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IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA *ex rel.* Victoria Starr, Plaintiffs, v. JANSSEN PHARMACEUTICA PRODUCTS, L.P., Defendant.	FILED NOV – 4 2013 CIVIL ACTION NO. 04-cv-1529
UNITED STATES OF AMERICA *ex rel.* Lynn Powell, Plaintiffs, v. JANSSEN PHARMACEUTICA PRODUCTS, L.P., and JOHNSON & JOHNSON, Defendants.	CIVIL ACTION NO. 04-cv-5184
UNITED STATES OF AMERICA *ex rel.* Camille McGowan and Judy Doetterl, Plaintiffs, v. JANSSEN PHARMACEUTICA, INC., JANSSEN PHARMACEUTICA PRODUCTS, L.P., and JOHNSON & JOHNSON, INC. Defendants.	CIVIL ACTION NO. 05-cv-5436

A TRUE COPY CERTIFIED TO FROM THE RECORD
DATED: 11/4/13
ATTEST: Richard Sala
DEPUTY CLERK, UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA, *et al.*, *ex rel.* Kurtis J. Barry, Plaintiffs, v. ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC. and JOHNSON & JOHNSON, INC. Defendants.	:	CIVIL ACTION NO. 10-cv-0098

UNITED STATES' COMPLAINT IN INTERVENTION

From at least 1999 through 2005, Johnson & Johnson (J&J) and its subsidiary Janssen Pharmaceuticals, Inc. ("Janssen") (collectively, "defendants") promoted Risperdal, an atypical antipsychotic drug, for uses that were not approved as safe and effective by the Food and Drug Administration (FDA) ("off-label uses") and, in some cases, were not covered by Medicaid and other federal healthcare programs. Defendants established a specialized ElderCare sales force to promote Risperdal. This sales force promoted Risperdal in nursing homes to control agitation, aggression, and other behavioral disturbances in elderly dementia patients. Janssen promoted Risperdal to control behavioral disturbances and conduct disorders in children and to treat attention deficit disorder and other off-label conditions. Janssen also promoted Risperdal for use in the general population to control mood and anxiety symptoms unrelated to any psychotic disorder. Clinical trials, including those sponsored by defendants, indicated that taking Risperdal increased the risk of strokes in the elderly and diabetes in all patients. In 2005, FDA requested that Janssen change the Risperdal label to include a "Boxed Warning," commonly known as a "black-box warning" – the agency's strongest warning – about the increased risk of death in the elderly. By knowingly and actively promoting Risperdal as safe and effective for off-label and

non-covered uses, defendants caused Medicaid and other federal healthcare programs to pay hundreds of millions of dollars for uncovered claims.

I. JURISDICTION AND VENUE

1. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1345 and supplemental jurisdiction over the common law causes of action pursuant to 28 U.S.C. § 1367(a).

2. This Court may exercise personal jurisdiction over defendants pursuant to 31 U.S.C. § 3732(a), because they transact business in this District.

3. Venue is proper in this District under 31 U.S.C. § 3732 and 28 U.S.C. § 1391(b) and (c) because defendants have transacted business in this District and have committed acts proscribed by 31 U.S.C. § 3729 in this District.

II. PARTIES

4. The United States brings this action on behalf of the Department of Health and Human Services (HHS) and the Centers for Medicare & Medicaid Services (CMS) (formerly known as the Health Care Financing Administration), which administers the Medicaid program in conjunction with the states; the TRICARE Management Activity (TMA); the United States Office of Personnel Management (OPM); the United States Department of Veterans Affairs (VA); and the Office of Workers' Compensation Programs of the United States Department of Labor (DOL-OWCP).

5. Relator Victoria Starr resides in Oregon. In April 2004, Ms. Starr filed an action alleging violations of the False Claims Act (FCA), 31 U.S.C. §§ 3729-33, on behalf of herself and the United States Government pursuant to the *qui tam* provisions of the FCA, 31 U.S.C. § 3730(b)(1) (2008).

6. Relator Lynn Powell resides in North Carolina. In November 2004, Ms. Powell filed an action alleging violations of the FCA on behalf of herself and the United States Government pursuant to *qui tam* provisions of the FCA.

7. Relators Camille McGowan and Judy Doetterl reside in New York. In December 2004, these relators filed an action alleging violations of the FCA on behalf of themselves and the United States Government pursuant to *qui tam* provisions of the FCA.

8. Relator Kurtis Barry resides in Colorado. In January 2010, Mr. Barry filed an action alleging violations of the FCA on behalf of himself and the United States Government pursuant to *qui tam* provisions of the FCA.

9. Defendant J&J is a New Jersey corporation with its principal place of business in New Jersey. J&J manufactures, markets, and sells a wide range of pharmaceutical, medical, and related products. J&J is qualified to do business in Pennsylvania and does business in Pennsylvania.

10. Defendant Janssen is a Pennsylvania corporation with its principal place of business in New Jersey. Janssen is a wholly owned subsidiary of J&J and the successor in interest to Janssen Pharmaceutical Products, L.P., Janssen Pharmaceutica, Inc., and Ortho-McNeil-Janssen Pharmaceutical Products, Inc. From 1999 through 2005, and at all times relevant to the complaint, Janssen marketed and sold Risperdal. Janssen is qualified to do business in Pennsylvania and does business in Pennsylvania.

11. During the relevant time period, J&J was Janssen's sole owner. Janssen's President and Chief Executive Officer (CEO) reported directly to a J&J Company Group Chairman, who in turn reported to J&J's Executive Committee and Board of Directors. J&J and Janssen executives were also members of a Pharmaceutical Global Operating Committee and a Pharmaceutical Global Strategic Marketing Committee, through which J&J set overall corporate

goals that guided Janssen's strategic and tactical plans for Risperdal. J&J established Janssen's business objectives and sales goals and regularly reviewed and approved Janssen's sales numbers and projections. During the relevant time period, J&J supervised and controlled corporate sales goals; drug research, development, and manufacturing; medical affairs; regulatory affairs and compliance; legal affairs; and public relations. Defendants worked together to achieve the common business purpose of selling Risperdal.

III. STATUTORY AND REGULATORY FRAMEWORK

A. The False Claims Act

12. The False Claims Act (FCA), 31 U.S.C. §§ 3729–3733, provides for the award of treble damages and civil penalties for, *inter alia*, knowingly causing the submission of false or fraudulent claims for payment to the United States, knowingly using a false record or statement material to a false claim, or conspiring to get a false claim paid. Specifically, the FCA provided, in part, that any person who:

> (a)(1) knowingly presents, or causes to be presented, to an officer or employee of the United States Government . . . a false or fraudulent claim for payment or approval;
>
> (a)(1)(B) knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim; [or][1]
>
> (a)(3) conspires to defraud the Government by getting a false or fraudulent claim allowed or paid . . .
>
> is liable to the United States Government for a civil penalty of not less than $5,000 and not more than $10,000 plus 3 times the amount of damages which the Government sustains because of the act of that person. . . .
>
> * * *

[1] The FCA was amended pursuant to Public Law 111-21, the Fraud Enforcement and Recovery Act of 2009 (FERA), enacted May 20, 2009. Section 3729(a)(1)(B) was formerly Section 3729(a)(2), and is applicable to this case by virtue of Section 4(f) of FERA, while Section 3279(a)(1) of the statute prior to FERA, and as amended in 1986, remains applicable here.

