ZYPREXA GLOBAL MARKETING PLAN
2003-2004

Please Return to Bill Dector

ZYPREXA Global Marketing Plan
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Answers That Matter.

ZY 8413 645
COLUMN I: ANALYSES AND GIVENS

Environmental Analysis

The following analysis provides an overview of the external environment that ZYPREXA will operate in over the plan period.

Political: In 2001, the industry faced one of the most challenging political environments in its history stemming from the fact that federal and state budgets were stretched and pharmaceuticals were a line item that legislators increasingly targeted. In the US, the government is proposing changes to Medicaid that would likely require increased rebates from drug manufacturers to cover drug costs; this move could be devastating on company revenues. In another effort to hold down Medicaid costs, some states are proposing “fail-first” policies for medications they consider too expensive. Under these policies, patients would be denied access to new medicines such as ZYPREXA until it could first be proven that lower-cost treatments are not as effective. Political pressures to hold prices down are also growing across the EU, Japan and ICR where all new medications are being scrutinized. This will require more lobbying activity to maintain access for ZYPREXA. The trend is for a decline in political support for the pharma industry.

Economic: The global economic slowdown is expected to continue while healthcare costs continue to escalate – as a result increasing pressure will be placed on healthcare budgets across the globe. As our portfolio composition shifts to ZYPREXA – with heavy dependence on the public payer system – we must increasingly manage access and price/value issues. Again, grass roots activity will be necessary to maintain access.

Competition: Despite the growing importance of key players in the decision process and the emergence of promising promotional tools, the competitive environment is still driven by share of voice, with physicians acting as the primary decision-makers. Physicians are now influenced through a variety of channels (congresses and meetings, medical education programs, and peer-to-peer initiatives, among others) decreasing the relative influence of the sales representative. The significance of Direct to Patient (DTP) initiatives has increased dramatically and in some markets is now seen as critical to the SOV (Share of Voice) equation.

In 2002, competitive activities will intensify with the launches of Risperdal Consta and Abilify as well as the re-launch of Geodon in the US and the launch in Europe. In addition, many of our competitors – Seroquel and Abilify, for instance – are seeking to expand their uses beyond schizophrenia with indications such as bipolar disorder (BPD) and the increased use of off-label promotion. Patent expirations and subsequent generic availability will have implications on competitive brand pricing. Competitors are also seeking to chip away at ZYPREXA market share with: 1) accusations of an alleged link to diabetes and other metabolic issues and 2) the spread of untrue rumors about impending black box warnings. Additionally, many competitors are experiencing stock
volatility which could lead to additional mergers and a ensuing distraction from implementation.

Social/Cultural: The advocacy community (especially OUS) will become better organized, educated and developed and make strides to lessen the stigma of mental illness. Developed markets will experience a swelling in their senior populations that will result in increased pressure on the healthcare and retirement systems. In this context, competition for healthcare dollars will increase and mental health medications will be forced to demonstrate their net worth to society. Additionally, economic pressures have triggered huge state budget problems in the US, leaving mental health advocates fighting to simply maintain 2001 local and state funding levels for mental health programs. Additional trends include: 1) patients seeking more information about health care due to the impact of DTP initiatives and the increased availability of information, 2) an increase in the role of non-traditional therapies to treat diseases, 3) a decrease in counseling and psychology services which are a necessary part of treating mental illness, and 4) a growing dissatisfaction with the level of care that patients receive due to budgetary and health care management constraints resulting in a consumer backlash against payors.

Technological: The launch of Risperdal Consta and Abilitat represent the biggest technology advances in the plan period. Other technology platforms are numerous but are currently in phases I/II.

Legal/Regulatory: In general, pharmaceutical companies are becoming increasingly litigious with each other and are using this intervention to impact market dynamics. In addition to company-to-company litigation, consumers have become more litigious against product manufacturers on a global basis. It is anticipated that both of the above trends will continue and intensify.

In the US, the regulatory environment continues to become more stringent in requiring more data to be generated by manufacturers for new product registrations and products currently on the market. Additionally, the FDA (Food and Drug Administration) continues to place increased scrutiny on all processes (clinical trial, manufacturing, data storage), which has impacted global product availability.

In the US, the WLF (Washington Legal Foundation)/FDAMA (Food and Drug Modernization Act) ruling that allows the dissemination of off-label information, is expected to continue. This is a positive for customers, who often look for information regarding ZYPREXA (and competitive products) that is outside of the approved label.

Healthcare: There is an increasing pressure to demonstrate clinical effectiveness of brands (e.g. NICE) prior to inclusion in national treatment guidelines and formularies. This requires the pharmaceutical industry to produce naturalistic health outcomes data to justify clinical use and adoption. This data requirement is in addition to regulatory approval.
Environmental Analysis – Insights and Implications for ZYPREXA

- The economic and political situation will create a difficult financial situation for healthcare budgets. It will become more critical for premium-priced medications to demonstrate value to maintain access.
- Consumers will demand more from the healthcare system. At the same time, budgetary pressures will continue to increase and challenge that demand.
- The environment will drive creative solutions to pricing and access issues – a drastic measure could be taken to dramatically change the game.
- The barriers of entry to compete in this market will increase due to increased data requirements, specifically in the area of health outcomes.
- Regulatory agencies have increased their scrutiny on manufacturing processes, resulting in delayed product availability.
- As market leader, ZYPREXA should expect competitors to use litigation as a market lever.
- As competition intensifies, the spread of brand misinformation will increase.

Disease State Overview

ZYPREXA is used to treat a variety of mental illnesses. Markets for the brand are:

Core markets: Schizophrenia and Bipolar Disorder
Borderline Personality Disorder will now be pursued. The ZPT is currently developing detailed plans to approach this new opportunity.

*Opportunistic market: Psychosis associated with Dementia

Market Opportunities: Post Traumatic Stress Disorder, High Dose, Child and Adolescent (Schizophrenia and Bipolar Mania)

The plan covers core and opportunistic markets. The ZPT defines opportunistic as a market with a total conversion rate of greater than forty percent.

Schizophrenia

Prevalence/Incidence

Schizophrenia is a severe mental disorder that manifests itself through positive and negative symptoms (see diagnosis below). It is generally considered to be a chronic and lifelong disorder. The one-year incidence rate is one per 10,000 and the lifetime prevalence rate is 1.0%.

Diagnosis

A diagnosis of schizophrenia is based on the presence of the following positive and/or negative symptoms:
<table>
<thead>
<tr>
<th>Positive Symptoms</th>
<th>Negative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions (false beliefs)</td>
<td>Diminished emotions</td>
</tr>
<tr>
<td>Hallucinations (non-existent voices)</td>
<td>Low motivation and general lack of interest</td>
</tr>
<tr>
<td>Disorganized speech (incoherence)</td>
<td>Reluctance to speak and socially interact</td>
</tr>
<tr>
<td>Grossly disorganized or catatonic behavior</td>
<td>General apathy</td>
</tr>
</tbody>
</table>

Acute psychosis is preceded by a prodromal phase that may last several months, if not years, before the onset of positive symptoms. In order to make a definitive diagnosis, positive symptoms must be present for at least one month, and a total duration of illness (acute and prodromal) must be at least six months. Due to a number of factors, the diagnosis of schizophrenia can be a lengthy and difficult process. A psychiatrist typically makes the initial diagnosis during a patient’s first hospitalization for an acute psychotic episode.

Since no definitive laboratory tests or other diagnostic technology exists, the psychiatrist must rely on family history, physical examinations, in-depth interviews with the patient and family/friends, and observation of the patient’s behavior. The diagnosis is often achieved by comparing the type and duration of the patient’s symptoms to criteria for schizophrenia and other psychotic disorders as outlined in standardized classification systems such as the DSM-IV-TR or ICD-10.

**Treatment**

The treatment for schizophrenia includes antipsychotic agents (typicals and atypicals), hospitalization and psychological and psychosocial interventions.

**Lifecycle**

About 25% of patients experience one acute psychotic episode and recover fully within a few months; 50% recover but suffer recurrent episodes throughout their lives; 25% will remain permanently disabled and require constant intensive care and treatment.

The clinical course of schizophrenia can be separated into four phases. The *premorbid phase* identifies the patient’s level of psychosocial functioning preceding any evidence of illness. The *prodromal phase* encompasses the onset of psychiatric symptomatology that does not reach a threshold for psychosis. The first episode of psychosis marks the formal onset of schizophrenia with its formal signs and symptoms. It also marks the *progressive phase* where clinical deterioration occurs (though this process may begin even in the pre-psychotic prodromal phase). Finally, those patients with enduring symptoms generally reach a plateau where deterioration ceases and the patient enters a *stable relapsing phase*. 
Complications

Schizophrenia is associated with social stigma, often derived from public misconceptions of what the condition is, and the symptoms associated with it. The impact of this on the sufferer can exacerbate some of the negative symptoms, such as social withdrawal.

