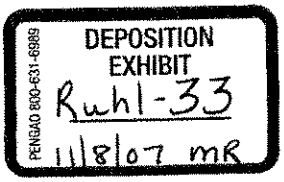
CONFIDENTIAL
FINAL DRAFT

SEROQUEL[R] Strategic Plan

1997 - 2001

Prepared by: Cathleen Hasulak
April 1996
rev. 7/1/96



SEROQUEL[R] Strategic Plan 1997-2001

I. EXECUTIVE SUMMARY

Schizophrenia, unlike most diseases, occurs with a consistent incidence rate throughout the world. Approximately 1% of the world's population is afflicted with this disease. Though its etiology is unknown, there is evidence to suggest that genetics may be involved in some cases. Because schizophrenia is an incurable, relapsing disease which causes it's sufferers to behave in socially unacceptable and sometimes dangerous ways, it's cost to society is staggering. $32.5 billion is the estimate of the annual burden of the disease on American society, with less than 5% of the total attributable to the cost of drug therapy[1,2]. Multiple sources estimate that more than 25% of all hospital beds in the US are occupied by schizophrenic patients, with 40% of all long term care days and 20% of all Social Security benefits attributable to the disease.

The antipsychotic market had been stagnant for many years. In the 1950's and 1960's a number of breakthrough compounds were introduced which, for the first time, provided clinicians the ability to control the overt psychotic symptoms of schizophrenia. Though effective, these drugs were not without significant drawbacks, having poor tolerability and long term safety profiles. Through the 1970's and 1980's no new products were brought to market and there appeared to be little hope of improving upon the existing neuroleptics, which were in wide use by that time.

The launch of clozapine (Sandoz, *Clozaril*) in 1990 marked the advent of a new era in the treatment of schizophrenia. It's characteristics: a broad range of brain receptor activity, efficacy in treatment resistant patients, no Extrapyramidal Symptoms (EPS), no Tardive Dyskinesia (TD), lack of sustained increase in prolactin, etc. have come to define the "atypical" antipsychotic agent. Thus, clozapine is the benchmark against which all new atypicals will be measured. Clozapine's use has been restricted to third line therapy due to a 1% incidence of agranulocytosis. Other atypicals appear at this time to have overcome this detrimental effect.

The US antipsychotic market has grown markedly in dollar value since the introduction of clozapine and in February 1994, Janssen's *Risperdal* (risperidone). In 1989 (pre-clozapine) the total market value was REDACTED compared to REDACTED in 1995[3,4]. *Risperdal* achieved REDAC in sales and an RE total Rx share in 1994, it's first 11 months on the market[3,4]. 1995 *Risperdal* sales have exceeded REDACTED with a consistent, strong rate of adoption, as measured by growth in new Rx share[3]. The value of the market will continue to increase with the expansion of the atypical segment, fueled by new product introductions in 1996 - 1998. Recent industry projections of a REDACT market by 2005 should be exceeded in 1996.

Even with the introduction of *Risperdal* there remains enormous unmet medical need. *Risperdal*'s performance to date, though solid, has not reflected the potential for new therapies in this field. This may be due in part to some reported disappointment with the drug's performance in clinical practice, eg limitations on dose to avoid significant EPS. The new entrants will be held to clozapine performance standards, as was *Risperdal*, though clinical trial data suggests they will be better able to meet clinical expectations.

There are currently four putative atypical antipsychotic agents in Phase III development. Lilly's olanzapine (*Zyprex*), Abbott/Lundbeck's sertindole, ZENECA's *SEROQUEL* (quetiapine), and

Pfizer's ziprasidone. Lilly and Abbott submitted NDAs in October and November, 1995, respectively, and anticipate marketing approvals within a year. The *SEROQUEL* NDA submission is slated for July, 1996 with approval expected between July and September, 1997. An executive from Pfizer has been quoted as saying that ziprasidone's NDA will be submitted in 1997, though competitive intelligence suggests that the drug may be experiencing some difficulties in clinical trials. A 12 month review would be expected for this compound as well unless specific areas of clinical concern are identified.

