
Stop: 1/97  
Final Report: Q2-97  
Est. Publication: Q4-97

*Contact:* Blachier/Martin  
*Cost:* None

#### 7.5 Outcome

- Essential for pricing negotiations in France
- QOL and economic publications to support launch in Europe

### 8.0 Treatment-Resistant Patient Study (Spain)

#### 8.1 Objective

- Economic pre and post treatment evaluation of most costly patient population

#### 8.2 Study Methods

- 1994 Template study
- Open-label pilot trial in treatment-resistant patients  
25 patients dosed for 6 months with indefinite extension

#### 8.3 Timelines

Start: 11/94  
Stop Enrollment: 2/96  
Final Report: 12/96  
Publication: 6/97

*Contact:* Sacristan/Martin  
*Cost:* Redacted

#### 8.4 Outcome

- Involve influential opinion leaders

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- Document efficacy of olanzapine in treatment resistant patients with impact on multi markets
- Pricing support in Spain
- Input for local adaptation of economic model

## 9.0 Schizophrenia Treatment Clinical Decision Model

### 9.1 Objectives

- Estimate the cost-effectiveness of olanzapine compared to haloperidol or risperidone via a model. Clinical decision model will simulate the pattern of possible health outcomes and use of medical services for patients with schizophrenia. The model is a simplification of reality and attempts to simulate the clinical management pathways and pattern of recurrence of psychotic episodes over 5 years.

### 9.2 Study methods

- Cost-Effectiveness Analysis model with units of cost per healthy day (via efficacy measurement of treatment success, treatment moderate outcome, & treatment failure) Primary analysis
- Cost-Utility Analysis model for support in CA, Australia, and UK Utility defined by combining efficacy, ADE, and QOL scales. Similar to Quality Adjusted Life Year (QALY) approach. Secondary analyses
- Core model to be developed first then country adaptations. Core and US models will be developed by MEDTAP. Schizophrenia Model Advisory Group assisted with development of core model. Advisory group members:

W.Glazer (US)  
 R.Goeree (Canada)  
 N.Keks (Australia)  
 M.Knapp (UK)  
 V.Kovess (France)  
 H.Meltzer (US)  
 J.Peuskens (Belgium)  
 G.Racagni (Italy)  
 L.Salvador (Spain)  
 G.Von der Schulenburg (Germany)  
 K.Wright (UK)

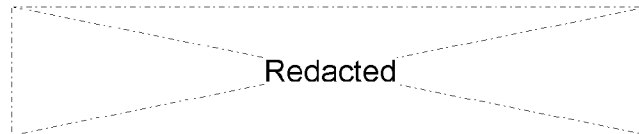
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### 9.3 Timeline

First paper draft of core model: 5/95  
Second paper draft of core model: 9/95  
Advisory group meetings: 5/95 (APA), 10/95 (ECNP)  
Core model to be finalized: 2/96  
Computer model: 3/96  
Country adaptations: start 2/96

Contact: Genduso/Hamilton/Martin

Costs:



### 9.4 Outcome

- Pricing Dossier data
- Support pricing, reimbursement and formulary listing in multi market
- Support launch through publications, presentations and detailing in multi market

## 10.0 European Epidemiology Cohort

### 10.1 Objectives

- Gather epidemiology data in schizophrenia
- Support ongoing research in the field
- Comprehensive collection of service use data in France

### 10.2 Study Methods

- European cohort of schizophrenic patients (**France, Germany, Ireland, Italy, Netherlands, Portugal, Spain**)
- Prospective data collection for 1- 5 years (including patients' assessment needs for services and direct resource utilization data).