Developing schizophrenia, with its associated losses in self-esteem, causes many patients to show symptoms of depression, appearing withdrawn and unable to cope with life. Co-morbid depression is often associated with the 40% suicide attempt rate, and 10% mortality rate for suicide in schizophrenia, 12 times that of the general population. Cognitive deficits, such as abnormal attention and memory function, are present early in the illness and may lead to failure at school and at work, which may then lead to economic hardship and dependence on family or social welfare.

Positive symptoms, if poorly controlled, may result in various problems. Positive symptoms may "command" the patient through auditory hallucinations to take their life. Positive symptoms may seriously interfere with concentration making it difficult to work and/or attend school.

Demographics

Demographic factors such as age at onset, marital status, living situation and employment status can significantly impact the prognosis of schizophrenia. A better prognosis is associated with a positive, supportive family situation and the opportunity to be gainfully employed as a member of society.

Onset is usually between the ages of 17 and 30 in men and between 20 and 40 in women. Schizophrenia occurs equally in both genders, however there may be differences in symptoms. Mood symptoms, particularly depression, tend to be more frequently identified in women than in men.

Patients may drift towards poorer socio-economic classes due to the illness. Employment, especially full-time, is unusual. Approximately 70% of the psychotic population is at home or unemployed. Seven percent are full-time students.

Economic Impact

The economic impact of the disease parallels its clinical impact. Total per capita costs for schizophrenia are close to that of a chronic illness like diabetes. For industrialized countries, this translates to annual costs of Canada’s $2.35 billion Canadian dollars (1996) to the cost in the United States of $65.2 billion (1991).

The costs of the disease are associated with both direct (treatment costs) and indirect (unemployment, housing, etc.) costs. In the US, the direct costs associated with the treatment of schizophrenia in 1991 were estimated at $18.6 billion, while indirect costs were $46.5 billion. In western countries direct costs account for 1.6% to 2.6% of total healthcare expenditures. Seventy-five percent of direct healthcare costs in western countries are due to inpatient or residential care.
Schizoaffective Disorder

Schizoaffective disorder is diagnosed when a patient has a combination of manic or major depressive symptoms along with symptoms of schizophrenia. The term schizoaffective is most commonly and usefully applied to acute psychotic illnesses in which schizophrenic and affective symptoms are present simultaneously and are equally prominent. Often the symptoms of schizophrenia are positive, with hallucinations or delusions being most common. The most characteristic outcome of schizoaffective illness is full recovery followed by recurrence with further episodes.

Schizophreniform Disorder

Schizophreniform Disorder is a schizophrenia-like illness of acute onset, somewhat atypical in character and rapid in recovery, in contrast to "true" schizophrenia. Schizophreniform patients often return to their premorbid level of functioning within six months of episode onset. For this reason, patients are included in this category if they meet clinical criteria for schizophrenia but have had the illness for less than six months at the time of diagnosis. If the symptoms last longer than 6 months, they are considered to have the diagnosis of schizophrenia and are no longer considered to have schizophreniform disorder.

Bipolar Disorder

Prevalence / Incidence

Bipolar Disorder is a chronic, episodic disorder with a lifetime prevalence of approximately 1.0% -1.5%. Typically, the disease begins in adolescence or early adulthood and continues throughout life.

Prevalence rates are based upon current prescribing patterns, but misdiagnosis is high. A number of authors have attempted to identify real prevalence rates for the full bipolar spectrum of disorder and have suggested ranges from 2.6% to 7.8%.

The following are prevalence rates from the Datamonitor 2000 report (definitions for Bipolar I and II are provided in the Diagnosis section):

<table>
<thead>
<tr>
<th>Country</th>
<th>Combined Bipolar I and II (%)</th>
<th>Bipolar I (%)</th>
<th>Bipolar II (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1.30</td>
<td>0.84</td>
<td>0.46</td>
</tr>
<tr>
<td>France</td>
<td>1.00</td>
<td>0.65</td>
<td>0.35</td>
</tr>
<tr>
<td>Germany</td>
<td>1.00</td>
<td>0.65</td>
<td>0.35</td>
</tr>
<tr>
<td>Italy</td>
<td>1.71</td>
<td>1.11</td>
<td>0.60</td>
</tr>
<tr>
<td>Japan</td>
<td>1.00</td>
<td>0.65</td>
<td>0.35</td>
</tr>
<tr>
<td>Spain</td>
<td>1.00</td>
<td>0.65</td>
<td>0.35</td>
</tr>
<tr>
<td>UK</td>
<td>1.09</td>
<td>0.65</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Diagnosis

Proper diagnosis of bipolar disorder is difficult. A recent survey of patients conducted by
the National Manic Depressive Association suggests that 35% of patients may go 10 years prior to receiving a correct diagnosis of their illness. Approximately 69% receive at least one misdiagnosis. The most frequent misdiagnoses are: depression (60%), anxiety disorder (26%), schizophrenia (18%), borderline personality disorder (17%) and alcohol/substance abuse (14%).

In all types of bipolar disorders, the patient undergoes oscillating mood swings, the intensity of which depends on the type of disease (e.g., Bipolar I, Bipolar II). The phases of the disorder are manic, depressive and the maintenance period. Although the exact cause of the disease is unknown, many researchers believe that the disorder has a strong genetic component. The following are the symptoms of the disease:

<table>
<thead>
<tr>
<th>Bipolar Manic Symptoms</th>
<th>Bipolar Depressive Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoric mood</td>
<td>(Identical to major depression)</td>
</tr>
<tr>
<td>Agitation</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>Pressured speech</td>
<td>Loss of interest or pleasure</td>
</tr>
<tr>
<td>Racing thoughts</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Risk taking activities</td>
<td>Inability to think or concentrate</td>
</tr>
<tr>
<td>Irritability</td>
<td>Guilt</td>
</tr>
<tr>
<td>Aggression</td>
<td>Agitation</td>
</tr>
<tr>
<td>Grandiose thoughts</td>
<td>Psychotic feature</td>
</tr>
<tr>
<td>Impaired judgment</td>
<td></td>
</tr>
<tr>
<td>Psychotic feature</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bipolar Hypomanic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same symptoms required to meet hypomania as mania</td>
</tr>
<tr>
<td>Episode not severe enough to cause marked impairment in social functioning</td>
</tr>
<tr>
<td>There are no psychotic features</td>
</tr>
</tbody>
</table>

Manic symptoms include a sense of grandiosity, a decreased need for sleep and racing thoughts. In general, bipolar manic patients are more functional than acute schizophrenic patients. Bipolar depression can present with or without psychosis. Symptoms include diminished interest or pleasure, insomnia, and an inability to concentrate. Approximately 70% of the bipolar patients experience psychotic features at some time during their illness (manic, depressed, or mixed episode).

The DSM-IV-TR diagnosis guidelines are for Bipolar I, Bipolar II, Cyclothymia and Bipolar Disorder Not Otherwise Specified.
Bipolar I (Mania and Major Depression): The essential feature of Bipolar I is a clinical course characterized by at least one manic episode. Patients who have had one or more depressive episodes will most likely have subsequent manic or depressive episodes; additional mixed (manic and depressive) episodes can also occur. It is not necessary to have a depressive episode to be diagnosed as bipolar.

Bipolar II (Hypomania and Major Depression): The essential feature of Bipolar II is a clinical course that is characterized by the occurrence of one or more Major Depressive Episodes accompanied by at least one Hypomanic Episode. The presence of a manic or mixed state precludes the Bipolar II diagnosis.

Cyclothymia: The essential feature of Cyclothymia is a chronic, fluctuating mood disturbance that involves numerous periods of hypomanic symptoms and numerous periods of depressive symptoms. The episodes are insufficient in number, severity, pervasiveness or duration to meet full criteria for either a Manic episode or a Major Depressive Episode.

Bipolar Disorder Not Otherwise Specified: This category includes mood symptoms that do not meet the criteria for any specific mood disorder.

Treatment
The treatment of Bipolar Disorder is complicated as a result of the complex nature of the disease. To compound the difficulty of differential diagnosis, there are numerous drug classes utilized in the treatment of Bipolar Disorder. Mood stabilizers, antipsychotics and antidepressants are all used in treating this disorder. With the exception of lithium, all of the drugs regularly prescribed as treatment regimens are indicated for other disease states. On average, a patient receives 2.2 medications (consisting of mood stabilizers, antipsychotics, and antidepressants) at any one time.

Lifecycle
The disease is characterized by phases of depression, mania and maintenance. Ninety percent of bipolar patients who have suffered a manic episode will have recurrent episodes. According to naturalistic studies, approximately 20% of bipolar patients have multiple acute or depressive episodes within a 12-month period, and about 50% exhibit at least one acute episode each year. These acute episodes are often interspersed with long periods of normal mood and behavior (maintenance phase). However, the length of these symptom-free intervals decreases with age and number of previous episodes. Rapid cycling can be included with Bipolar I and Bipolar II Disorders and applies to patients that have four affective episodes within a year (approximately 5-15% of the above patients are rapid cycling).

Complications
The major complications are: 1) high suicidal tendency (15% suicide mortality rate, 25-50% of sufferers makes at least one suicide attempt), 2) substance abuse (estimated at
60% in the US), 3) inability to maintain relationships, and 4) inability to remain employed.