SEROQUEL will face considerable competition at launch given its timing to the market relative to olanzapine and sertindole, as well as the formidable presence of Janssen, Lilly, Abbott, and Pfizer in the psychiatric marketplace. *SEROQUEL*'s clinical profile is strong but not unique in having demonstrated efficacy vs positive and negative symptoms, EPS no greater than placebo across the dose range, and lack of sustained increase in prolactin levels, with a receptor binding profile that closely resembles that of clozapine. The strategic positioning statement for *SEROQUEL* at launch is:

> "***The*** atypical antipsychotic agent for first line treatment, with proven efficacy against positive and negative symptoms ***plus*** no EPS or prolactin liability compared to placebo across the *SEROQUEL* dose range."

Risperidone's positioning has been "The only first-choice serotonin-dopamine antagonist" ... emphasizing efficacy against both positive **and** negative symptoms, and "EPS comparable to placebo at doses ≤10mg/day". This positioning will be weakened by the new entrants, including *SEROQUEL*.

Olanzapine's positioning is expected to revolve around once daily dosing, no titration needed, and EPS comparable to placebo at low doses (like risperidone).

Sertindole is also expected to emphasize once daily dosing but is likely to be hampered by a very long titration period (2 weeks). Their EPS and prolactin message is similar to *SEROQUEL* in that the data suggests no increase over placebo at any dose.

SEROQUEL will not have relapse prevention data to support long term use at launch, a previously anticipated differential advantage. Qualitative marketing research conducted in early 1996 has suggested that the success or failure of any one of these products will be a direct reflection of time to market and effective sales and marketing efforts, given the similarities among the new products at launch. Pricing sensitivity analysis will need to be conducted to better understand how this factor will contribute to market adoption.

In addition to traditional marketing initiatives, resources to reach patient advocacy groups will be important to the success of *SEROQUEL*. These groups are increasingly well organized and influential in the adoption of new therapies by clinicians and payers alike.

Base case forecast for *SEROQUEL* achieves gross sales of REDACTED in 2000, with peak year gross sales of REDACTED in 2010. This compares favorably to the 1995 Strategic Plan forecast

of REDACTED in 2000 and REDACTED peak year (2008). The increase is due to both volume and price. Additionally, revision of the estimated patent expiration date for *SEROQUEL* has impacted the year of peak sales.

REDACTED

II. OBJECTIVES

- Submit *SEROQUEL* NDA by end of June, 1996.

- Launch 3rd quarter 1997, no more than 12 months after olanzapine and sertindole.

- Achieve [redacted] market share and [redacted] gross sales in 1997.

- Achieve [redacted] share of the total antipsychotic in 1998, representing [redacted] of the atypical segment. Peak year target of [redacted] of total market share, [redacted] of the atypical market.

- Achieve [redacted] in gross sales by end of first full year on the market (1998) and peak year sales of [redacted] in 2010.

- Launch once daily tablet and liquid formulations within 3 years of initial product introduction (3Q00).

- Demonstrate safe and effective use in special populations: treatment resistant, elderly, Parkinson's disease, children and adolescents within 3 years of launch (3Q00).

- Demonstrate significant health outcome and economic benefit for *SEROQUEL* vs "usual care" medications within 3 years of launch (3Q00).

III. SITUATION and SWOT ANALYSIS

SITUATION ANALYSIS

A. Internal Analysis

SEROQUEL represents the first product that ZENECA will launch to psychiatrists. As such, we are at a competitive disadvantage in entering the antipsychotic market. The psychiatry market is dominated by several large, long-time players: Lilly, Pfizer, Janssen, SKB, Sandoz and Abbott. Additionally, the late market entry of *SEROQUEL* relative to other new atypicals will be an obstacle to adoption. ZENECA must therefore commit significant resource in order for *SEROQUEL* to achieve it's potential. Prelaunch activities for olanzapine, as demonstrated by meeting/convention presence and product awareness among psychiatrists, have been significant. Sertindole, though not as well recognized as olanzapine, has been fully resourced at Abbott, having surpassed *SEROQUEL* in submission of its NDA when it had been behind only 18 months ago. Pfizer has kept a very low profile with ziprasidone. This stance has caused some speculation that the drug is underperforming in clinical trials.

Although there are over 30,000 licensed psychiatrists in the US, only 12,000 - 15,000 actively treat schizophrenia. These physicians will form the basis of sales targets for *SEROQUEL*. Current *Risperdal* detailing levels (>160,000 annually[4]) provide a benchmark for planning the necessary detailing level for *SEROQUEL*. Given the level of competition in the market at the time of launch and beyond, *SEROQUEL* expenditures must be allocated so as to maximize share of voice. Equally important will be the support of peer influence programs and outreach through patient advocacy groups, eg the National Alliance for the Mentally Ill (NAMI).