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One center (Prof Pellet) to collect direct and indirect cost data on 50 pts for 6 months (see Section 1.3)

- 503 patients enrolled by April 30,1995

### 10.3 Timeline

One-year study completion: 12/96  
Report on baseline data: 12/96  
Report on 1year data: 10/97

Contact: Blachier/Martin

Cost: Redacted

1. One-year study: Redacted
2. Additional cost per year of follow up: Redacted for as many years as we choose to support
3. Evaluating request for centralized data collection support at Redacted

### 10.4 Outcome

- Support pricing re-negotiation in France
- Data on the evaluation of comprehensive care in France
- Long-term support and epidemiology information on other antipsychotic compounds in multi markets

## 11.0 Treatment-Resistant Patient Study (Austria)

### 11.1 Objective

- Economic pre and post treatment evaluation of most costly patient population
- Follow patients in an open study design to determine real life economic impact

### 11.2 Study Methods

- Resource utilization collection every 3 months for hospitalizations, outpatients visits, day hospital, medications, laboratories and para-medical care. Retrospective data collection for 2 years prior to study

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entry and prospective collection for 2 years after study entry. Patients discontinuing the trial early followed for the same time period

- QOL using the QLI-MH, QLS
- open-label olz vs usual care medications
- 1994 Template study

### 11.3 Timelines

Start: 8/95	Interim Analysis: 3/97
Stop: 8/98	Interim Report: 6/97
Final Report: Q4-98	Interim Publication: 6/98
Publication: Q4-99	(for all pts. with 6 months data)

Contact: Dossenbach/Martin

Cost - Redacted

### 11.4 Outcome

- Two year pre-treatment economic evaluation
- Comparison to best treatment available, promote olanzapine as 1st line and 2nd line treatment
- Case management and budgetary planning guidance for health care providers in Austria

## 12.0 Family Burden Study (Italy, possibly Germany) (design under discussion)

### 12.1 Objectives

- To study family burden in Italy where the primary care of pts with schizophrenia is with the family
- To gather family burden data in a naturalistic setting.

### 12.2 Study methods

### 12.3 Timeline

### 12.4 Budget

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- HE to support analyses

*Contact:* Martin/Rossi

## 12.5 Outcome

## 13.0 Phase III Japan Study with QLS

### 13.1 Objectives

- Determine the efficacy of olanzapine tablet
- Determine the effect of olanzapine on QOL
- Prior to study, translate and validate QLS into Japanese (done)

### 13.2 Study methods

- Open trial
- 30 patients

### 13.3 Study

- Olanzapine Phase III clinical trial by tablet - Japan

### 13.4 Timelines

Start: Q4-95

QLS translated : Q2-95

Stop: Q4-96

QLS validated: Q2-95

*Contact:* Gomyo/Gendusio

*Cost:* Redacted

### 13.5 Outcome

- First Lilly QOL data in Japan

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**14.0 Olanzapine in the Treatment of Schizophrenia: Safety, Efficacy, and Impact on Quality of Life (US) (Herman study)**

14.1 Objective

- Safety and efficacy data collection
- Neuropsychological testing of brain functionality
- Use the Quality of Life Index-Mental Health for data collection of patient outcome via patient's, clinician's and caregiver's view

14.2 Study Methods

- 1995 Template open-label olanzapine
- 20 patients inpatients/outpatients

14.3 Timelines

Start: 5/96

Contact: Kiesler/Genduso

Cost: Redacted

14.4 Outcome

- Comprehensive patient data on quality of life, efficacy, ADE, daily living and functioning from progressive mental health center; high impact on US and medium impact on other markets
- Possible assistance in state appropriation of antipsychotics to Medicaid patients in US markets

**15.0 Schizophrenia Care and Assessment Program ("Pt. Registry") (US)**

15.1 Objectives

- An information system in place to collect complete information on olz and other antipsychotics at/around the time launch
- Measure indicators of health status

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- Collect and analyze data within outcome domains and overall
- Data to feed Disease Prevention and Management and the Continuous Quality Improvement Process
- Outcomes measurement helps to identify which medical practice processes produce the best patient care at the best price (potential Disease Prevention and Management opportunities)
- Export methodology to other interested affiliates