Demographics

The onset of Bipolar Disorder is rarely seen before the age of 12 and is less common in the 65+ age group, with the average onset at 21 years. Patients that have depressive psychoses are more likely to be female. Meanwhile, the manic and hypomanic state is exhibited more in males. This observation may coincide with other findings that women with bipolar may experience more depressive episodes and suffer more from mixedmania than men with bipolar, who experience more manic episodes.

While there are no significant gender differences in the diagnosis rate for bipolar disorder as a whole, men tend to be diagnosed more often as Bipolar I and women as Bipolar II. Rapid cycling tends to be more common in women than in men, although there is no strong evidence or explanation for this tendency. According to the American Psychiatric Association (APA), there are no known racial differences in prevalence rates for Bipolar Disorder.

Economic Impact

In an economic evaluation conducted in 1991, the total US costs for bipolar disorder among adults were estimated at $45 billion. Eighty-five percent of total costs were indirect (arising from reduced productivity of sufferers and their carers), 5% were due to hospitalization, 5% were due to costs of the criminal justice system and 1.6% was due to costs of substance abuse services.

A detailed search of information sources in 5 European countries (France, Germany, Italy, Spain and the UK) found scarce evidence assessing the epidemiology, treatment patterns and service/resource use associated with Bipolar Disorder. However, studies indicate that hospitalization accounts for the majority of health sector costs of the disorder. Mania/hypomania episodes drive this hospitalization cost, with hospitalization rates four times those for BPD depression episodes.

The costs of lost productivity with BPD were also substantial. The impact on the quality of life of carers and sufferers is well documented, with BPD ranked as the sixth highest cause of disability-adjusted-life years by the World Health Organization. The morbidity associated with BPD leads to productivity losses for the sufferer and carer, with early onset affecting sufferers in the prime of their working lives. Treatments and therapies affecting the severity of illness may have an effect on the magnitude of costs of lost productivity for the sufferer and their caregiver.

Evidence on the productivity loss in Germany shows 24.9 affective psychosis cases per 10,000 insured had time off work with a mean of 46.8 lost workdays per year. Increased lifetime mortality is caused by suicide, cardiovascular and respiratory diseases in BPD sufferers. A retrospective follow up of BPD patients in the UK found significantly greater
lifetime mortality from suicide (15.7% vs 0.7%), respiratory (33% vs 1%) and cardiovascular causes (42% vs 14%) compared to the general population.

The episodic nature of BPD will lead to varying resource use and costs across the cycle of the disorder, peaking during acute phases of illness, when more intensive management often involving hospitalization is required. UK evidence points to more than 4 times as many hospitalizations relating to mania and hypomania episodes as to BPD depression episodes. This indicates that the majority of hospitalization costs (and so the majority of overall BPD health sector costs) is due to mania and hypomania episodes. New treatments/therapies have the potential to reduce the overall health sector cost of BPD if they can reduce the rate of inpatient hospitalization.

**Dementia**

Prevalence/Incidence

Dementia is a chronic neurological disorder affecting approximately 5 – 7% of the world’s elderly (65 years and older). Dementia disorders share a common symptom presentation but are differentiated by etiology. Psychosis in dementia occurs at any stage of the illness. The worldwide incidence of psychosis associated with dementia is 17.5%. It tends to be associated with an increased rate of decline and can usually be distinguished from cognitive dysfunction. Psychosis in dementia may lead to unsafe or violent situations or institutionalization.

Alzheimer’s disease represents about 70% of dementia cases. Approximately 20 million people suffer from Alzheimer’s dementia worldwide. Some authorities estimate that approximately one in ten people over age 65, and half of those over 85, have moderate or severe Alzheimer’s dementia. Vascular dementia represents about 15% of the dementia cases, followed by Mixed dementia (10%) and Lewy body (5%).

Diagnosis

A definitive diagnosis of Alzheimer’s disease can only be done through direct examination of brain tissue. Since this is only available post mortem, diagnosis is done by exclusion.

Several clinical criteria for Alzheimer’s dementia exist. The presentation of the disease is gradual with the first complaint typically being loss of memory. There are two basic categories of symptoms: 1) cognitive and 2) non-cognitive (behavioral and psychological).

The clinical presentation of cognitive symptoms includes memory loss, dysphasia (impaired speech) or aphasia, disorientation, apraxia (impairment to carry out motor activities despite intact motor function), impaired calculation and impaired judgement and problem solving. The clinical presentation of non-cognitive symptoms includes depression, psychotic symptoms, and non-psychotic disruptive behaviors. Non-psychotic
disruptive behaviors could include functioning problems such as with planning, organizing, sequencing and abstracting.

Treatment

The first line drugs to treat the symptoms of dementia are cholinesterase inhibitors, which have an effect on cognition. As the disease progresses, antipsychotics are often used as they have been shown to effectively manage psychotic and some behavioral disturbances. Dementia currently accounts for 33% of antipsychotic prescriptions in the elderly population. Typical antipsychotics are the most frequently used antipsychotic drugs in this segment with lower conversion rates than in the younger population. However, extrapyramidal symptoms, sedation, and cardiovascular side effects often complicate the use of typical antipsychotics.

Lifecycle

In the early stages, memory impairment may be the only apparent cognitive deficit. With time, however, a multifaceted loss of intellectual abilities occurs affecting memory, judgment, abstract thought, and other higher cortical functions; changes in personality and behavior are also inevitable. Symptoms often lead to institutionalization and/or significant caregiver stress. A patient can expect to live an average of 10 years (range = 2-25 years) after symptom onset, and an average of five of those years are usually spent in a nursing facility or receiving continuous care at home.

Complications

Patients suffering from psychosis in dementia experience a loss of independence due to behavioral problems and a marked cognitive decline. They must rely wholly on their caregivers for their everyday needs. The patients’ family often finds it very difficult to connect with elderly family members and then leaves the role of caregiver to the institutional staff.

Demographics

Late-onset Alzheimer’s dementia (where symptoms first become apparent after age 65) accounts for more than 95% of all cases. Only 34% of dementia sufferers below age 65 have Alzheimer’s dementia; this percentage rises to approximately 65% among patients above age 65. It is anticipated that the number of people suffering from dementia will rapidly increase as the world population ages.

Today the world population is about six billion, with some 580 million over the age of 60. By 2025, close to 14% of the population will be considered old, of which the very old (85+) will form an increasing part. By the year 2025, more than three-quarters of the world’s elderly population will be living in developing countries.

The fundamental differences in the impact of the gender dimensions on the demographic transition are important for mental health. In view of the fact that the majority of older
persons are female (60%), it is crucial that our strategies surrounding an aging population reflect this situation.

Economic Impact

Aging populations are putting pressure on federal and local governments. The elderly population consumes health care resources at a much greater rate than younger populations. Countries are responding to the increased need for care of the elderly in a variety of ways, from health promotion and mental health awareness to modification of payment systems and alternative insurance systems.

Extreme budgetary pressures on already strained health and social services systems make increased care more difficult to deliver. The number one reason for institutionalization of elderly individuals is psychosis and behavioral disturbances.

Disease State Summary – Insights and Implications for ZYPREXA

- Lifelong therapy is required for Schizophrenia and Bipolar Disorder.
- There are significant unmet needs in these populations and there are significant opportunities for therapies that go beyond symptom control (e.g. improved attention).
- Bipolar Disorder represents a huge market potential and it is currently in the early stages of development. Treatment for Bipolar Disorder will grow dramatically if a solution to under- and misdiagnosis is created.
- There is a high degree of symptomatology overlap in Schizophrenia, Bipolar Disorder and other related disorders. This overlap provides ZYPREXA with access to a wider market beyond these two indications.
- Schizophrenia and Bipolar Disorder are associated with stigma – it is important for ZYPREXA to support efforts to reduce this stigma.
- With suicide so prevalent among patients suffering from schizophrenia and bipolar disorder, it is critical to: 1) ensure patients stay on their medications to help prevent suicide and 2) provide data showing ZYPREXA’s role in suicide prevention.
- The economic impact of Schizophrenia, Bipolar Disorder and Dementia is profound. With access and pricing pressures escalating, health outcomes data showing the value of ZYPREXA will become increasingly important.

Product Profile

In September 1996, ZYPREXA was launched in the US and several EU countries for the treatment of schizophrenia (with or without related psychoses). ZYPREXA is now approved in 93 countries and has been used to treat more than 8 million patients. Its broader usage beyond psychosis has led certain regulatory authorities to class ZYPREXA as a psychotrophic in recognition of this broader activity.

ZYPREXA is a molecule of the thienobenzodiazepine class. It belongs to the novel or
atypical subset of antipsychotics. While its precise mechanism of action is unknown, its antipsychotic activity is believed to be attributable to a combination of dopamine (D2) and serotonin type 2 (5-HT2A) antagonism.