> For purposes of this section, the terms "knowing" and "knowingly" mean that a person, with respect to information, (1) has actual knowledge of the information; (2) acts in deliberate ignorance of the truth or falsity of the information; or (3) acts in reckless disregard of the truth or falsity of the information, and no proof of specific intent to defraud is required.

31 U.S.C. § 3729(a)(1) (2008), (a)(1)(B) (2009), and (a)(3) (2008).

13. Pursuant to the Federal Civil Penalties Inflation Adjustment Act of 1990, as amended by the Debt Collection Improvement Act of 1996, 28 U.S.C. § 2461 (notes), and 64 Fed. Reg. 47099 47103 (1999), the FCA civil penalties were adjusted to $5,500 to $11,000 per false claim for violations occurring on or after September 29, 1999.

B. The Anti-Kickback Statute

14. The federal anti-kickback statute, 42 U.S.C. § 1320a7b(b), arose out of Congressional concern that remuneration given to those who can influence healthcare decisions would result in goods and services being provided that are medically unnecessary, of poor quality, or even harmful to a vulnerable patient population. To protect the integrity of the Medicare and Medicaid programs from these harms, Congress enacted a prohibition against the payment of kickbacks in any form.

15. The anti-kickback statute prohibits drug companies from knowingly and willfully offering, paying, soliciting, or receiving remuneration, in cash or in kind, directly or indirectly to induce physicians or others to prescribe drugs for which payment may be made by federal health care programs.

C. The Federal Healthcare Programs

1. Medicaid Federal-State Health Care Program

16. Medicaid is a joint federal-state program that provides health care benefits for certain groups, primarily the poor and disabled. The federal portion of each state's Medicaid

payments varies by state and is generally between 50 and 83 percent, depending on the state's per capita income. 42 U.S.C. § 1396d(b).

17. Although prescription drug coverage is an optional benefit for states under Medicaid, all states and the District of Columbia have opted to cover prescription drugs under their Medicaid state plan. Before the beginning of each calendar quarter, each state submits to CMS an estimate of its Medicaid federal funding needs for the quarter. CMS reviews and adjusts the quarterly estimate as necessary, determines the amount of federal funding needs for the quarter, and determines the amount of federal funding each state will be permitted to draw down as it actually incurs expenditures during the quarter. The state then draws down federal funding as actual provider claims are presented for payment. At the end of each quarter, the state submits to CMS a final expenditure report, which provides the basis for adjustment to the quarterly federal funding amount (to reconcile the estimated expenditures to actual expenditures). 42 C.F.R. § 430.30.

18. The Medicaid Drug Rebate Program ("Rebate Program") is a partnership between CMS, State Medicaid Agencies, and participating drug manufacturers that helps to offset the Federal and State costs of most outpatient prescription drugs dispensed to Medicaid patients. The Rebate Program requires, among other things, that a drug manufacturer enter into, and have in effect, a national rebate agreement ("Rebate Agreement") with the Secretary of HHS in exchange for State Medicaid coverage of most of the manufacturer's outpatient prescription drugs. Manufacturers are then responsible for paying rebates to states for those drugs based in part on the part on utilization by Medicaid patients. These rebates are paid by drug manufacturers on a quarterly basis and are generally shared between the States and the Federal government to offset the overall cost of the prescription drugs under the Medicaid program.

19. Under the Rebate Program, all states are generally required to provide coverage for drugs that meet the definition of a covered outpatient drug, as defined in the federal Medicaid Drug Rebate Statute, 42 U.S.C. § 1396r-8(k)(2). Once the manufacturer enters into a Rebate Agreement, a state is generally required to cover that manufacturer's covered outpatient drugs under the state plan (with certain limited exceptions) unless "the prescribed use is not for a medically accepted indication." 42 U.S.C. § 1396r-8(d)(1)(B)(I).

20. The Medicaid Rebate Statute defines "medically accepted indication" as any FDA approved use or a use that is "supported by one or more citations included or approved for inclusion in any of the compendia" set forth in the statute. 42 U.S.C. § 1396r-8(k)(6).

21. A drug does not generally meet the definition of a "covered outpatient drug" if it is prescribed for a use that is neither FDA-approved nor supported by a citation included or approved for inclusion in the compendia. 42 U.S.C. § 1396r-8 (k)(3). CMS has stated that the statutory definition of medically accepted indication "requires coverage of off-label uses of FDA-approved drugs for indications that are **supported** (as opposed to listed) in the compendia." Medicaid State Rebate Release No. 141 (May 4, 2006) (emphasis added). Thus, even if a drug is FDA-approved for one indication, Medicaid ordinarily does not cover other uses that do not qualify as medically accepted indications.

2. The TRICARE Program

22. TRICARE is a managed health care program established by the Department of Defense. 10 U.S.C. §§ 1071-1110. TRICARE provides health care benefits to eligible beneficiaries, which include, among others, active duty service members, retired service members, and their dependents.

23. The regulatory authority establishing the TRICARE program does not cover drugs not approved by the FDA. *See* 32 C.F.R. § 199.4(g)(15)(i)(A).

24. TRICARE does not cover drugs used for off-label indications unless such off-label use is proven medically necessary and safe and effective by medical literature, national organizations, or technology assessment bodies. *See* 32 C.F.R. § 199.4(g)(15)(i)(A)(Note).

3. The Federal Employee Health Benefits Program

25. The Federal Employee Health Benefits Program ("FEHBP") is a federally-funded health care program established by Congress in 1959, pursuant to the Federal Employees Health Benefits Act. 5 U.S.C. §§ 8901 *et seq.*

26. OPM administers this program and contracts with various health insurance carriers to provide services to FEHBP members. *Id.* at §§ 8902, 8909(a).

27. Monies for the FEHBP are maintained in the Employees Benefits Fund ("Treasury Fund"), which OPM administers. *Id.* at § 8909(a). The Treasury Fund — which the United States Treasury holds and invests — is the source of all relevant payments to the insurance carriers for services rendered to members. *Id.* at § 8909.

4. The Veterans Administration

28. The VA maintains a system of medical facilities from which all pharmaceutical supplies, including prescription drugs, are purchased directly or indirectly by the VA and dispensed to beneficiaries. It also supports a mail service prescription program as part of the outpatient drug benefit. The system serves approximately four million veterans.

5. The Labor Department

29. DOL-OWCP administers the following programs: the Federal Employees' Compensation Act, 5 U.S.C. § 8101 *et seq.*, which provides medical benefits to federal employees injured in the performance of duty; the Energy Employees Occupational Illness Compensation Program Act, 42 U.S.C. § 7384 *et seq.*, which provides medical benefits to eligible Department of Energy nuclear weapons workers; and the Black Lung Benefits Act,

30 U.S.C. § 901 *et seq.*, which provides medical benefits to coal miners who are totally disabled by pneumoconiosis arising out of coal mine employment.