### 15.2 Study Methods

Modeling, epidemiologic, outcome research, clinical methods, DM strategies

- Phase I Retrospective economic modeling springboarding from gov. grant works on schizophrenia; using the databases of MarketScan and Georgia Medicaid (understand the nat. history and cost implications)
- Phase II Design the prospective study, train the sites, develop Schizophrenia Outcome module/scale
- Phase III Longitudinal prospective program
  - data on diagnosis, medical resources, outcomes, continuity of care, coordination of care, assessment of severity, co-morbidity, ADE
  - Non-randomized, no CT supplied, care and assessment program, run at least 5 years

### 15.3 Study

Partners: MEDSTATS, Johns Hopkins University, U of Maryland, U of Arkansas

### 15.4 Timelines

Start: 12/95	Phase 1: 12/95-7/96
Stop: open	Phase 2: 1/96-9/96
Manuscript: phase 1 - 8/96	Phase 3: 9/96 - open
Publications: many	

*Contact:* Genduso/Croghan/Burns

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## 15.5 Outcome

- Credible complete outcomes study(ies) with high impact in US and medium impact in multi markets
- Preparedness to answer challenging questions on outcomes in multi markets
- Identify potential leverage points in the schizophrenia disease process which may help to define opportunities for disease prevention and management initiatives
- Establish partners in disease prevention and management in US
- Develop a program, customize to sites, analyze their data and feedback information generating revenue in US

### References:

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Work Product	Country	Date Final Report Ready	Lead Author or Lead Contact	Targeted Mtg Location Dates of Mtg	Date abstract submitted/ accepted	Date Manuscr. Submitted	Targeted Journal	Date Manuscr. accepted	Date of Publ.
1.0 Cost of Illness (COI) Studies	Spain	N/A	J. Sacristan	ECNP 96 ? Amsterdam 9/22 - 26/96	Due 4/1/96	7/96			
	Germany	N/A	A. Oberender			4/97			
	Belgium	N/A	P. Gilis	Winter Workshop oral poster Swit. 3/16-22/96	9/5/95 submitted 10/95 accepted Poster received an award for young researcher	10/96			
Conducting Cost of Illness Studies for Schizophrenia	France	12/96	C. Blachier	WPA	submitted 1/96	12/96			
	Multi-country	N/A	L. Genduso	APA symposium, Miami, 5/22/95	done	3/96	Schizophrenia Bulletin		
	Methodology/review No olz data		C. Martin	AEP symposium, London, 7/8-12/96	submitted 1/96				
2.0 Olz Vs Hal Phase II Studies		QOL	HGAD-QOL	HGAD-QOL Winter Workshop oral Swit. 3/16-22/96 C. Martin	9/8/95 submitted 10/95 accepted	3/96	Neuropsycho		
		(NDA, NDS and EU submission: HGAD-QOL 7/95 E003-QOL 8/95)	S. Hamilton						

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3.0 Olz Vs. Hal Phase III Study	Multi-Country	Main QOL (NDA, NDS, and EU submission: HGAI-QOL 8/95)	L. Genduso	HGAJ-QOL APA, NYC 5/4-9/96	submitted 1/15/96 for new research oral (alt. new research poster)	3/96	Archives of GP		
			C. Martin	WCP Madrid 8/23-28/96	submitted 1/96	N/A			
			C. Martin	AEP 1996 Satellite Symp. London 7/8-12/96	submitted 1/96	N/A			
			S. Hamilton	Am. Society of Clinical Psychopharm., Inc. (ASCP) Jamaica Feb 15-19, 1996	submitted 1/96	N/A			

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3.0 Olz Vs. Hal Phase III Study (Continued)		QLS Validation	C. Martin	International Society for QOL Research 10/96?		4/96			
		QOL Predictors		International Conference on Health Policy Research 12/96?		10/96			
		Tx deficit interaction affect							
		Deficit/ Non Deficit		Schizophrenia 1996 Vancouver 10/6-9/96?	due 4/3/96				
		QLS and SF-36 methods/ correlation		ACNP ? San Juan 12/9-13/96				DIJ	