Indications

The following chart provides an overview of indications by country/region:

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>ZYPREXA Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1) Schizophrenia- short-term and maintenance of treatment response, 2) Short-term treatment of acute manic episode associated with Bipolar I, 3) Agitation in schizophrenia, bipolar mania and dementia (approval pending)</td>
</tr>
<tr>
<td>Europe</td>
<td>1) Schizophrenia 2) Agitation and disturbed behaviors in patients with schizophrenia 3) Moderate to severe episodes in bipolar</td>
</tr>
<tr>
<td>ICR</td>
<td>1) Acute and maintenance treatment of schizophrenia and other psychoses, for which + and/or – symptoms are prominent</td>
</tr>
<tr>
<td>Canada</td>
<td>1) Acute and maintenance treatment of schizophrenia and related psychotic disorders</td>
</tr>
<tr>
<td>Australia</td>
<td>1) Schizophrenia and related psychoses, 2) Short-term treatment of acute manic episodes associated with Bipolar I 3) Rapid control of agitation and disturbed behaviors in patients with schizophrenia and related psychoses and in patients with acute mania associated with Bipolar I Disorder</td>
</tr>
<tr>
<td>Japan</td>
<td>1) Schizophrenia</td>
</tr>
</tbody>
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Dosage and Formulations

ZYPREXA is dosed once daily and oral dosages from 2.5 to 20 mg/day are available. ZYPREXA is marketed as film-coated tablets and as an orally disintegrating formulation known as Zydis in the US/ROW and Velotab in Europe. RAIP is also scheduled to be available in 2002 in a 10 mg vial.

Patent Situation

<table>
<thead>
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<th>COUNTRY</th>
<th>EXPIRATION DATE</th>
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<td>Australia*</td>
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*Includes term extension from supplementary protection certificate
Japanese extension possible due to timing and regulatory process and/or change of law
Product Profile – Insights and Implications for ZYPREXA

- With schizophrenia, bipolar disorder and agitation indications, ZYPREXA became the first in its category with three indications – a source of authority for the brand.
- Availability of a wide range of formulations allows ZYPREXA to differentiate in its target market.
- A robust pipeline continues to fuel future growth for ZYPREXA (indications).
- The ZYPREXA submission forecast from 2003 through Q1 2006 is very strong. If the Pediatric indications for schizophrenia and bipolar disorder are approved, the ZYPREXA patent will be extended by six months in the US.

Please see Appendix A for a more detailed Product Profile.

Market Overview

Overall Market Opportunity

As of Q3 2001, the worldwide antipsychotic market totaled $7.4 billion in sales and 5.2 billion in DOTs. Overall DOT market growth is 4% over 2000. While Bipolar Disorder accounts for only a small percentage of all antipsychotic DOTs, it holds the greatest potential for market expansion (the mood stabilizer market).

<table>
<thead>
<tr>
<th>Market Category</th>
<th>DOT Size</th>
<th>DOT Growth Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total A/P Market</td>
<td>5.2 Billion</td>
<td>104</td>
</tr>
<tr>
<td>Schizophrenia (A/P use)</td>
<td>2.4 Billion</td>
<td>104</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>1.6 Billion</td>
<td>113</td>
</tr>
<tr>
<td>A/P use</td>
<td>296 Million</td>
<td>127</td>
</tr>
<tr>
<td>Anti-depressant use</td>
<td>745 Million</td>
<td>110</td>
</tr>
<tr>
<td>Mood Stabilizer use</td>
<td>590 Million</td>
<td>100</td>
</tr>
<tr>
<td>Dementia (A/P use)</td>
<td>288 Million</td>
<td>115</td>
</tr>
<tr>
<td>Other A/P use (includes neuroses, affective disorders, paranoia, alcohol/drug abuse, confusional states, personality disorders)</td>
<td>2.1 Billion</td>
<td>100</td>
</tr>
</tbody>
</table>

Schizophrenia Market Opportunity

The majority of all antipsychotic use is in schizophrenia where total DOTs are fairly static. In this case, market conversion from typicals to atypicals, increased dosing and
increased length of therapy (LOT) represent growth opportunity areas. (See the sections below on conversion and LOT for further explanation.)

**Bipolar Disorder Market Opportunity**

The Bipolar disorder market is two-thirds the size of the schizophrenia market with 1.6 billion DOTs. The majority of Bipolar Disorder patients receive older, well-established mood stabilizers (i.e. lithium) for treatment. However, antipsychotic use for Bipolar Disorder is growing quickly, with DOTs up 27% over 2000. This growth is driven largely by the indication of ZYPREXA for bipolar mania in the US and the off-label "halo" use it generated for other atypical antipsychotics. As ZYPREXA and/or other atypical antipsychotics gain indications in Bipolar Depression and Bipolar Maintenance globally, significant additional DOTs will flow into the N5A market from the antidepressant and mood stabilizer markets.

Bipolar Disorder is often misdiagnosed as unipolar depression by psychiatrists and primary care physicians alike. It can take years before the manic aspects are detected. Development of a diagnostic tool to help clinicians differentiate bipolar from other disorders could significantly grow the market.

**Dementia Market Opportunity**

With the aging of the population, the use of antipsychotics for dementia with aggression, agitation and/or related psychoses will continue to increase. Atypical have fueled this increase with their more tolerable safety profiles.

**Conversion**

As was mentioned, a major source of potential growth is increased conversion. Roughly 75% of the worldwide antipsychotic DOTs are typicals. Conversion rates vary considerably from close to 70% in the USA to only 8% in Japan (see chart below).
Length of Therapy

Another avenue for growth is to increase the duration of therapy. Patient compliance is a critical issue in both schizophrenia and bipolar disorder. Many of the atypicals are launching line extensions such as depot formulations to address this concern.

Geographical Market Size/Opportunity

Annual sales of antipsychotic agents have increased from US $2.5 billion to more than US $7.4 billion worldwide during the period between 1996 and 2001. This growth is driven by the increased usage of atypical antipsychotics at prices per DOT higher than typical antipsychotics. As the chart below indicates, Japan is an increasingly significant market with almost the same percentage of DOTs as the U.S.

![Market Breakdown Charts]

- **Total World US$ = $7.4 billion**
- **Total World DOTs = 5.2 billion**

**Market Overview – Insights and Implications for ZYPREXA**

- The schizophrenia market is becoming fiercely competitive while at the same time total DOTs are fairly static. Conversion, increased LOT and higher dosing are growth levers for ZYPREXA to offset this lack of organic growth.
- The bipolar market presents a vast opportunity for dollar growth as it is less developed than the schizophrenia market primarily due to under- and misdiagnosis. ZYPREXA needs to capitalize on its first mover advantage in this market.
- Primary care physicians will play a role in developing the bipolar market, but the use of ZYPREXA as a mood stabilizer needs to be established first with psychiatrists.
- Increased conversion will add to growing global pricing and access issues due to the higher cost of atypicals. The ability to demonstrate the superior value of ZYPREXA will become more critical to maintain equal and unrestricted access.
Market Segmentation

Market research with more than 3,000 physicians in eight countries guided the development of the following market framework. (The US map is shown as an example – other markets are similar but not identical).

The segmentation involves patient types (across the top of the map) covering four disease states and a range of severity as well as physician types (along the left margin). The combination of patient types and physician types forms distinct needs-based segments. The patient segmentation identified groups of patients according to the differences in their needs as seen through the eyes of the physician.

A segment comprises patients who are:

- Defined by common needs
- Described by distinct, observable characteristics

"Stabilize" and "Hope" are the primary targets for ZYPREXA. "Motivate" is the secondary target (see descriptions of the segments on the following pages). The strategy is to capture patients in the "Stabilize" and "Hope" segments and retain them in "Motivate". These three segments capitalize most successfully on the current strengths.
of the brand as well as future strengths represented by new indications and brand line extensions.

The patients falling into “Stabilize” and “Hope” are uncontrolled meaning that the physician has to take action. Although patients experience peaks and valleys in the “Motivate” segment, the physician is not compelled to take action. These three segments form a type of “revolving door” where patients may move from one to the other over the course of their illness. Patients will relapse, become stabilized and then potentially relapse again in the future. This represents a huge opportunity for ZYPREXA to prove that it effectively stabilizes patients in the decompensated state (the capture opportunity) and then provides superior relapse prevention (the retention opportunity).

The following graph helps to further explain the ZYPREXA patient targets in the Stabilize, Hope and Motivate segments.

The Optimize segment is opportunistic in highly converted markets (greater than 40% of the total market converted to atypicals).

The bipolar depression opportunity was briefly discussed in the market overview section. Patients with bipolar depression do not have a clearly defined place on the segment map. If the bipolar depression patient possesses “no control” or “insufficient control,” he or she would fit in the Stabilize or Hope segment. However, if this patient displays “sufficient control,” he or she would belong in Motivate under the current patient title of “depressive psychosis.”
The following chart helps to further explain these four needs-based segments:

### Segment 1—Stabilize

These patients can be extremely agitated and violent. Often they end up in a hospital setting. Physicians' goals are to control symptoms, prevent patients from hurting themselves and others, prevent suicide, and increase compliance. If these patients flow into Motivate, their symptoms are controlled and they move into the maintenance phase.