IV. THE RISPERDAL LABEL

30. Risperdal is an atypical antipsychotic drug. On December 29, 1993, FDA approved Risperdal for "management of the manifestations of psychotic disorders" in adults. The approved label explained that "[t]he antipsychotic efficacy of RISPERDAL was established in short-term (6 to 8-weeks) controlled trials of schizophrenic inpatients."

31. The approved Risperdal label included a statement in the Precautions section that "[c]linical studies of Risperdal did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients." The label also provided special dosing instructions for the elderly, stating that "[i]n general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal or cardiac function, and therapy greater tendency to postural hypotension." Janssen later sought FDA approval for 0.5 mg and 0.25 mg Risperdal tablets to address special dosing requirements of certain patient populations, including the elderly. In 1999, FDA approved the lower-dose Risperdal tablets.

32. On March 3, 2002, FDA approved revised labeling for Risperdal to state that Risperdal is indicated for "the treatment of schizophrenia."

33. On December 4, 2003, FDA approved Risperdal for the short-term treatment of acute manic or mixed episodes associated with Bipolar I disorder in adults.

34. Between 1999 and 2005, Risperdal was not approved by FDA for any other conditions in adults or for use in children for any purpose.

35. In 2006 and 2007, FDA approved Risperdal for the treatment of irritability associated with autistic disorder in children and adolescents, schizophrenia in adolescents, and Bipolar I disorder in children and adolescents.

V. PROMOTION OF RISPERDAL

A. Janssen Promoted Risperdal for Elderly Nursing Home Residents

36. From the time Risperdal was first approved in 1993, FDA repeatedly advised Janssen not to market the drug as safe and effective for the elderly. In addition, clinical studies, including those sponsored by defendants, indicated health risks in elderly dementia patients taking Risperdal, including the risk of strokes. In 2005, FDA requested that Janssen add a black-box warning to the Risperdal label about the risk of death in elderly patients taking the drug. Janssen promoted Risperdal to control behavioral disturbances in the elderly until at least 2005.

1. FDA Warned Janssen Against Promoting Risperdal as Safe and Effective in the Elderly.

37. When Janssen asked FDA to review certain marketing materials in August 1994, FDA advised Janssen "it would be misleading to suggest that the safety and efficacy of Risperdal has been established in the elderly." (Exhibit 1).

38. Janssen subsequently informed FDA that it was conducting a clinical trial (RIS-USA-63) aimed at determining the effectiveness of Risperdal in treating "behavioral disturbances in demented patients." In a letter dated April 28, 1995, FDA responded that the proposed label expansion would improperly suggest that Risperdal was effective for "all the various signs and symptoms that fall under such an umbrella, e.g., anxiety, depression, phobic fears, panic attacks, diurnal rhythm disturbances, etc. We would consider such a claim misleading in that sense. . . ." FDA also cautioned that behavioral disturbances in dementia patients were not necessarily psychotic manifestations and "might even be construed by some as

appropriate responses to the deplorable conditions under which some demented patients are housed, thus raising an ethical question regarding the use of an antipsychotic medication for inappropriate behavioral control." (Exhibit 2).

39. In a 1997 meeting with FDA, Janssen suggested that it might seek an indication for "aggression in dementia." FDA raised concerns about an indication for "aggression":

> [I]f a patient screams (one of the measured behaviors in the aggressive subscale of the BEHAVE-AD), is it because he/she is demented, or because he/she is trying to communicate displeasure or even pain? Many demented patients, particularly those included in our trials, have limited verbal skills. Therefore, an indication for 'aggression' could allow a patient's limited capacity for self-expression to be reduced.

(Exhibit 3).

40. In January 1999, FDA reviewed selected Janssen sales aids for Risperdal and issued an Untitled Letter informing Janssen that "presentations that focus on this [elderly] population are misleading in that they imply that the drug has been found to be specifically effective in the elderly." In its letter, FDA stated that "Janssen is disseminating materials that imply, without adequate substantiation, that Risperdal is safe and effective in specifically treating hostility in the elderly." (Exhibit 4). When Janssen asked FDA to reconsider its position that the promotional materials in question made claims of specific efficacy in the elderly population, FDA explained that "the safety and efficacy in the elderly was not particularly examined in 'fragile' individuals" and that "the campaign 'Hostile Outside, Fragile Inside' implies without adequate substantiation, that Risperdal has been specifically shown to be effective in treating psychotic elderly patients with hostility." (Exhibit 5).

2. Defendants' Clinical Studies Showed That Risperdal Increased Health Risks in the Elderly.

41. In 1998, Janssen began pursuing an indication for dementia. In support of a potential indication, defendants funded a series of clinical studies involving the use of Risperdal

to treat behavioral disturbances in the elderly and psychosis in Alzheimer's patients. One study (RIS-USA-63), published in 1999, failed to show a statistically significant improvement in dementia patients taking Risperdal versus a placebo, but appeared to show some efficacy in treating psychosis and aggression in elderly patients. A second study (RIS-INT-24), also published in 1999, failed to show a statistically significant difference in effectiveness between Risperdal and placebo on any scale.

42. In March 2001, defendants received the top-line results of a third study (RIS-AUS-5) that suggested efficacy in some symptoms, but also revealed more cerebrovascular adverse events (CVAEs), including strokes, in elderly dementia patients taking Risperdal than in the placebo group.

43. After receiving the top-line results, one senior Janssen executive objected to immediate submission of an abstract summarizing the study's results for a medical symposium. In an internal e-mail dated March 22, 2001, the executive stated:

> I am very reluctant to have these data in the public domain that soon.
>
> You may have noticed in the topline results that there are substantially more CVD A.E.s [cerebrovascular disease adverse events] in the Risperdal group. They are of substantial concern to us and we are reviewing all the narratives of these cases as well as CVD A.E. in our other dementia studies. It is crucial we have a better understanding of these data before we make the data public. I propose to keep this discussion and concern in house, though, until we have better understanding.
>
> So, I cannot endorse a rapid submission of an abstract end March [sic].

(Exhibit 6).

44. On May 11, 2001, a senior Janssen statistician and co-author of the RIS-AUS-5 study circulated an internal memorandum reporting that the CVAE disparity in the raw statistics was similar in RIS-AUS-5 and RIS-INT-24 and that "this risk was statistically significant in these two trials individually and when they were combined with USA-63." On May 15, 2001,

Janssen made a non-public submission to FDA under applicable regulations of the CVAE data from RIS-AUS-5. On August 22, 2001, Janssen submitted to FDA a separate analysis of records from more than 10,000 patients who had taken Risperdal.

45. In September 2001, three senior Janssen executives assessed whether, in light of RIS-AUS-5 and relevant business considerations, the pursuit of a dementia indication should be terminated. Among other issues, the executives discussed the financial implications of discontinuing the pursuit of a dementia indication, noting that "Risperdal is the foundation of the J&J LTC [long-term care] portfolio." The executives ultimately recommended to the J&J Development Commitment Committee continuing the pursuit of a dementia indication at least through the completion of another ongoing trial (RIS-USA-232). (Exhibit 7). Defendants continued pursuing a dementia indication.