If ZENECA goes it alone, a new sales force of at least 100 representatives will have to be hired to detail *SEROQUEL*, with additional details possibly provided by the existing hospital sales force where appropriate. As *SEROQUEL* will be the only product promoted to psychiatry, it will bear the full detailing expense for the specialty force. Copromotion options currently under consideration, if pursued, will ease this cost (estimated at $150 per call) and result in an increase in launch year -peak year market shares.

B. Market Overview

Schizophrenia affects approximately 1% of the world's population over the age of 15. Onset is typically in the late teens or early 20's, with diagnosis often delayed due to clinical confusion with behavioral disorders and/or depression. The widespread stigma attached to serious mental illness is an additional obstacle to diagnosis.

Schizophrenia is a clinical psychiatric syndrome with diverse presentations characterized by two major types of symptoms:

- Positive symptoms
  - delusions
  - hallucinations
  - cognitive deficits

- Negative symptoms
  - social withdrawal/isolation
  - blunted or inappropriate affect
  - lack of energy
  - low levels of emotional arousal
  - low levels of mental activity (cognitive function)

There is no known cause of the disorder, thus the treatments which are available are for the management of its symptoms and do not "cure" the disorder itself. The chronic, relapsing nature of schizophrenia contributes significantly to the difficulties in successful long term management.

A diagnosis of schizophrenia often does not occur until a patient's positive symptoms become severe enough to warrant hospitalization. Upon hospitalization, the primary clinical goal is to stabilize the patient's condition, principally through the management of their positive symptoms. This period of stabilization in the hospital usually lasts several weeks, due to the need for gradual titration to an effective dose and a high interpatient variability in response to antipsychotic medications. Although drug treatment has proven to be effective in most patients, the vast majority (upwards of 80%) of diagnosed schizophrenics suffer multiple relapses and are likely to require rehospitalization for exacerbation of psychotic symptoms.

After discharge from the hospital, treatment is continued on an outpatient basis for the rest of the patient's life. The most commonly prescribed medications are the old, "typical" neuroleptics which are divided by potency, with haloperidol (*Haldol* and generics) representative of a high potency agent and thioridazine (*Mellaril* and generics) representative of a low potency agent. High potency agents are considered more effective in controlling positive symptoms but cause more EPS than the low potency agents.

The variable efficacy and tolerability of these compounds results in a very high "switch" rate by psychiatrists. The average clinician has 7 or 8 different antipsychotics in their usual armamentarium, switching among brands regularly. 20% of patients started on any one drug are

eventually switched over to another drug, as no one antipsychotic medication is effective and/or well tolerated by most patients[5]. A recently initiated market research project will help to answer the question of when patients are switched and why.

Clozapine was introduced in 1990 as the first "atypical" antipsychotic and represented a major breakthrough in pharmacotherapy. It's usage has been restricted to third line therapy due to a 1% incidence of agranulocytosis, a potentially fatal blood dyscrasia. Despite the high cost and need for weekly blood monitoring, clozapine continues to gain market share[4]. This is a manifestation of the enormous unmet medical need in this market.

The second putative atypical agent to launch was risperidone, introduced in February 1994. It is considered "putative" because it's receptor binding profile does not match that of clozapine, which "defines" atypicality. This is particularly so in the minds of the FDA. The market has been somewhat less academic in it's definitions.

Risperidone has had a significant impact on the market in several ways. Firstly, it has established the treatment of negative symptoms as an achievable clinical goal. The neuroleptics are relatively ineffective at treating this aspect of the disease. Risperidone has also increased the dollar value of the market tremendously and set a benchmark for premium pricing vs generics. The total market value was REDACTED in 1989 as compared to REDACTED in 1995[3]. Risperidone is ranked third in new Rx and total Rx, according to industry audits[4] and is poised to overtake second place ranking from thioridizine and challenge haloperidol's leadership position in 1996. *Risperdal* achieved REDACTED in sales and an RE total Rx share in 1994, it's first 11 months on the market. 1995 *Risperdal* sales have exceeded REDACTED with a consistent, strong rate of adoption, as measured by growth in new Rx share[3,4]. This is remarkable in light of the reported general disappointment with the drug's clinical performance[5,6].