**Stabilize comprises patients with**

- Acute schizophrenia
- Mixed/rapid cycling bipolar
- Manic bipolar

### Segment 2—Hope

Unlike patients in Stabilize, these patients are less advanced in the course of their illness. Here physicians are still concerned with preventing threat to self and others, but they also hope that they can help control symptoms, prevent hospitalization, and help the patient gain insight into his/her condition. In general, physicians express more hope with these patients as many of them are presenting with their first psychotic break.

**Hope patients are typically**

- Manic bipolar
- First-break schizophrenia
- Depressive psychosis

### Segment 3—Motivate

At this stage, patients' symptoms are controlled; physicians are most concerned with preventing relapse (regression into Stabilize or Hope) as well as helping the patient gain more insight and feel more productive.

**Motivate contains patients with**

- Depressive psychosis
- Controlled schizophrenia
- Controlled bipolar disorder

### Segment 4—Optimize

Optimize patients are usually institutionalized or on the borderline of being institutionalized due to aggressive behavioral symptoms. Therefore, caregiver burden relates more here to the institution staff. Patients with Alzheimer's tend to present in multiple care settings and across physician types. Pathways of care vary significantly from country to country.

**Optimize contains patients with:**

- Alzheimer's type with psychosis
- Alzheimer's type dementia
Patient Types
Within the population afflicted with schizophrenia, bipolar disorder, dementia and depression, physicians globally identified a total of 11 discrete patient types (along the top axis of the market map). This was based on patients' presenting symptoms reflective of disease state and stage. The 11 patient types*, spanning four disease states and a range of severity, are listed below. Next to each patient type is an indication of whether they are a target for capture or retention. Three of the patient types are not in scope.

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute schizophrenia</td>
<td>Capture</td>
</tr>
<tr>
<td>Schizophrenia/first break</td>
<td>Capture</td>
</tr>
<tr>
<td>Schizophrenia/controlled</td>
<td>Retain</td>
</tr>
<tr>
<td>Bipolar mixed/rapid cycling</td>
<td>Capture</td>
</tr>
<tr>
<td>Bipolar manic</td>
<td>Capture</td>
</tr>
<tr>
<td>Bipolar/controlled</td>
<td>Retain</td>
</tr>
<tr>
<td>Mild dementia</td>
<td>Not in scope</td>
</tr>
<tr>
<td>Alzheimer's type with psychosis</td>
<td>Capture/Retain</td>
</tr>
<tr>
<td>Alzheimer's type with dementia</td>
<td>Not in scope</td>
</tr>
<tr>
<td>Depressive psychosis</td>
<td>Capture/Retain</td>
</tr>
<tr>
<td>Major depression</td>
<td>Not in scope</td>
</tr>
</tbody>
</table>

* Please refer to Appendix B for a more detailed profile of each patient type.
Physician Types

Research was also conducted to help identify target physician types who are most likely to prescribe and stay loyal to ZYPREXA. Of the different physician types identified along the left axis of the market map, two to three per country are identified as primary and secondary targets. While physician attitudes were very similar across all researched markets, their resulting behaviors do vary. The following physician types, based on the US segmentation, are provided as an example:

**Physician Type 1**
- Has a strong familiarity with diagnosing and treating mental illness
- Wants to be certain of diagnosis before moving ahead with treatment
- Is uncomfortable dosing outside a drug's recommended range
- Is a slow adopter of new drugs/new usage areas
- Is heavily influenced by Physician Type 2

**Physician Type 2**
- Has the highest level of self-perceived expertise in diagnosis and treatment
- Seeks input from a narrower treatment team
- Engages in a high level of experimentation with psychiatric medications
- Likes atypicals but tends not to differentiate among them
- Is more likely to be a key opinion leader

**Physician Type 3**
- Has a lot of experience with severely ill patients but is less likely than Physician Type 2 to remain loyal to one brand for treatment
- Typically works in a community mental health center
- Is very familiar with diagnosing and treating mental illnesses
- Tends to concentrate more on the symptoms than the diagnosis
- Has the highest likelihood of trying drugs in new ways (dosages, indications, off-label)
Market Segmentation – Insight and Implications for ZYPREXA

- The ZYPREXA brand strategy is to capture patients in the Stabilize and Hope segments and retain them in the Motivate segment. This strategy provides focus that positions ZYPREXA to meet the segment-specific patient needs, while capitalizing on the relationship among the segments (the “revolving door”).
- Stabilize, Hope and Motivate represent 92% of the market dollar volume in the U.S. and similar percentages in other affiliates. Opportunities outside of these segments are opportunistic by definition. Pursuing these opportunities can distract from the focus on the target segments.

Competitive Analysis

See Appendix C for a more thorough competitive analysis including the positioning, strengths and weaknesses of each of the targeted competitors’ products.

See Appendix D for a competitive analysis of indications and formulations and Appendix E for competitive resource strategies.

Bristol Myers Squibb (BMS) – aripiprazole (Abilify)

Company:

BMS is a US-based multinational that has been described as a sales and marketing powerhouse with a weak late-stage product pipeline. Aripiprazole is a joint venture with Otsuka of Japan and represents a new growth opportunity for BMS. Aripiprazole is critical for BMS so they will focus significant resources on it. Despite previous experience with CNS products, BMS’s core competencies are in cardiovascular medicine and oncology.

Product:

BMS will position aripiprazole as the next generation antipsychotic for the treatment of serious mental illness with a new method of action and “better treatment adherence” due to few side effects. They claim equivalent efficacy to other atypicals and a clean safety profile, particularly with minimal weight gain. BMS says that this molecule is a mixed dopamine agonist/antagonist – this method of action has the potential issue of a narrow therapeutic window. In addition, compounds with this mixed mechanism have been unable to demonstrate sustained efficacy, sometimes described as the “poop out syndrome”. Market research indicates that interest in this product is high. Expected global sales are between $500-$800 million by 2005.

Janssen – risperidone (Risperdal)

Company:
Janssen is a pharmaceutical subsidiary of Johnson and Johnson. They have a relatively narrow product portfolio but have developed a strong neuroscience image based on a series of successful brands. Since Risperdal represents a significant portion of revenues and is required to fund new product introductions, Janssen has aggressively resourced the brand.

Product:

Risperdal is the global market leader in terms of prescriptions. With this product, Janssen continues to commoditize efficacy and focus on competitor side effects to differentiate their product. At therapeutic doses, Risperdal has the significant side effect liabilities of EPS, TD and prolactin elevation. EPS and TD are uniquely associated with this atypical brand.

Janssen will introduce risperidone depot (Risperdal Consta), the first atypical depot product to market, as early as Q2 2002 to enhance the overall perception of the risperidone molecule. Their expected positioning is to be the first-choice antipsychotic where compliance is an issue. Janssen has prior experience with Haldol depot and claims that risperidone depot has comparable efficacy to ZYPREXA without the weight gain. Market research indicates that interest in an atypical depot is very high. Risperidone oral 2001 global sales were $1.9 billion.

AstraZeneca – quetiapine (Seroquel)

Company:

Following the merger, AstraZeneca became a significant player in this market driven by their improved organizational marketing capability. Significant patent expirations (e.g. Prilosec), combined with a relatively weak late-stage pipeline, will result in a renewed focus on the current portfolio.

Product:

Seroquel is the fastest growing product in terms of prescription market share. At launch, it was positioned as a niche product for adjunct therapy in schizophrenia and in some cases to improve sleep. This resulted in its use being restricted to low doses. AstraZeneca has now begun to pursue a more moderate to severe patient with Seroquel. To achieve this, they have pursued a strategy of increasing their dosage (“Start at four and go explore”).

Seroquel has a perceived relatively benign side effect profile in low doses, thus their message of “Well Accepted” was created. However, at recommended doses its ability to maintain efficacy in moderate to difficult-to-treat patients remains unproven. In addition, it has a slow and complicated titration schedule and needs to be taken twice daily. Their main differentiation message is low EPS and minimal weight gain. Global sales were $700 million in 2001.

Abbott – divalproex sodium (Depakote)
Company:
Abbott is a highly diversified healthcare company with an emphasis on nutrition, pharmaceuticals and diagnostics. Depakote is a key revenue driver for Abbott in light of a significant number of patent losses during the plan period. In Europe, Depakote is marketed by Sanofi-Synthalabo where it has been registered on a country-by-country basis.

Product:
Depakote is viewed as the gold standard mood stabilizer in the US despite its safety concerns (three black box warnings) and its limited label (bipolar mania). This equity was attained in a period of limited competition. The availability of a once-a-day formulation has rekindled product interest. Global sales were $850 million in 2001.

Pfizer – ziprasidone (Geodon, Zeldox)

Company:
Pfizer is considered a sales and marketing powerhouse. The revenues generated by their extensive portfolio enable them to more easily resource new opportunities. Through Zoloft, Pfizer has built a strong franchise in neuroscience primarily focused on primary care and institutional markets.