46. Starting in 2002, when presenting the results of RIS-AUS-5 to physicians, Janssen pooled the adverse event data from that study with the adverse event data from two other studies (RIS-USA-63 and RIS-INT-24). Janssen advised paid speakers and sales representatives that the pooled data showed "a significantly higher incidence of cerebrovascular adverse events in patients treated with [Risperdal] compared to patients treated with placebo." However, pooling the data resulted in a lower overall rate of cerebrovascular adverse events than RIS-AUS-5 standing alone.

47. On February 22, 2002, Janssen submitted a manuscript documenting the results of RIS-AUS-5 for publication. The manuscript was published in February 2003.

48. On September 19, 2002, FDA notified Janssen that it was requesting additional warnings on the labels for all antipsychotics, including Risperdal, because of the increased incidence of strokes and other cerebrovascular adverse events reported in elderly dementia patients treated with antipsychotics.

49. On April 3, 2003, at FDA's request, Janssen modified the Risperdal label to include a new warning regarding adverse events in elderly patients with dementia, which stated:

> **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia:** Cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients with placebo. RISPERDAL has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

Janssen also sent out a letter to doctors on April 16, 2003, as FDA requested, warning them of the CVAE risk in elderly dementia patients.

50. After the label change and letter to doctors, Janssen instructed ElderCare sales personnel to affirmatively communicate the CVAE warning to doctors and to inform doctors that the risk of CVAEs increases with age and that patients who experienced CVAEs in Risperdal trials had a mean age of 85.

51. On March 21, 2003, Janssen received the top-line results of the fourth study involving the use of Risperdal in elderly dementia patients (RIS-USA-232). The study failed to demonstrate efficacy in treating dementia and confirmed the increased risk of CVAE in elderly patients treated with Risperdal. The RIS-USA-232 results showed that four patients treated with Risperdal experienced CVAEs compared to one patient in the placebo group. Internally, Janssen concluded that the results of RIS-USA-232 "confirmed the imbalance" of the risk of cerebrovascular events in patients taking Risperdal.

52. Janssen filed a non-public safety report with FDA under applicable regulations in June 2003 that included the CVAE data from RIS-USA-232.

53. On September 1, 2003, one of the physicians who designed the protocol for the RIS-USA-232 trials sent an e-mail to a senior Janssen executive encouraging Janssen to publish the RIS-USA-232 results. The physician stated:

> Janssen has been sitting on the [RIS-USA-232] trial results for a long time. Yet it has a moral and ethical responsibility to publish results quickly and in a way that they can be understood and makes clinical sense. It has an obligation to publish not just the clinical efficacy data which could very well be informative and supportive of the use of risperidone if considered properly, but also the safety data, including events that have been labeled in the past as "cerebrovascular adverse events" and deaths.

(Exhibit 8).

54. Janssen finalized its internal analysis of the results of RIS-USA-232 and completed its internal Clinical Study Report for RIS-USA-232 on February 26, 2004. The same month, at the meeting of the American Association of Geriatric Psychiatry, an FDA representative presented a paper regarding CVAE that included data from RIS-USA-232. In March 2004, Janssen began including data from RIS-USA-232 in medical information packets the company provided in response to requests for information submitted by physicians.

55. Through 2004, Janssen continued to disseminate the "pooled data" from the three earlier studies to doctors and sales representatives, not updating the "pooled data" to include the results of RIS-USA-232. Janssen retained physicians identified as Key Opinion Leaders ("KOLs") to present the "pooled" data that omitted the results of RIS-USA-232.

56. On March 25, 2004, another physician – a Janssen KOL – urged Janssen to include the RIS-USA-232 results in the pooled data with the three earlier dementia studies:

> At this point, so long after RIS 232 has been completed, I think it is wrong to continue to submit abstracts of the three pooled studies. At this point, we must be concerned that this gives the strong appearance that Janssen is purposely withholding the findings from RIS 232.
>
> Adverse effect findings from 232 are available on the web through the British government's regulatory site. It was also mentioned by someone

> from FDA at the AAGP annual meeting. It is not a secret that a fourth study has been conducted. As an investigator who is loyal to this program, I really do have to speak out and urge that Janssen avoids embarrassment and accusations about suppressing information that is relevant to providers and consumers.

(Exhibit 9). In response, a Janssen executive agreed: "[A]t this point it is my opinion that all pooled analysis should include -232."

57. Janssen presented some of the RIS-USA-232 data, including safety data, at a medical symposium in June 2004. Janssen submitted a poster documenting the results of RIS-USA-232, including safety data, at another medical symposium in October 2004. The full study results, including safety data, were submitted for publication on February 1, 2005 and published in March 2006.

58. Separately, FDA conducted a meta-analysis of data from seventeen clinical trials involving four atypical antipsychotic drugs, including clinical trial data unavailable to Janssen. On April 11, 2005, FDA issued a safety alert referencing risk of death in elderly dementia patients taking Risperdal and other atypical antipsychotics. FDA's safety alert also announced the agency's intention to ask manufacturers of all atypical antipsychotics to add a black-box warning to their label. In subsequent correspondence with the company, FDA noted that "[a]lthough the signal for increased mortality is somewhat weaker and somewhat less consistent for risperidone than for several other drugs in this class, it is strong enough, in our view, for us to conclude this is likely a class effect." The Risperdal package label was subsequently modified to state:

> **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**
>
> Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated

> patients of between 1.6 to 1.7 times that seen in placebo treated-patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

3. Janssen Promoted Risperdal as Safe and Effective for Elderly Patients

59. From 1999 through 2005, Janssen aggressively marketed Risperdal as having an "unparalleled safety profile" and being effective in controlling behavioral disturbances in the elderly. In its 1999 business plan for the ElderCare market, one of Janssen's express objectives was to "[e]xpand [the] geriatric market and enhance leadership position for the treatment of late life mental disorders." (Exhibit 10). That year, Janssen increased the size of its ElderCare sales force to 136 sales representatives. This specialized sales force focused on nursing homes, long term care facilities, and doctors who treated the elderly. It marketed Risperdal as effective to treat symptoms such as hostility, aggression, agitation, wandering, and depression, regardless of whether the patients exhibited any evidence of psychosis or schizophrenia. In 2000, one of Janssen's business plan objectives was to "[m]aximize and grow RISPERDAL's market leadership in geriatrics and long term care. Dementia share goal is 57% with sales of $302 MM." The core sales messages for 2000 included: "RISPERDAL has proven efficacy in treating geriatric patients" and "RISPERDAL has an excellent safety and tolerability profile in geriatric patients." (Exhibit 11).

60. In a 2001 ElderCare Sales Force update, Janssen congratulated its ElderCare sales force for helping to increase Risperdal's market share in the elderly population, noting that:

> [A]s a result of your focused efforts and dedication, RISPERDAL continues to be the market leader in the LTC/geriatric market. . . . RISPERDAL continues to dominate the dementia market, with a share of 52.5% for the 12 months ending February 2001.