The value of the market will continue to increase with the expansion of the atypical segment, fueled by new product introductions in 1996 - 1998. Recent industry projections of a REDACT market by 2005 should be exceeded in 1996. The following graphs illustrate the dynamics of the marketplace since the launch of *Risperdal*.

C. Competitor Analysis

Sandoz and Janssen are currently the two major players in the antipsychotic market with several others preparing to launch new products in 1996 and 1998. These include Lilly, Abbott, and Pfizer. Each of these competitors has been actively promoting other products to the psychiatric community and therefore has a significant advantage over ZENECA.

Lilly's olanzapine (*Zyprex*) is expected to be the first new market entrant and command the largest share of all antipsychotic drugs, both typical and atypical, within 4 years of launch[7]. Sales estimates of REDACTED in US revenues have been posited by the year 2000[7]. Physician feedback obtained during market research interviews supports this projection[6]. Once daily dosing, high visibility leading to positive perception prelaunch, an aggressive publications plan, and significant financial and human resource, will help to secure this market leadership role for olanzapine. It is anticipated that Lilly will launch olanzapine at a RED price premium to risperidone given it's once daily dosing and no titration advantages.

Abbott's sertindole (*Serlect*) is not expected to fair nearly as well. External analyst forecasts for sertindole project a market share of one fifth that of olanzapine, equating to approximately REDA in US sales[7], though we think this is pessimistic. Our view is that sertindole will gain a REDA share, less than half that of olanzapine at peak. This is unless Abbott is required to do further study or have restricted labeling due to QT prolongations reported in sertindole clinical trials. The lengthy titration period (13 days) is also seen as a liability. Abbott will likely price sertindole at parity with risperidone.

Pfizer's ziprasidone is expected to submit its NDA in mid-1997 with launch anticipated in mid-late 1998[8]. Ziprasidone is seen as a relatively weak competitor due to late market entry and surprisingly little premarket awareness. Pfizer has keep a very low profile on this compound, leading some to speculate that it may be experiencing some difficulties in clinical trials. Clinical trial data expected to be presented at the 1996 American Psychiatric Association convention in May should yield further insight into the status of ziprasidone. Current forecast models project a market share of RED Pfizer may chose to introduce ziprasidone at a discounted price relative to risperidone, sertindole and *SEROQUEL* given it's late entry and apparent lack of differentiating features.

Extensive competitive intelligence is being gathered on all atypical antipsychotics and will be reported in May (final report from the Dunn Group). The findings of this research will add substantially to our understanding of the likely strategies of our competitors.

D. Environmental Analysis

The rising cost of healthcare in the US is causing profound changes in the healthcare marketplace. In this environment, the same business pressures which threatened medical product companies in the 1980's are surfacing in the pharmaceuticals market, namely the growth of large buying groups which increase pricing pressure and result in intensified competition for market share; the emergence of non-clinician decision makers in product selection; the growing trend to commodisize products as customers attempt to diminish the value of new technology and thwart product differentiation; and the increasing importance of value-added services in contract negotiations.

Schizophrenia is one of the most costly diseases in America and is *the most costly* mental illness[1,2]. Multiple sources estimate that more than 25% of all hospital beds in the US are occupied by schizophrenic patients, with 40% of all long term care days and 20% of all Social Security benefits attributable to the disease. The annual economic burden exceeds $32 billion[1]. Schizophrenics are high utilizers of medical care and tend to concentrate in subpopulations that are highly dependent on public assistance. The majority of treated patients are covered by Medicaid (43%) and Medicare (31%). Medicaid is important because a) government pays for oral medications, sometimes less a small co-pay, b) best price issues, and c) potential for future involvement in MCOs. Medicare is less important currently, but may well become important if, as projected, these patients become managed by MCOs, which pay for oral medication and therefore have an interest in managing those costs. It is expected that increasing numbers of Medicaid and Medicare recipients will be transferred into managed care plans, as the government tries to curb escalating health care costs. This shift in plan coverage is exemplified by the recent implementation of a Medicare contract for one of the nation's largest HMOs, US Healthcare. Trends such as this will need to be watched closely and proactive initiatives set forth to capture the business of mental health carve outs. This is particularly relevant for *SEROQUEL* given the alliances of Lilly with PDS, Abbott with Caremark, and Pfizer with ValueRx.