Product:
Geodon’s track to market was delayed due to regulatory concerns related to its cardiovascular profile. To date, it has achieved very limited success in the markets in which it has launched due to a combination of its safety/efficacy profile and inconsistent efficacy. Pfizer is set to use its IM formulation to relaunch and reposition the product in the US and downplay QTc issues. In selected European markets, they are expected to launch the IM and oral formulations together to take advantage of this new positioning. A number of European countries approved ziprasidone in Q1 2002. The product has differentiated itself based on cardiovascular risk factors (weight gain, lipids and insulin levels). Global sales were $150 million in 2001.

Competitive Analysis – Insights and Implications for ZYPREXA

- Due to the attractiveness (growth, dollars) of the markets in which ZYPREXA competes, competitors will focus here as a key source of revenue generation, especially to offset patent losses. Competitors will become increasingly creative and look for new opportunities within the current market to steal ZYPREXA share.
- To remain competitive, ZYPREXA will have to increase marketing spending levels and also recognize that the incremental return per dollar may decrease.
- Aripiprazole and risperidone depot are the two most significant short-term threats to ZYPREXA.
• Continued vigilance around AstraZeneca (Seroquel) and Pfizer (Geodon/Zeldox) is required because of their sales and marketing capabilities.
• ZYPREXA’s perceived liabilities will continue to be a focus as competitors have failed to achieve efficacy advantages.

Primary and Secondary Target Segment Analysis

After a thorough environmental, market and competitive analysis, as well as a look at the ZYPREXA product profile and the core diseases the brand treats, an introduction to market segmentation followed. The following is an analysis of the primary and secondary target segments providing support for why they were chosen. All of the analysis and information up to this point feeds into the segment analysis.

Stabilize Segment

The “Stabilize” segment contains patients with a history of mental illness who are in need of physician intervention to control break-through symptoms. Their illness is not in a controlled state. Initiating some form of new treatment is an attractive option from a risk/benefit perspective. The degree of agitation and the severity of symptoms vary significantly among “Stabilize” patients and it is important to remember that not all are IM candidates.

Compliance is often an issue with these patients, as many patients enter “Stabilize” on a regular basis (the revolving door patient). Therefore, when these patients cycle into this segment from a previously stable state, it is likely that they have stopped taking medication. Of those who enter on medication, approximately one-third will be switched to another therapy and the rest will have the dose of their medication increased. The majority of patients will flow into “Motivate”, but approximately 30% will remain in “Stabilize”, requiring further treatment modifications before their symptoms disappear (higher prevalence among schizophrenia patients).
## HCTM Analysis: Stabilize

<table>
<thead>
<tr>
<th>Node</th>
<th>Leakage</th>
<th>Current Opportunities</th>
<th>Current Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perception/Seek Treatment</strong>&lt;br&gt;- does problem exist?&lt;br&gt;- seek treatment in right place?</td>
<td>0%</td>
<td>• Easy to identify patients in this acute segment</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong>&lt;br&gt;- will correct diagnosis be identified?</td>
<td>5%</td>
<td>• Emergency Room physicians don’t care about diagnosis&lt;br&gt;• Agitation and aggressive behavior easily identified&lt;br&gt;• Symptoms are obvious&lt;br&gt;• Substance abuse</td>
<td>• Difficult to track patient information due to multiple institutions&lt;br&gt;• Residents in ER and ward misdiagnose due to inexperience&lt;br&gt;• Substance abuse</td>
</tr>
<tr>
<td><strong>Treatment Plan A</strong>&lt;br&gt;- Any drug therapy</td>
<td>0%</td>
<td>• Will get treated</td>
<td>• Physicians are very satisfied with current treatments (typicals) - specifically Haldol IM and depot&lt;br&gt;• Ativan often used instead of antipsychotic in ER and ward settings</td>
</tr>
<tr>
<td><strong>Treatment Plan B</strong>&lt;br&gt;Competitive set:&lt;br&gt;- Ativan IM, Haldol IM&lt;br&gt;- atypicals &amp; typicals&lt;br&gt;- mood stabilizers</td>
<td>20%</td>
<td>• Concerns with dystonia/EPS&lt;br&gt;• Less price sensitivity in acute&lt;br&gt;• Safety concerns for substance abusers with some antipsychotics&lt;br&gt;• Lack of alignment between ER and psych ward&lt;br&gt;• Weight gain less of an issue in acute setting&lt;br&gt;• NICE endorsement of atypicals could increase usage</td>
<td>• Physician perception of lack of efficacy/onset of atypicals vs. typicals&lt;br&gt;• ER physicians are not as concerned with long-term threats of treatment&lt;br&gt;• Lack of alignment between ER and psych ward may not facilitate transition to long-term oral therapy&lt;br&gt;• Expanded health outcomes data requirements</td>
</tr>
<tr>
<td><strong>Delivery</strong>&lt;br&gt;- can patient get drug?</td>
<td>0%</td>
<td>• Controlled/Supervised setting</td>
<td>• Increasing formulary price pressures</td>
</tr>
<tr>
<td><strong>Compliance</strong>&lt;br&gt;- will patient comply?&lt;br&gt;- - perceived consequences of non-compliance?</td>
<td>20%</td>
<td>• Physicians believe positive IM experience leads to oral efficacy and compliance&lt;br&gt;• Physicians seeking atypical depot</td>
<td>• Some patients check and spit medication</td>
</tr>
<tr>
<td><strong>Evaluation</strong>&lt;br&gt;- will customer attribute success or failure to drug therapy?</td>
<td>Long-term 50%</td>
<td>• Controlled/Supervised setting of care allows efficacy to be easily identified</td>
<td>• Emergency room and inpatient physicians never see the long-term outcome of their therapy&lt;br&gt;• Pressure to get patients out the door as quickly as possible</td>
</tr>
</tbody>
</table>

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OTSW Analysis: Stabilize

 Superior efficacy (speed of onset, symptom control) and safety easily observed as patients are in controlled setting ⇒ can easily demonstrate speed of onset and symptom control

 Agitation is easy to diagnose and requires treatment ⇒ demonstrate control of agitation

 Atypicals are seen as the new paradigm in this segment ⇒ demonstrate drug’s competitive advantage over other atypicals

 Physicians are satisfied with and have experience with current treatments (e.g. Haldol/depots) ⇒ highlight ZYPREXA’s advantages relative to competition in establishing control

 Ativan alone or with typicals (Haldol) seen as gold standard in ER, thus new entrants need to demonstrate some advantage ⇒ leverage drug’s advantages (speed of onset, monotherapy)

 Intensification of competitive activity (Geodon IM, Abilify, Risperdal Consta) ⇒ proactively position competition by creating messages and consistently communicating them in market

 IM approved for multiple indications ⇒ use to demonstrate that it controls multiple symptoms in thought and mood disorders

 Therapeutic dose has a low risk of EPS and QTC ⇒ this helps enable trust between patient and physician

 Broader range of available formulations ⇒ allows physician to tailor treatment to specific patient needs and begin trusting relationships

 Can cause weight gain ⇒ effectively manage issues and improve customer perceptions

 Brand linked to metabolic issues ⇒ effectively manage issues and improve customer perceptions

 Lack of transition data from IM to oral ⇒ actively seek this data

 Insufficient and untimely competitive data ⇒ develop and communicate data to proactively position competitors
Stabilize Segment Analysis – Insights and Implications for ZYPREXA

- Efficacy in controlling symptoms can be rapidly demonstrated in this segment with the appropriate drug and formulation.
- To capitalize on the opportunity in this segment, a broad range of formulations is required to meet the physician/patient needs.
- ZYPREXA must clearly differentiate itself (on an emotional and rational level) due to the following: 1) physicians believe existing therapies currently meet the treatment goals for this segment and 2) the introduction of Geodon IM.
- To maximize revenue, ZYPREXA needs to establish the paradigm of ‘Start on IM ZYPREXA and transition to oral ZYPREXA’.