61. In 2001, Janssen created a Business Plan titled "Risperdal LTC/Geriatrics Business Plan" reflecting its continued focus on marketing Risperdal for behavioral disturbances in the elderly. (Exhibit 12). That year, Janssen produced a series of 2,100 continuing medical education ("CME") presentations called "Senior Care Seminars" attended by thousands of healthcare providers nationwide. Sales representatives tracked prescriptions written by doctors who attended the programs.

62. In 2002, Janssen indicated in its Business Plan that it would continue to focus its marketing message on the elderly. Its position statement was that "RISPERDAL is 1st choice for psychotic & behavioral disorders," including behaviors associated with dementia. In one study completed in early 2002, Janssen tracked physicians' recall of sales messages, including "Effective for Geriatrics," "Effective for Dementia," and "Effective for Agitation," to confirm that the sales representatives were delivering these sales messages and to identify opportunities for better market penetration.

63. In 2003, Janssen indicated in its Business Plan that dementia "remains an important strategic area of focus for RISPERDAL and the company." At the 2003 ElderCare National Meeting in Atlanta, Janssen encouraged sales representatives to deliver the following core message:

> Risperdal is the #1 prescribed product in its class BECAUSE it offers *superior efficacy* in the treatment of behavioral, psychotic, mood and anxiety related symptoms of schizophrenia in patients 65+ with a low risk for diabetes/DKA, movement disorders and falls.

64. In April 2003, FDA approved quick dissolving Risperdal tablets, commonly referred to as "M-Tabs." In an April 2, 2003 memorandum to the J&J Global Pharmaceutical Pricing Committee, Janssen stated that their marketing strategy was to promote M-Tabs in the long-term care market, given the high prevalence of swallowing difficulties in the elderly.

65. Janssen's 2004 Business Plan indicated that one of its main themes for the year would be to "Re-establish growth in the LTC market."

66. Janssen did not disband the ElderCare sales force and exit the nursing home market until 2005.

67. From at least 1998 through 2004, thousands of records of sales calls by Janssen sales representatives (known as "call notes") and individualized instruction provided by district managers following sales calls (known as "field conference reports") reflect promotion of Risperdal as safe and effective in controlling behavioral disturbances in the elderly. For example:

Examples from 1998 Call Notes

New York: "DISCUSSED HOW RIS[PERDAL] IS EFFECTIVE AND SAFE IN THE TX [TREATMENT]: OF BEHAVIORAL DISTURBANCES IN THE ELDERLY, ESPECIALLY THOSE WITH DEMENTIA."

California: "Left a note introducing myself and ElderCare with Ref[erence] to Risp[erdal] for Geriatric hostility/behavioral problems . . . ."

Examples from 1999 Call Notes

Ohio: "detailed her on ris[perdal] - she said she would think about pts [patients] who display behavior symp[tom]s we talked about, ensured her ris[perdal] safe in elderly. . . ."

Florida: "risp[erdal] - core message - safe and effective in elderly pt [patient] with behavior problems. . ."

Examples from 2000 Field Conference Reports

Minnesota: "We had the opportunity to meet with five of your targeted psychiatrists. . . .All five psychiatrists confirmed their support of Risperdal in the treatment of behavioral problems due to Dementia."

Examples from 2001 Call Notes

Washington: "spoke to dr [doctor] about using RIS[perdal] for pts [patients] w/behavioral disturbances assoc [associated] w/dementia, described positive and negative symptoms, agitation"

Maryland: "She [the doctor] attended an inservice program today that was held at Menno Village addressing behavioral problems with or w/o dementia."

Examples from 2002 Call Notes

Michigan: "Detailed on Risperdal efficacy, dosing and side-effect profile vs. competitors for dementia patients w/behavioral problems"

New Jersey: "Risp[erdal] works not only for agitation in the elderly but at low doses acts like an SSRI [antidepressant]. People live longer . . . ."

Examples from 2003 Call Notes

Connecticut: "Risp[erdal]: Admits to not using as much as he could, not comfortable with APS [antipsychotic] meds. So, I went over dosing .25mg for his elderly patients, 1 mg maintenance dose. Stressed use for agitation and anxiety, esp when current SSRI [anti-depressant] therapy is not responding. . . ."

Delaware: "[F]ocused on mixed dementia w/ Dr this trip & Ris[perdal] as adjunct therapy for the mood & behavioral problems assoc. w/ dementia"

Michigan: "Dr . . . [s]aid he has very little experience with Risperdal and the elderly. Explained how it could help with sundowning syndrome. Told me that he would try it on Gloria's mother."

Examples from 2004 Call Notes

Tennessee: "ris[perdal]: efficacy on behavioral problems in dementia patients"

Texas: "Risp[erdal]: . . . Said he writes in nursing home. Asked for nxt [next] pt [patient] w/ anxiety/depression. Said he will consider as adjunct w/ ssri [antidepressant]."

4. Janssen Recruited Consultant Pharmacists to Assist In Off-Label Promotion.

68. A J&J subsidiary entered into agreements with long-term care pharmacy providers that provided financial incentives for increasing the use of Risperdal in the facilities they serviced. Defendants recognized that consultant pharmacists could influence doctors to write Risperdal prescriptions for off-label uses. As part of the off-label marketing campaign, Janssen recruited consultant pharmacists to attend advisory boards and worked with those pharmacists to identify patients to be placed on or switched to Risperdal.

69. In addition to nursing homes, the long-term care pharmacy providers also serviced mental health facilities. In its 2002 business plan, Janssen identified mental retardation and developmental disability (MRDD) as a target market and encouraged sales representatives to market Risperdal as "the first choice for psychotic and behavioral disorder, including MRDD." Janssen trained speakers and consultant pharmacists and sponsored advisory boards or round table discussions to promote Risperdal for behavioral and conduct symptoms in MRDD patients.

B. Janssen Promoted Risperdal for Use in Children

70. Until late 2006, Risperdal was not approved for use in children for any purpose. The Risperdal label stated that "[t]he safety and effectiveness in children have not been established." Nonetheless, from at least 1999 through 2005, Janssen promoted Risperdal to treat children for a variety of unapproved uses, including conduct disorders, attention-deficit-hyperactivity disorder (ADHD), and bipolar disorder.

71. On August 15, 1996, Janssen asked FDA to approve an addition of language to the Risperdal label regarding pediatric use. FDA rejected Janssen's request, stating:

> [Y]ou have not identified any pediatric indications for which you believe Risperdal could be approved and you have provided no data from adequate and well controlled trials to support any such approvals. . . To permit the inclusion of the proposed vague references to the safety and effectiveness of Risperdal in pediatric patients and the nonspecific cautionary advice about how to prescribe Risperdal for the unspecified target indication would only serve to promote the use of this drug in pediatric patients without any justification.

(Exhibit 13).

72. On March 3, 2000, Janssen met with FDA to discuss a clinical development plan for an indication for "conduct disorder" in children. Although FDA recognized that "conduct disorder" is a diagnosis listed in the Diagnostic and Statistical Manual of Mental Disorders, the agency questioned whether it could approve Risperdal for "conduct disorder," explaining that its

"main concern is that RISPERDAL or any other product would be used as a chemical straight jacket." In addition, FDA expressed concern that conduct disorder was "synonymous with aggression" and that Janssen was "trying to get approval of aggression under the guise of CD [conduct disorder]." (Exhibit 14).