Capitation and disease management programs may also play a role in the treatment of schizophrenia in the future. It is believed that Lilly has already established a disease management pilot program[8]. Similar activities should be explored with Stuart Disease Management Services.

The gap between research/clinical data and treatment patterns may be particularly important in schizophrenia. For example, the combination of antipsychotic medication and psychosocial intervention which is considered the most effective approach to the management of the disease is not widely practiced. Since schizophrenia is such an expensive illness, creating a link between effective medicines and overall cost savings will be paramount to the lasting growth of the antipsychotic market.

Market research conducted in 1994 indicates that 65-71% of schizophrenia treatment occurs in the outpatient setting[5]. 17%[4] of treatment occurs in acute care hospitals with the remainder in long term care facilities such as nursing homes. With the aging population it will be important to consider detailing efforts for the long term care market, particularly in the later years of the product life cycle.

1996 SWOT ANALYSIS

STRENGTHS:

- Efficacy in positive and negative symptoms established in Phase III
- Clinical results to demonstrate reduction in negative symptoms as compared to placebo.
- No greater extrapyramidal symptoms of (EPS) than placebo across the complete clinical dose range. Competitive advantage vs olanzapine, Risperdal, & standard neuroleptics
- Implications of no Tardive Dyskinesia due to low incidence of EPS
- Lower co-administration of anti-cholinergic medications vs standard neuroleptics
- No increase in prolactin levels across the dose range - A competitive edge over risperidone and standard neuroleptics
- Sedative effect of Seroquel a benefit in aggressive and/or agitated schizophrenics.
- Health economic benefit vs "usual care" (to be proven in trial underway)
- Efficacy in treatment resistant patients
- Efficacy in elderly patients
- Efficacy in adolescents
- Efficacy in Parkinson's
- Improvement in cognitive function in select patient populations
- Brand name recognition versus competition: "Seroquel" trademark.
- Sales and Marketing organization that has proven it's ability to change traditional medical practice
- Corporate history of advocacy group support
- Zeneca has established, strong relationship with Managed Care
- Licensing/co-promotion opportunities

WEAKNESSES:

- Risperidone will have had >3 years of "market exclusivity" by the time Seroquel launches.
- SEROQUEL launch will be after risperidone, olanzapine (Lilly) and sertindole
- Seroquel has bid dosing vs QD dosing for olanzapine & sertindole.
-
- Titration: SEROQUEL dose titration will be more complicated than olanzapine but less complicated than sertindole. It is similar to typical antipsychotics.
- Sedative effect may be a detriment in certain patient types
- Seroquel is perceived as having low efficacy due to low potency profile
- Possible negative thyroid effects
- Limited formulation: olanzapine and sertindole have plans for IM injection and depot formulations; olanzapine may have Zydis "fast melt" tablet. Seroquel will not have an IM, depot, or fast melt.
- Limited tablet strengths.
- Limited package sizes
- ZENECA inexperience and lack of presence in CNS/psychiatry arena.
- Limited range of psychiatric products and services available to provide cost effectiveness to customers (disease management)

OPPORTUNITIES:

- Janssen, with risperidone, has established the receptivity of the antipsychotic market to the new atypical agents. There will be continued expanding and segmentation of the market as other atypicals are launched.
- Unsaturated, unsatisfied market. Even with the successful launch and penetration of risperidone, there is significant unmet need for new agents with improved efficacy and safety.
- Need for improvement in management of negative symptoms (acute and chronic).
- Need for improved efficacy in positive symptom control (e.g., treatment refractory patients, partially responding patients).
- Need for agents with better side effect profile in terms of minimal/no EPS (despite risperidone launch) - opportunity to improve patient compliance and earlier treatment
- Potential for use in adolescents (to be quantified)
- Potential for use in other high unmet medical need diseases, e.g. dementia, due to lack of EPS
- In addition to non-compliant patients, there are a significant number of untreated schizophrenic patients.
- High switch rate in use of antipsychotic agents by psychiatrists, which implies significant unmet need. This also implies each product is unique, making formulary control difficult.
- Need for products with health economics packages or outcome benefits that illustrate direct benefits to payers and society - especially in terms of reductions in hospitalizations and other cost-intensive services.