Hope Segment

Like the Stabilize segment, Hope also contains patients in need of physician intervention to control symptoms, but they are much earlier in the course of their illness (first break schizophrenia) or are higher functioning individuals (bipolar mania). When treating a “Hope” patient, a physician will seek not only to control their symptoms, but also restore hope of leading a normal life and help them realize their potential. Generally, expectations are higher for Hope than for typical Stabilize patients.
### HCTM Analysis: Hope

<table>
<thead>
<tr>
<th>Node</th>
<th>Leakage</th>
<th>Current Opportunities</th>
<th>Current Threats</th>
</tr>
</thead>
</table>
| **Perception/Seek Treatment**  
  - does problem exist?  
  - seek treatment in right place? | 30% | • Family relationships are still intact so family can recognize problems and have them seek treatment  
• Increased awareness of mental illness | • Patient & family lack of awareness, acceptance & understanding of disease  
• Patients seek treatment from clergy, social worker  
• Stigma associated with mental illness  
• Some patients living away from family that knows their history  
• Behavior perceived as normal |
| **Diagnosis**  
  - will correct diagnosis be identified? | 50% (short-term) | • Family knowledge of patient history and symptoms communicated to physicians when patients come in for treatment  
• Increased noise level around bipolar enhances physicians' awareness of bipolar diagnosis | • Variability of physician experience/understanding of disease & available treatments (PCP as entry point)  
• Lack of time in apt to diagnose  
• Bipolar patients are often misdiagnosed  
• Non-physician unwilling to refer  
• Patient activities are perceived as normal by physician  
• Patient lacks history of past mental illness  
• Differential diagnosis difficult  
• MDs do not want to label patient early on |
| **Treatment Plan A**  
  - Any drug therapy | 5% | • Patients have a fear of losing their life  
• Legal obligation to treat | • Psychosocial therapy  
• Perceived lack of severity of illness  
• Don't want patient on drugs for life |
| **Treatment Plan B**  
  - Competitive set: atypicals & typicals - mood stabilizers | 5% | • Fear of patient worsening  
• Make patient "good as new", aspire to maintain hope & promise with higher functioning patients  
• Lack of MD price sensitivity  
• Physicians believe that newer medications can keep patients out of the hospital (i.e., prevent the revolving door)  
• NICE endorsement of atypicals could increase usage  
• Higher patient functionality allows more patient/caregiver/family influence on treatment choice | • Fear/stigma of using strong mental health drugs  
• Fear of side effects  
• Fear of being labeled by others due to drug choice  
• Lack of experience w/ meds (PCP)  
• Drug category § will increase in private pay patients  
• Higher patient functionality allows more patient/caregiver/family influence on treatment  
• Expanded health outcomes data requirements |
| **Delivery**  
  - is patient able to get prescribed drug? | 15% | • Social relationships still intact to help patient comply  
• More customer-focused information exists today | • Patients lack disease insight  
• Fear/stigma of using strong mental health drugs  
• Fear of side effects  
• Fear of being labeled by others due to drug choice  
• Cost of medication |
| **Compliance**  
  - will patient comply?  
  - how difficult to adhere to treatment plan?  
  - what are perceived consequences of non-compliance? | 50% | • Social relationships still intact to help patient comply  
• More customer-focused information exists today  
• Ease of medication use | • Patients lack disease insight  
• Fear/stigma of using strong mental health drugs  
• Fear of side effects  
• Fear of being labeled by others due to drug choice  
• Cost of medication  
• Lack of supervision  
• Lack of efficacy  
• Need to take med each day |
| **Evaluation**  
  - will customer attribute success or failure to drug therapy? | 15% | • MD reinforcement of link to therapy and outcome | • Patients often worsen and do not return  
• Lack of patient compliance may obscure evaluation  
• Lack of time with patient in appointment  
• Efficacy does not meet patient's expectations |

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30  
Answers That Matter.
OTSW Analysis: Hope

Close family involvement at this stage encourages patients to seek treatment ⇒ presents opportunity for brand expansion

Physician's aspirations for patients are higher since prognosis is better if treated correctly ⇒ demonstrate drug's competitive advantage for these patients

Patients want a more trusting relationship with their physicians and greater involvement in their treatment ⇒ leverage the control (overall favorable side effect profile, ease of use) that enables a more trusting relationship between patient and physician

Increased noise around bipolar increases physician awareness and reduces misdiagnosis ⇒ presents an opportunity for brand expansion

QOL expectations raised by atypicals are resulting in increased conversion ⇒ demonstrate long-term outcomes

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Stabilizes mood/controls mania without depression ⇒ use to support control message

Gives families hope that they have done their best ⇒ reinforce the competitive advantage of drug

Physicians feel successful due to patient progress ⇒ reinforce the trusting relationship between patient and physician enabled by drug

First in class approved for multiple indications ⇒ reinforce controls multiple symptoms in thought and mood disorders

Innovative research – prodromal, 1st episode ⇒ use to demonstrate corporate commitment to neuroscience

Broader range of available formulations ⇒ allows physician to tailor treatment to specific patient needs and develop trusting relationships

Physicians do not want to 'label' patients early due to stigma resulting in poor treatment plans ⇒ presents an opportunity for brand expansion through education

Intensification of competitive activity (Abilify, Risperdal Consta, others) ⇒ proactively position competition by creating messages and communicating flawlessly to the market

Can cause weight gain ⇒ effectively manage issues and improve customer perceptions

Value/price relationship needs to be justified ⇒ demonstrate value relative to competitors

Brand linked to metabolic issues ⇒ effectively manage issues and improve customer perceptions

Therapeutic dose seen as too sedating for bipolar patients ⇒ provide physicians with answers that will help enable a trusting relationship between patient and physician

Not first to market with depot ⇒ proactively influence use of Risperdal Consta while demonstrating ZYPREXA's competitive advantage

Lack of understanding of the power of selling the emotional benefits of the brand ⇒ need to deepen our corporate understanding and commitment
Hope Segment Analysis – Insights and Implications for ZYPREXA

- Despite being a relatively small segment, it is strategically important for ZYPREXA to own this segment to ensure long-term brand differentiation.
- Psychiatrists have emotionally-driven aspirations for patients in this segment. If ZYPREXA can leverage these emotions, this could have ‘halo’ benefits in other segments.
- Showing prevention of disease progression in first episode or prodromal patients would differentiate a brand in this segment and have ‘halo’ benefits in other segments.

Motivate Segment

Motivate contains patients whose symptoms are controlled. Patients in this segment may be at various levels of functioning, as well as have varying levels of severity of underlying symptoms and response to medications. For a patient with severely impaired functioning, just being able to think clearly enough to read a bus timetable might be a significant step forward.

HCTM Analysis: Motivate

<table>
<thead>
<tr>
<th>Node</th>
<th>Leakage</th>
<th>Current Opportunities</th>
<th>Current Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception/Seek Treatment</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- does problem exist?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- seek treatment right place?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0%</td>
<td></td>
<td>Increased noise level around bipolar enhances physicians’ awareness of bipolar diagnosis</td>
</tr>
<tr>
<td>- will correct diagnosis be identified?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Plan A</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Any drug therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Plan B</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Competitive set:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- atypicals &amp; typicals</td>
<td></td>
<td>Physician fear of lawsuits due to side effects (TD)</td>
<td></td>
</tr>
<tr>
<td>- mood stabilizers</td>
<td></td>
<td>Higher patient functionality allows more patient/caregiver/family influence on treatment choice</td>
<td></td>
</tr>
<tr>
<td>- Potential to differentiate on efficacy (efficacy “plus”)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- can patient get drug?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- will patient comply? what are perceived consequences?</td>
<td></td>
<td>Patient/caregiver/family influence on treatment choice can lead to higher compliance</td>
<td></td>
</tr>
<tr>
<td>Evaluation</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- will customer attribute success or failure to drug therapy?</td>
<td></td>
<td>Patients have more access to treatment team</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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OTSW Analysis: Motivate

Competitor efforts are to commoditize efficacy
put the differentiating focus on safety ⇒ opportunity exists to differentiate brand and achieve competitive advantage

Room for growth in LOT ⇒ need to investigate ways to retain patients and extend use

Patients want a more trusting relationship with physician and greater involvement in treatment ⇒ leverage the control that enables a more trusting relationship between patient & doctor

Brand offering superior relapse prevention is likely to demonstrate superior outcomes and differentiation ⇒ demonstrate superior relapse prevention

Caregiver/family influence on treatment choice can lead to longer length of therapy and compliance ⇒ leverage family influence to establish more trusting patient/physician relationships that lead to patients becoming more engaged in their therapy

Mis- and under-diagnosis of bipolar implies large market potential ⇒ influence to grow

Higher doses may offer greater efficacy and longer length of treatment ⇒ demonstrate superior relapse prevention with higher doses

Full dose range has low risk of EPS/TD/QTC/Prolactin ⇒ reinforce ease of use(full dosing flexibility)

Label and studies on relapse prevention ⇒ leverage relapse prevention data

Provides the best opportunity for patients to “think more clearly” ⇒ leverage data and emotional benefits

Patients lack insight into disease resulting in poor compliance ⇒ leverage caregiver/family and benefits of drug in helping patients gain insight into disease through a more trusting patient/physician relationship

Competitors are changing tolerability liability into safety liability ⇒ effectively manage issues and improve customer perceptions

Increased pricing pressure ⇒ demonstrate better value relative to competitors in long-term treatment

Physicians are reluctant to change therapies for fear of relapse ⇒ ensure more patients are captured and then retained on drug

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Can cause weight gain ⇒ effectively manage issues and improve customer perceptions

Value/price relationship needs to be justified ⇒ demonstrate value relative to competitors

Brand linked to metabolic issues ⇒ effectively manage issues and improve customer perceptions

Company defensive rather than offensive in positioning competitors ⇒ develop new data to proactively position competitors

Not first to market with depot ⇒ proactively influence use of Risperdal Consta while demonstrating ZYPREXA’s advantage

Identified lifecycle planning is relatively weak beyond 2005 ⇒ identify new opportunities for brand and molecule expansion

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Motivate Segment Analysis – Insights and Implications for ZYPREXA

- Long-term patient retention is the key to success in this segment. It is driven by: 1) positive differentiation on long-term patient outcomes (relapse prevention, health outcomes) and 2) the effective management of liabilities.
- Significant revenue growth can be gained for ZYPREXA through capitalizing on physician fear of relapse that can be reduced through higher dosing and increased LOT.
- Competitors will continue to focus on ZYPREXA's safety liabilities because they have failed to differentiate on efficacy in this segment.