73. Defendants knew that Risperdal could cause elevated levels of prolactin, a hormone released by the pituitary gland that stimulates breast development and milk production. Since launch, the FDA-approved label stated that Risperdal, like other antipsychotics, "elevates prolactin levels." The Risperdal label further stated that "the clinical significance of elevated serum prolactin levels is unknown for most patients."

74. One of Janssen's Key Base Business Goals was to grow and protect share in the child/adolescent market, which Janssen defined to include patients 19 years and under. Janssen's 2001 Base Business Plan stated that the fastest-growing market for Risperdal was pediatrics, with the use of Risperdal "exploding" at a growth rate of 17 percent, for a total market share of $340 million per year. Janssen recognized that Risperdal was used in children primarily for non-psychotic diagnoses: bipolar disorder (21%), autism (18%), ADHD (15%). Janssen also noted that Risperdal was typically prescribed in children "to control aggressive/impulsive behavior."

75. Janssen instructed its sales representatives to call on child psychiatrists as well as on mental health facilities that primarily treated children and to market Risperdal as effective to treat symptoms associated with various childhood disorders such as ADHD, OCD, and autism. The company sponsored numerous advisory boards with child psychiatrists and speakers programs concerning "Risperdal in Children and Adolescents with Severe and Disruptive Behaviors and Below-Average IQ."

76. Janssen prepared two plans for addressing the child and adolescent market in 2002: a business plan ("Risperdal Child and Adolescent Market Segment: 2002 Business Plan

Summary") and a tactical plan ("2002 Tactical Plan RISPERDAL Child and Adolescent Segment: Reach New Heights with Risperdal in 2002"). Janssen identified four key business strategies:

- Understand the level of awareness of RISPERDAL in the child and adolescent market segment;
- Educate health care providers on therapeutic options for treating mental illness in children;
- Develop a child and adolescent public relations and media management plan; and
- Clarify FDA requirements and accelerate JRF program to obtain child and adolescent labeling.

77. In 2002, Janssen created a "C&A Educational Initiative" to promote the use of Risperdal in children and adolescents ("C&A"). As part of this Initiative, Janssen developed advisory boards and CME programs and utilized national and regional opinion thought leaders in child psychiatry. For example, in March 2002, Janssen sponsored a meeting attended by 1,000 physicians, which Janssen executives later described as "[a] great way to get the word out to a big part of the child and adolescent prescribing community." Similarly, at an "Advisory Summit" in February 2003, Janssen presented data promoting Risperdal to treat conduct disorders in children with disruptive behavior disorders.

78. When FDA approved M-Tabs in April 2003, Janssen district managers encouraged contests and other incentives to promote this quick-dissolving Risperdal formulation in children:

> In the San Antonio District, district managers encouraged "Risperdal 'Back to School' Bashing" and proposed ice-cream parties, snacks and lunches as an effective way to deliver an efficacy message of fast onset of M-Tabs and use in the pediatric population.
>
> Notes from a District Managers' Conference Call on August 11, 2003 state: "'There is a very large market for the M-TABs* for children/adolescents!"

In an August 20, 2003 Field Conference Report, a district manager praised the sales representative, stating " You have a great idea for M-Tab starter kits by including lollipops or small toys to be included in the kit along with a coupon and a 1 box of sample. These will be great to use on any child & adolescent psychiatrists that you have....Plan to have these made for our next work session." (Exhibit 15).

79. From at least 1997 through 2004, call notes by Janssen sales representatives and field conference reports from their managers reflect promotion of Risperdal as safe and effective in controlling behavioral disturbances in children and adolescents. For example:

Examples from 1997 & 1998 Call Notes

Maryland: "remind her [doctor] that risperdal is very effective and safe because she sees lots of children and aldolescence [sic]."

Michigan: "sold him on efficacy and safety in children."

Examples from 2000 Field Conference Reports

New York: "I observed that prolactin was a concern with several of your customers. [Y]ou have a good understanding of prolactin and how to handle this objection with your customers. For example, Dr. H[] stated that she sees prolactin related side effects quite often with Risperdal . . . You did a nice job of discussing how rare prolactin related side effects occur, how to manage it i.e. lowering the dose, and brought the discussion back to side effects that are not easily managed, i.e. diabetes."

Examples from 2001 Call Notes

Texas: "Discussed . . . proper dosing in children. Warned him about competition putting side effects out of centext [sic] regarding R[isperdal] in children. Asked for starts/switches in aggression"

Virginia: "INSERVICE FOR THE GROUP, WENT OVER RISPERDAL USE IN ADULTS AND CHILDREN, THE SYMPTOMS IT COVERS . . ."

Examples from 2002 Call Notes

Washington: "Dr. has not received information on conduct disorder and recent published articles. We reviewed efficacy of risperdone on aggression and hostility in special populations and doses."

New York: "[D]oesn't see adhd but will rx [prescribe] when sees."

Examples from 2002 Field Conference Reports

Minnesota: "[The doctor] then told you a story about a young woman who developed some prolactin related side effects on Risperdal. Based on his comments it was clear prolactin was an issue of his. You handled his objection and issue perfectly by explaining that any drug that blocks D2 [dopamine] can have an effect on prolactin however the incidence of seeing side effects is very low. You then went onto explain that he may be able to decrease the dose and maintain the great efficacy that he is seeing with Risperdal and at the same time hopefully the side effect will subside. He agreed that this was a good idea and would give it a try."

Examples from 2003 Call Notes

North Carolina: "Sees 30% kids, 40% adolescents, 30% adults . . . With kids – discussed serotonin profile page – lower doses equate to efficacy in treatment of agitation, aggression – symptoms with behavioral problems."

Indiana: "Next call remind him of the type of syms [symptoms] he can treat with Ris[perdal]. [P]aint the picture of a younger patient suffering from these sym [symptoms] and what ris can do for them."

Examples from 2004 Call Notes

South Carolina: "[B]rief follow up on use of Risperdal and moa [mechanism of action] that will treat anxiety and depressive symptoms. [E]mphasized the importance of dosing and how if dosed appropriately will treat odd [Oppositional Defiant Disorder] symptoms that present with adhd."

Maryland: "Goal: aggitated [sic]/aggression in children. Response: must rule out ADHD in children before rx [prescribing] atypical – Risperdal effectively treat[s] resistant depression at lower doses."

C. Off-Label Promotion in the General Population

80. In addition to marketing Risperdal for use in the elderly, children, and the mentally disabled, Janssen used many of the same tactics to promote Risperdal for off-label use in the general population. Janssen's business and tactical plans aimed at expanding the use of Risperdal to any patient who exhibited mood and anxiety symptoms.