THREATS:

- Olanzapine & sertindole to be marketed by Lilly & Abbott; both have significant presence with the psychiatric audience already (Prozac, Depakote).
- Olanzapine & sertindole will be launched ahead of SEROQUEL and as once daily capsules, followed by depot formulations.
- Competitors (e.g Janssen/risperidone) have already taken the lead to promote use in treating negative symptoms.
- "Specialized niches" are being created by competitive companies, simply by novel analysis of data and outline of clinical trials (e.g. , data against primary negative symptoms by Lilly/olanzapine).
- Increased competition will result in need for increased/significant promotional spend.
- Greater number of newer agents will lead to further market segmentation and create niches for products based on profile and cost, etc.
- Experience in development of line extensions by competition will elevate competitive hurdles.
- Lilly's ownership of PCS and Pfizer's ownership of Caremark/Value Rx will give these companies a wealth of patient information.
- Lilly's disease management program for schizophrenia.
- Managed Care groups may create more restrictive formularies if the perception is that all atypicals are similar.
- There is still a social stigma associated with the diagnosis of schizophrenia. This creates barriers for patients to seek treatment and manage schizophrenia (e.g., through improved compliance).

OPPORTUNITIES:

- Build on documented studies which support the fact that drug therapy for schizophrenia decreases overall cost of treating the illness.
- Strong patient advocacy groups (e.g., NAMI) and other health care institutions (e.g. NIMH) are increasing awareness of the need to better treat and manage schizophrenia (e.g. through improved compliance)
- Because the disease of schizophrenia has a significant impact on family members, there is an opportunity to influence family regarding type and level of care.
- Heterogeneity of schizophrenic population - not all patients respond equally to the same therapies.
- Heavy Medicaid population currently, but movement to Managed care for administering health care benefits is already happening (shift in provider; increased number of patients treated).
- REDACTED
- Licensing/co-promotion opportunities.
- Significant discounting is not anticipated in the forecast period.
- Shorter FDA review period (12-15 months vs. 24 months)

IV. FIVE YEAR STRATEGIC PLAN

A. Summary of Previous Strategies

Previous strategic plans for *SEROQUEL* have included the original Commercial Development Plan (1995-2000), written by the Commercial Strategy Team and accepted by the PDC in October 1994, as well as a five year strategic plan for the US, written in April 1995 and endorsed by US upper management. The strategic intent of these plans remains valid, although the tactical approach to achieve sustainable competitive advantage, as well as timing of deliverables, have changed significantly. The previous strategic objectives were:

1) To submit the *SEROQUEL* NDA, including relapse prevention data, no later than April 1996.

2) To launch *SEROQUEL* in the US in 1Q98, being the third atypical on the market (behind risperidone and olanzapine).

3) Gain REDACTED market share by the end of the first year, increasing to REDACTED share by end of second year. Achieve third atypical market share ranking by 2002.

4) Exceed REDACTED in sales by the end of the third full year from launch (2000).

5) Achieve early trial and usage of *SEROQUEL* by 85% of practicing psychiatrists within two years of launch.

6) Achieve awareness of *SEROQUEL* among 8% of APA attendees one year prior to launch (1997).

7) By launch, develop a cadre of at least 10 top opinion leaders with sufficient experience and influence to serve on advisory panels, to present at meetings, and publish *SEROQUEL* clinical data.

8) In 1995, develop a life cycle management strategy to identify additional needs to augment the growth phase for *SEROQUEL* and to maximize or extend profits.

The pivotal Phase IIIA trials (Studies 12 and 13) were designed to compare *SEROQUEL* to placebo, measuring efficacy against positive and negative symptoms, assessing the safety profile including EPS and prolactin, and establishing a dosing schedule. These trials have been completed and support the position of *SEROQUEL* as an atypical antipsychotic agent.

To further enhance the competitive position of *SEROQUEL*, relapse prevention, treatment resistance, and health outcomes trials were initiated. It was anticipated that these ground-breaking clinical studies would provide compelling selling messages at or about the time of launch, and

safeguard price integrity. It was also felt that studying the large unsatisfied segment known as "partial responders" would strengthen the perception of *SEROQUEL* as a broadly effective first line agent. The previous positioning statement for *SEROQUEL* was:

"SEROQUEL is the best available first-line antipsychotic - unique in possessing demonstrable efficacy across the full spectrum of positive symptomatology (including "partial responders" and treatment resistant patients), coupled with the attractive safety profile including no or decreased EPS and improved outcomes/quality of life over all other antipsychotic agents."