Opportunistic Segment Analysis

Optimize Segment

The focus for ZYPREXA within the Optimize segment is on the difficult-to-treat dementia with patient with symptoms such as aggression, agitation and psychosis.

HCTM Analysis: Optimize

<table>
<thead>
<tr>
<th>Node</th>
<th>Leakage</th>
<th>Current Opportunities</th>
<th>Current Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception/Seek Treatment</td>
<td>20%</td>
<td>- Agitation and aggressive behavior are easily recognized by family/caregivers</td>
<td>- Symptoms viewed or accepted as elderly behavior (normal part of aging)</td>
</tr>
<tr>
<td>- does patient exist?</td>
<td></td>
<td>- Caregiver burnout</td>
<td>- Elderly individual living alone (family/caregivers not nearby)</td>
</tr>
<tr>
<td>- seek treatment in right place?</td>
<td></td>
<td>- Persistence of illness</td>
<td>- Stigma of mental illness</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>30%</td>
<td>- Supervised/controlled environment</td>
<td>- Physicians lack of time in appointment for proper diagnosis</td>
</tr>
<tr>
<td>- will correct diagnosis be identified?</td>
<td></td>
<td>- Agitation and aggressive behavior are easily recognized</td>
<td>- Lack of patient medical history</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Symptoms accepted as elderly behavior</td>
</tr>
<tr>
<td>Treatment Plan A</td>
<td>30%</td>
<td>- Accepted drug treatments available &amp; reimbursed</td>
<td>- Non-pharma options are mandatory (according to regulations, physicians must first try behavior modific)</td>
</tr>
<tr>
<td>- Any drug therapy</td>
<td></td>
<td>- Severity &amp; persistence of illness necessitate the use of drug therapy</td>
<td>- Physicians' concerns with polypharmacy (prevalent in elderly)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Liability issue (without drug, patients could harm others)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Institutions: need to maintain order</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Concerns with ↑ caregiver burden</td>
<td></td>
</tr>
<tr>
<td>Treatment Plan B</td>
<td>25%</td>
<td>- Severity &amp; persistence of illness</td>
<td>- Cost &amp; reimbursement issues</td>
</tr>
<tr>
<td>Competitive set</td>
<td></td>
<td>- Liability issue (if patients do not get drug, they can harm someone)</td>
<td>- Expanded health outcomes data requirements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>35%</td>
<td>- Institutions: controlled &amp; supervised environment</td>
<td>- Cost &amp; reimbursement issues</td>
</tr>
<tr>
<td>- is patient able to get prescribed drug?</td>
<td></td>
<td></td>
<td>- Inability to pay for medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Physically unable to take prescription to pharmacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Stigma attached with treatment</td>
</tr>
<tr>
<td>Compliance</td>
<td>25%</td>
<td>- Institutions: controlled &amp; supervised environment</td>
<td>- Family concerns over long-term use of drugs to control behavior</td>
</tr>
<tr>
<td>- will patient comply?</td>
<td></td>
<td></td>
<td>- Long-term cost of treatment</td>
</tr>
<tr>
<td>- how difficult to adhere to treatment plan?</td>
<td></td>
<td></td>
<td>- Cognitive decline-lack ability to remember to take meds</td>
</tr>
<tr>
<td>- what are perceived consequences of non-compliance?</td>
<td></td>
<td></td>
<td>- Patients may refuse to take meds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lack of physician time</td>
</tr>
</tbody>
</table>

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Answers That Matter.

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ZY 8413 678
OTSW Analysis: Optimize

Agitation and aggressive behavior are easily recognized and require immediate treatment ⇒ demonstrate control of agitation

Superior efficacy (speed of onset, symptom control) and safety easily observed as patients are in controlled setting ⇒ can easily demonstrate speed of onset and symptom control

Institutions need to maintain orderly environment & are looking for drug that provides rapid control ⇒ demonstrate speed of onset/rapid control

Symptoms are viewed or accepted as normal elderly behavior so treatment is not sought or provided ⇒ demonstrate the difference between normal elderly behavior and disease symptoms

Physicians are concerned with polypharmacy and are resistant to adding more drugs to therapy ⇒ demonstrate safety

Economic environment drives increased formulary restrictions and cost constraints for provision of elderly health care ⇒ demonstrate better value relative to competitors in long-term treatment

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Therapeutic dose has low risk of EPS ⇒ reinforce the favorable side effect profile as an enabler of a trusting patient/physician relationship

Good value given its safety profile ⇒ reinforce value by demonstrating safety

IM label contains agitation in dementia claim ⇒ leverage new indication to establish rapid control

Broadest range of available formulations ⇒ allows physician to tailor treatment to specific patient needs

Dementia indication limited to control of agitation with RAIM ⇒ demonstrate advantage in control of agitation

Lack of new comparative outcomes data in this segment ⇒ develop new data to demonstrate outcomes while proactively positioning competitors

Lack of transition data from IM to oral ⇒ actively seek this data

Little influence on caregiver/family education on mental illness ⇒ Educate families/caregivers for better diagnosis and better compliance

Limited resources to focus on this segment
Optimize Segment Analysis – Insights and Implications for ZYPREXA

- Efficacy in controlling symptoms can be rapidly demonstrated in this segment with the appropriate drug and formulation.
- With the current economic and political environment, companies are offering discount prescription programs for seniors. This could limit the revenue stream for ZYPREXA in this segment in the US.
- The agitation in dementia claim on the ZYPREXA IM label offers the first opportunity to address this segment.
- Lack of strong ZYPREXA data in this segment further limits this relatively small opportunity.
- Focusing on this segment means a distraction from the primary and secondary targets and involves an opportunity cost that requires evaluation.

ZYPREXA Archetype

In terms of its lifecycle, ZYPREXA is firmly in the growth phase, which will be further fueled by registrations in bipolar, launches of ZYPREXA RAIM and continued conversion of the global market. It is important to refer to the online archetype training module for a full understanding of the archetypes.

Description of Archetype

The current ZYPREXA product archetype is "Profile Improvement in a Crowded Market." Due to ZYPREXA and competitive launch timing variation in other geographies, there may be instances where the archetype varies. The following factors help define the situation for a Profile Improvement product:

- Product Improvement is incremental
- Significant competition already exists in the market
- Often one dominant product is setting the pace
- Some consider the market "satisfied" due to multiple options
- There is high physician experience and established treatment patterns
- Patients have a higher awareness of the disease
- Considerable information is available to physicians, patients and payers
- High familiarity with therapeutic area at regulatory agencies
- Pricing and reimbursement benchmarks are in place
- Product share of voice will be shrinking

Implications of Archetype

The following levers are being used to further the success of ZYPREXA in this lifestage.

1. **Aggressively Segment the Market and Position the Brand:**
   The segment strategy determined by brand architecture clearly positions ZYPREXA

2. **Focus on Differentiation:**
   Delivering on the Brand Promise will clearly differentiate ZYPREXA.
3. **Establish Leading SOV:**
   Leading SOV across all targeted channels at both a ZPT and affiliate level is fundamental to success.

4. **Establish Competitive Promotional Levels:**
   ZYPREXA must be competitive in promotional activities in all key markets.

5. **Price Strategically:**
   Pricing Architecture is being used to develop brand pricing strategy.

The levers were used in conjunction with the previous Column I analysis to guide the development of the critical success factors (CSFs) and marketing objectives (MOs) outlined in Column II. Many of these levers are also captured in the Column III programs and the Column IV implementation plans.

**Competitor Archetypes**

It is important to look not only at our product archetype, but also at the archetypes of our major competitors. In so doing, competitive behavior can be anticipated based on the levers typically used as a result of archetype. Although the ZYPREXA team believes that our brand represents a greater degree of true profile improvement than our competitors, this is how the following competitors would view their archetypes and therefore act as a result:

- **Risperdal (risperidone)** - Threatened Market Leader
- **Seroquel (quetiapine)** - Profile Improvement in a Crowded Market
- **Geodon (ziprasidone)** - Profile Improvement in a Crowded Market
- **Depakote** - Second and Better
- **Abilitat (aripiprazole)** - Profile Improvement in a Crowded Market

*See Appendix F for more information on the levers associated with each archetype.*

### Column I – Insights and Implications for ZYPREXA

- The ZYPREXA brand strategy is to capture patients in the Stabilize and Hope segments and retain them in the Motivate segment. Market leadership will only be maintained by relentless focus on this core strategy.
- As the market leader, attacks on ZYPREXA’s safety profile will intensify.
- ZYPREXA will be faced with intense competition during the plan period that will necessitate aggressive sales and marketing spend along with active positioning of new entrants.
- Access is an increasing threat making it more critical than ever to establish the superior value of ZYPREXA.
- The ZYPREXA brand must be kept “fresh” with new data, indications and formulations.