81. At a National Meeting in 2001, Janssen directed sales representatives to emphasize that Risperdal was effective in treating a broad range of symptoms. Janssen's Mood and Anxiety Positioning statement for 2001 was:

> Broad spectrum RISPERDAL is 1st choice for psychotic, behavioral, and mood disorders (bipolar disorder with/without psychosis, refractory depression and refractory anxiety disorders) because it is the only therapy to deliver rapid and sustained efficacy across the full range of symptoms (anxious, manic, depressed) and is uncompromised by safety concerns . . . .

82. Janssen's 2002 Business Plan continued to emphasize marketing to behaviors and mood and anxiety symptoms:

> Broad spectrum RISPERDAL is 1st choice for psychotic and behavioral disorders (Schizophrenia, Schizoaffective disorder, Psychotic depression, Dementia, Bipolar Mania, MRDD) because it is the only therapy to deliver rapid, sustained (within 30 min and for at least 1 year) efficacy across the full range of symptoms (PANSS, cognition, anxiety, mood and behavioral disturbances as well as improved patient function) . . . .

83. In 2002, pursuant to FDA's request, Janssen modified the Risperdal label to state that Risperdal was approved only for the treatment of "schizophrenia." Nonetheless, Janssen instructed the sales managers that there was "No need to notify customers of the label change" because "Our strategy remains the same - **SYMPTOM** focus!" One of Janssen's "core message" for 2002 was:

> For patients with mood disorders (anxiety/depression), Risperdal is the #1 prescribed product in its class because it offers superior efficacy in treating mood symptoms versus both Zyprexa and Haldol with less frequency to cause diabetes in your patients.
>
> Turn off-label use into symptom WAR!

84. In 2002, defendants created a new sales force, "the 500 Gold," to market Risperdal to primary care physicians (PCPs), who do not generally treat schizophrenia or psychotic disorders.

85. One sales representative summarized the direction she received in a 2002 memorandum she sent to other sales representatives and her district manager:

Summary: Mid-Cycle Meeting

Discussion Regarding Off Label Uses for Risperdal

Risperdal has a large volume of studies with proven efficacy in a wide variety of symptoms. There are studies on file for treatment-resistant depression, bipolar disorder and pediatrics usage. We can and should request information medical services whenever these issues arise.

However, in the meantime . . .BRING IT BACK TO THE SYMPTOMS . . . with ANY disease state we can sell Risperdal instead of any of the competition using the studies we currently have in our hands.

Bipolar Disorder. BRING IT BACK TO THE SYMPTOMS (Excitability, Agitation, Aggression, Depression, Delusions)

Pediatrics: BRING IT BACK TO THE SYMPTOMS (Impulsiveness, Agitation, Aggression, Depression, Anxiety).

86. At the National Sales Meeting in February 2003, Janssen identified mood and anxiety among the fastest growing market segments. Janssen told representatives that "[f]ocusing your discussion around these symptoms (hostility, anxiety, depression and impulsiveness) is important because it will help physicians identify appropriate patients for whom low dose (.25mg and .50mg) is an ideal option."

87. Janssen developed a "Mood Backgrounder" and provided sales representatives with the following direction:

Sell symptoms not disease states.

Use patient profiles to make connection to broader usage.

Sell the geriatric benefits of Risperdal.

Ask for female mood and anxiety patients because of weight gain with Zyprexa

Sales representatives were also taught to use the following technique to "Cement the Sale:"

Ask for a specific outcome. Dr. based on the information we've discussed will you use Risperdal for your female mood and anxiety patients? Dr.

can I ask you to use Risperdal for 5 of your next 10 patients suffering from hostility and aggression?

88. In 2004, defendants set a business goal of establishing Risperdal as "a broad spectrum (mood & anxiety symptom patients, and agitated aggressive patients) psychotropic that helps improve patient functioning through its unique mechanism of action."

89. Sales representative call notes and district manager field conference reports reflect sales representatives' efforts to promote Risperdal for non-psychotic disorders and non-schizophrenic patients exhibiting mood and anxiety symptoms:

Examples from 2001 Field Conference Reports

"you then bridged into risperdal and explained to Dr. G. the benefits of risperdal in the adult population over others, specifically mood symptoms, by discussing the symptom he is trying to manage."

"Risperdal has proven superior to Zyprexa on positive symptoms and mood disorders."

Examples from 2002 Call Notes

Pennsylvania: "We went over treatment-resistant depression concept again with Risperdal use over Zyprexa."

New Hampshire: "confirmed Risperdal to be first line choice for PTSD [post-traumatic stress disorder] patient."

Examples from 2003 Call Notes

California: "[T]old him how risp[erdal] is appropriate for pts [patients] with mood disorders or treatment resistant depression. Went over dosing. He said he will rx [prescribe]."

Arizona: "He does not have elderly pts [patients], and prefers to leave Risp. up to psychs. We did discuss use of Risp. by PCPs [primary care physicians] for treatment resistant depression and other mood symptoms."

Examples from 2004 Call Notes

Texas: "Reminded him of using Risp[erdal] for that stubborn depression and sleep problems."

Alabama: "Discussed mood, irritability, depressive symptoms and or aggressive symptoms as they relate to serotonin and norepinephrine. . . ."

VI. RISPERDAL'S KNOWN DIABETES RISKS

90. In marketing Risperdal, Janssen claimed that there was a low risk of developing diabetes associated with the use of Risperdal and that Risperdal was therefore safer than other atypical antipsychotic drugs.

91. In its 2002 Business Plan, one of Janssen's messages was that Risperdal was "uncompromised by safety concerns (does not cause diabetes)." In an October 13, 2002 letter, a district manager praised a sales representative, stating, "You shared with [the doctor] that the prevalence of diabetes was not a class effect, highlighting that Risperdal has a less than one percent incidence. Good Job!"

92. Janssen sponsored a retrospective study of insurance billing data for 6,641 patients to determine the rate of diabetes in patients taking Risperdal and Zyprexa (the "Fuller Study"). When the initial study results were circulated internally, a Janssen medical affairs employee stated: "These are hot off the presses . . . . The general gist is there is no difference between Risperdal and Zyprexa in diabetes risk."

93. Janssen subsequently hired an outside consultant to review the results of the Fuller Study. The consultant reported that the association between medication group and diabetes was "not reliable" due to switching of medications. The outside consultant subsequently re-analyzed the data to control for switching, removed patients from the study, and changed its primary end-point. In 2003, the Fuller study was published in the journal Pharmacotherapy in an article entitled "*A Comparative Study of the Development of Diabetes in Patients Taking Risperdal and Zyprexa.*" The article described the revised analysis and stated that "Zyprexa was associated with a 37% increased risk of development of diabetes compared to Risperdal in a VA population." Janssen disseminated the Fuller Study to sales representatives and through advisory boards and CMEs.

94. In September 2003, FDA requested that additional language be added to the Warnings section of the label for all atypical antipsychotics, including Risperdal, regarding the risk of hyperglycemia and diabetes. Defendants were concerned that the diabetes warning would lead doctors to conclude that diabetes risk was a "class effect" and that all atypical antipsychotics presented the same risk of diabetes. Janssen instructed its sales representatives to cite the Fuller Study as evidence that Risperdal was safer than other antipsychotics for use in patients with diabetes or who were at high risk of developing diabetes.