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Work Product	Country	Date Final Report Ready	Lead Author or Lead Contact	Targeted Mtg Location Dates of Mtg	Date abstract submitted/ accepted	Date Manuscr. Submitted	Targeted Journal	Date Manuscr. accepted	Date of Publ.
3.0 Olz Vs. Hal Phase III Study (Continued)		Cost-Effectiveness Analysis (CEA):	L. Genduso (consultant-D. Revicki)	HGAJ-Cost 1. ECNP Amsterdam 9/22-26/96 ? 2. Institute for Psychiatric Services (IPS), formerly the H & CP, Chicago 11/18-20/96 ?	due 4/1/96	6/96			
4.0 Global Olz Vs Resp. Study	Multi	Patient Targeted Resource Utilization Data Analysis HGBG QLS and cost Interim report on 8 week and 6 month:6/96	S. Hamilton	ECNP 97? International Congress on Schizophrenia Research 4/97? ACNP 97?		8/96			
5.0 Australian Olz Vs. Resp. Study	Austral.	Interim Report: 11/96 Final Report: 10/97							
6.0 Olz Vs. Hal Vs Resp Study	Canada	Start: 7/95 Final: est. 1Q97							
7.0 Olz Vs Amisulpride Study	France	Report 1Q97							
8.0 Tx Resistant	Spain	Report 12/96	J. Sacristan						

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Work Product	Country	Date Final Report Ready	Lead Author or Lead Contact	Targeted Mtg Location Dates of Mtg	Date abstract submitted/ accepted	Date Manuscr. Submitted	Targeted Journal	Date Manuscr. accepted	Date of Publ.
9.0 Schizophrenia Treatment Clinical Decision Model	Multi	Core model to be finalized: 2/96 Computer model: 3/96 Country adaptations: 2/96 onwards		ECNIP? Amsterdam 9/96 ISTHAC 97 or Society for Medical Decision, Fall 96?	due 4/1/96		Pharmacoeconomics Br. J. M Econ Clinical Therapeutics		
10.0 European Epidemiology Cohort		Baseline Report: 12/96 1 year Report: 10/97							
11.0 Treatment - Resistant Patient Study	Austria	Interim Report: 6/97 Final Report: Q4/98							
12.0 Family Burden Study									
13.0 Phase III Japan Study with QLS	Japan								

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Work Product	Country	Date Final Report Ready	Lead Author or Lead Contact	Targeted Mtg Location Dates of Mtg	Date abstract submitted/ accepted	Date Manuscr. Submitted	Targeted Journal	Date Manuscr. accepted	Date of Publ.
140 Olz in Treatment of Schizophrenia - QOL (QLI-MH) Herman Study	US			International Conference on Pharmaco-epidemiology 05/97?					
15.0 Schizophrenia Care and Assessment Program (Pt. Registry	US		L.Genduso Partners: Medstat, U Maryland, Hopkins, U Ark.			Phase I 8/96			

Note: Numbers (ie 1.0, 2.0, 3.0, etc...) relate to detailed description in "Health Economics Olanzapine Plan"

Potential Journals:

- |  |  |
|--|--|
| Acta Scand.  | Journal of Clinical Psychopharmacology |
| American Journal of Manage Care  | Journal of Internal Psychopharmacology |
| American Journal of Psychiatry   | Journal of Hospital Psychiatry         |
| Annals of Psychiatry   | J. Clin. Psychiatry                    |
| Archives of General Psychiatry   | Medical Care                           |
| Br. Journal of Psychiatry  | Medical Decision Maker                 |
| Clinical Therapeutics  | Neuropsychology                        |
| Drug Information Journal (DIJ)   | Pharmacoeconomics                      |
| Health Economics   | Psychiatric Annals                     |
| Health Services Research   | Quality of Life Research               |
| Hospital & Community Psych. Services (new name of the org. = Institute for | Schizophrenia Bulletin                 |
| Psychiatric Services)  | Schizophrenia Research                 |
| Human Psychopharmacology   |  |
| Journal of Affective Disorders   |  |

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