This positioning was based on what was expected to be the likely deliverable clinical characteristics of *SEROQUEL* and assessment of market research and consultant views on needs from antipsychotic therapies. The relapse prevention study (Study 15) failed, with neither the *SEROQUEL* or the haloperidol arm demonstrating efficacy in preventing psychotic relapse due to clinical trial design flaws. The treatment resistance trial has been plagued with recruitment and drug supply problems and is currently expected to deliver in 2Q96, approximately 6 months - 1 year after original planned delivery.

The Phase IIIB Health Outcomes trial is underway though recruiting slowly. This study compares *SEROQUEL* to "usual care" (any first line therapy) in the treatment of "revolving door" patients. These patients are a subset of schizophrenics who do not adequately respond to current therapies, leading to a high level of noncompliance and resource utilization. The primary endpoint of the study is the rate of hospitalization. It is expected that *SEROQUEL* will provide effective and better tolerated treatment, resulting in fewer hospitalizations over time. The clinical team is addressing ways to ensure timely completion of the study and what other trials might be done on a smaller scale to provide meaningful economic data in the short term.

Given these events, the Strategy Team has addressed ways to adjust the risk and delivery of clinical data to support a differentiated position (see Five Year Strategic Direction).

New formulations of *SEROQUEL* are also being investigated. These include the current immediate release formulation administered on a once daily basis (based on suggestive PET data); an in-house sustained release formulation of the immediate release tablet; a sustained release formulation from Eurand; and a sustained release granule formulation for reconstitution, also from Eurand. The competition continues to pursue alternate formulations also, working on depots (not possible with *SEROQUEL*), Zydis fast melt tablets, and so on. Given that olanzapine and sertindole will be launched with once daily dosing schedules, it is imperative that ZENECA provide innovative dosing options for *SEROQUEL* as soon as possible post approval.

B. Five Year Strategic Direction

As the treatment of schizophrenia becomes more sophisticated, new rating scales, receptor binding theories and patient categorizations are emerging. Janssen initially capitalized on the new categories and product attributes to create a position for risperidone as effective in controlling the positive *and* negative symptoms of schizophrenia. Promotional efforts for all the new atypicals entering the market between 1996 and 1998 will attempt to create differential positioning built on unique combinations of features addressing the needs of the various patient subgroups and symptomatology. Recent marketing research indicates, however, that the perception of these drugs is that they are all very similar[4]. This suggests that the success or failure of any of these products will largely rest on the timing to market and effective sales and marketing efforts.

SEROQUEL's strength lies in it's safety and tolerability profile. Strategically, this must be capitalized on in order for the brand to achieve its potential. As such, the proposed direction for brand augmentation is to study *SEROQUEL* in patient populations who are known to be particularly sensitive to the adverse effects of antipsychotic medications as outlined below.

- Differential tolerability vs risperidone, especially EPS
- Effect of *SEROQUEL* on TD
- Treatment of adolescents with schizophrenia, schizoaffective disorder, and bipolar disease
- Elderly schizophrenics
- Parkinson's Disease patients with treatment-induced psychosis or dyskinesias
- Dementia in Parkinson's and Alzheimers patients
- Effects of *SEROQUEL* on cognitive function

With the failure of Study 15, the Strategy Team reevaluated the Phase IIIB program and determined that the level of risk had to be reduced, as failure of another large scale trial, eg treatment resistance, would result in significant damage to the brand's market perception if there weren't other trials successfully completed in parallel. To lower the future risk, a decision to cancel a high risk trial (US Partial Responders) was made. The European partial responder trial (PRIZE) will continue as planned and, if successful, will provide support for further differentiation in the US.

The resources which were allocated for the US Partial Responders trial are being reinvested in these smaller, lower risk studies which will further augment *SEROQUEL*'s advantages relative to EPS/overall tolerability, and expand its application into new patient populations. These trials are being designed to deliver in relatively short timeframes (1-2 years post launch). The revised positioning statement for *SEROQUEL* developed by the Strategy Team in February 1996 is:

"***The*** atypical antipsychotic for first line treatment of schizophrenia with proven efficacy against positive and negative symptoms ***plus*** no EPS or prolactin liability compared to placebo across the *SEROQUEL* dose range."

This positioning is based on an evaluation of the deliverable clinical characteristics of *SEROQUEL* which will be included in the NDA/MAA and was supported by qualitative market research conducted in February 1996[5]. It will require definitive testing in 1996.

Key Promotional Messages

At launch *SEROQUEL*:

- Is an atypical antipsychotic agent which is active at multiple brain receptors.
- Is a first-line antipsychotic agent with efficacy against both positive and negative symptoms.
- Is well tolerated, with EPS no greater than placebo across the dose range.
- Does not cause sustained increases in prolactin.
- Requires less coadministration of anticholinergic medications.

Post launch *SEROQUEL*:

- Can be administered once daily with either a tablet or liquid form.
- Is more effective than chlorpromazine in treatment resistant schizophrenia with response rates similar to those reported for clozapine.
- Is more effective than usual care medications at reducing the rate of hospitalization, thus providing significant cost-benefit.
- Is effective and well tolerated in special patient populations: elderly, Parkinson's, dementia, Alzheimer's, and adolescents.
- Is effective in improving cognitive function in schizophrenic patients.
- Is well tolerated in patients intolerant of risperidone.

Five Year Strategic Direction

Strategic Action	Resp. Function	Priority	Timing	Resource Needs
Assign Product Management Team	Marketing	High	1Q96	Full time product manager and APM/PPM
Submit NDA/MAA	CMA, DRAD, Development	High	1H96	Adequate clinical and biometrics staff plus CRO budget
Complete Phase IIIA Trials	CMA, Development	High	Completed 3Q95	Centrally funded
Implement Revised Phase IIIB Program, including US and European studies	CMA, MRD, NPP, PSD, DRAD, IRD, Development	High	1Q96 - 4Q98	Centrally Funded
Implement Drug Interaction & Switching Studies	CMA, DRAD, Development	High	4Q95 - 4Q96	Centrally Funded
Evaluate Options for QD Dosing; Submit NDA(s)	CMA, MRD, NPP, PSD, DRAD, IRD, Development, Licensing	High	2Q95 - 4Q98	Centrally Funded
Evaluate Liquid Formulation; Submit NDA	CMA, MRD, NPP, PSD, DRAD, IRD, Development, Licensing	Medium	2Q95 - 4Q98	Centrally Funded
Initiate second US treatment resistant study to obtain indication	CMA, DRAD, Marketing	High	1Q97 - 4Q98 sNDA 1Q99	Locally Funded
Implement 1996 Operational Plan including comprehensive communications plan	NPP, Marketing, EA, CMA*, Seroquest, Discovery Int'l	High	Ongoing	Outside Services Budget *CMA resources constrained

Five Year Strategic Direction Continued

Strategic Action	Resp. Function	Priority	Timing	Resource Needs
Conduct marketing research to support strategic plan initiatives, eg pricing, positioning, managed care, CI	NPP, Marketing, BMR*, Market Strategy Dept., Sales, Sudler & Hennessey	High	1995 - 1997	Outside Services Budget *Full time market research analyst needed
Determine field sales personnel requirements	Marketing, NPP, Sales, Sales Administration	High	Ongoing	Sales Budget

VII. REFERENCES

1. Rice, D., Schizophrenia, 1995.

2. *"Schizophrenia": $32.5 Billion to Treat Schizophrenia, Costliest Mental Illness for Medicaid*, Weber & Associates, March 1996.

3. IMS Audit, December 1995.

4. Scott Levin/PDDA Audit, December 1995.

5. *Schizophrenia Market Study*, Ziment Associates, Inc., 1994, 1995.

6. Gallagher, J., *Qualitative Study of Current vs Future Prescribing of Antipsychotics for Schizophrenia*, 1996.

7. Hecht, E.M., Brooke, P.A., *Schizophrenia: The Next Major CNS Opportunity*, Morgan Stanley & Co. Industry Update, March, 1996.

8. Jones, K., *Regulatory and Strategic Marketing Assessment of the Antipsychotic Marketplace* (preliminary findings), The Dunn Group, March 1996.

9. COGNOS, *Schizophrenia*, Decision Resources, 1995.

10. Scott Levin, SPA Audit, December 1995.

11. Epidemiology of Schizophrenia: 1915 - 2015, Matson Jack, 1995.