95. In September 2003, Janssen obtained summary results of a prospective, double-blind, controlled study comparing the diabetes risk of Risperdal versus Zyprexa (RIS-USA-275), which indicated that Zyprexa had no greater tendency to increase the risk of diabetes than Risperdal. In March 2004, Janssen retained outside consultants to review the results of RIS-USA-275. Janssen ultimately removed 17 of the original 59 patients from the study as "not evaluable" based on an assessment of drug levels, medical history, fasting levels, body composition, and glucoregulatory parameters. Janssen finalized its internal Clinical Study Report in May 2004 and first presented the study results at a medical symposium in May 2005.

96. On September 26, 2003, a Voicemail Message Confirmation distributed by the Director of Sales to inform the sales force that Janssen:

> [c]ontinues to believe the scientific evidence shows a difference in the incidence of diabetes among the different atypical antipsychotics. The data DOES NOT show an association between RISPERDAL and an increased risk of diabetes. However, the data DOES SUGGEST a greater association with some of the other products. We are in the process of submitting this data to the FDA for their review and anticipate that they will respond asap. As always, patient safety is our first priority as we share FDA's interest in ensuring that physicians and patients have accurate safety information about our products. You should also be confident that you will be the first to know if or when the FDA makes any decision regarding this issue. In the meantime, you should follow our company position and sales direction and continue to emphasize that RISPERDAL has a 'low' risk of diabetes and DKA (diabetic ketoacidosis) compared to

other drugs in this class utilizing our diabetes reprint carrier combined with our new sales brochure. So let's ensure that we stay FOCUSED on promoting RISPERDAL based on it's [sic] EFFICACY AND SAFETY."

97. On November 6, 2003, Janssen submitted supplemental new drug applications to FDA that included a diabetes warning in the label, as requested by FDA. As revised, the label stated:

> Hyperglycemia, in some cases extreme and associated with kekoacidosis or hypersmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes milletus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-relates adverse events is not completely understood. However, epidemiologic studies suggest an increased risk of treatment emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

98. On November 10, 2003, Janssen sent approximately 753,000 doctors a letter informing them about the addition of the diabetes warning to the Risperdal label. The letter stated that FDA had requested that all manufacturers of atypical antipsychotics include a diabetes warning on their product labels and enclosed a copy of the complete prescribing information for Risperdal that included the diabetes warning. However, the letter also asserted that the evidence indicated that Risperdal was ***not*** associated with an increased risk of diabetes when compared to untreated patients:

> Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-8] suggests that Risperdal is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that Risperdal is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

Notes 1 through 8 referred to a list of all eight published, peer-reviewed epidemiological studies addressing atypical antipsychotics and diabetes risk.

99. On April 19, 2004, FDA sent a Warning Letter to Janssen that identified several concerns regarding the way Janssen characterized the diabetes risk of Risperdal in its November 10, 2003 letter (Exhibit 16).

100. Janssen sent a second letter to doctors on July 21, 2004, which reported the concerns that FDA had identified in its Warning Letter.

VII. PAYMENTS TO HEALTHCARE PROVIDERS

101. Janssen paid doctors who participated in the speakers program and other programs related to Risperdal to influence the doctors to write more prescriptions for Risperdal, and certain of the prescriptions written by these doctors were reimbursed by Medicaid and other public healthcare programs.

102. Sales representatives identified local doctors to be trained as speakers based on their potential for writing Risperdal prescriptions. Sales representatives told doctors that if they wanted to speak, they had to increase their Risperdal prescriptions. For example, in an October 7, 2003, e-mail, one sales representative told her district manager that a doctor in her district wanted to be a speaker for Janssen, but only 16 percent of his antipsychotic prescriptions were for Risperdal. The representative discussed plans to tell the doctor that he could qualify to speak the following year if he wrote 50 percent of his prescriptions for Risperdal. The doctor subsequently increased his Risperdal prescriptions and became a paid speaker in 2004.

103. Like local speakers, attendees at advisory boards were chosen by sales representatives based on their ability to write prescriptions for Risperdal. Attendees were paid an honorarium of approximately $1,500 to $2,000. Janssen intended to induce these attendees to

write prescriptions for Risperdal and tracked their prescriptions before and after their attendance at advisory boards to measure whether they increased their prescriptions.

VIII. SUBMISSION OF FALSE CLAIMS TO FEDERAL HEALTHCARE PROGRAMS

104. Defendants' fraudulent conduct resulted in the submission of false claims to federal healthcare programs. From 1999 through 2005, domestic sales of Risperdal increased from $892 million to $2 billion per year. Defendants targeted patient populations that they knew included large numbers of Medicaid beneficiaries, such as nursing home residents. As a result, during the same time period, defendants caused the Medicaid reimbursements for Risperdal to more than double from $500 million to over $1 billion annually. Defendants also closely tracked the effect of their sales and marketing on both on-label and off-label utilization. According to defendants' own market research, in 2002 as much as 70 to 75 percent of the prescriptions for Risperdal were for off-label uses, some of which were not medically accepted indications for which the United States and state Medicaid programs provided coverage.

FIRST CAUSE OF ACTION
(False Claims Act: Presentation of False Claims)
(31 U.S.C. § 3729(a)(1) (2008))

105. The United States re-alleges the preceding paragraphs as if fully set forth herein.

106. Defendants knowingly caused to be presented false or fraudulent claims for payment or approval to the United States for Risperdal prescriptions that were not covered by Medicaid and/or were ineligible for payment as a result of illegal kickbacks.

107. By virtue of the false or fraudulent claims that defendants caused to be made, the United States suffered damages and therefore is entitled to treble damages under the False Claims Act, to be determined at trial, plus civil penalties of not less than $5,500 and up to $11,000 for each violation after September 29, 1999. Prior to September 29, 1999, civil penalties are not less than $5,000 and up to $10,000.

SECOND CAUSE OF ACTION
(False Claims Act: False Statements)
(31 U.S.C. § 3729(a)(1)(B) (2009))

108. The United States re-alleges the preceding paragraphs as if fully set forth herein.

109. Defendants knowingly made, used, or caused to be made or used, false records or statements material to a false or fraudulent claim.

110. By virtue of the false records or statements that defendants made, used, or caused to be made or used, the United States is entitled to treble damages and civil penalties of not less than $5,500 or more than $11,000 for each such false record or statement.

THIRD CAUSE OF ACTION
(False Claims Act: Conspiracy)
(31 U.S.C. § 3729(a)(3) (2008))

111. The United States re-alleges the preceding paragraphs as if fully set forth herein.

112. Defendants and others conspired to defraud the Government by getting false or fraudulent claims allowed.

113. By virtue of the conspiracy, defendants and others got false or fraudulent claims paid and the United States is entitled to treble damages and civil penalties of not less than $5,500 or more than $11,000 for each such false or fraudulent claim.

FOURTH CAUSE OF ACTION
(Unjust Enrichment)

114. The United States re-alleges the preceding paragraphs as if fully set forth herein.

115. As a consequence of the acts set forth above, defendants were unjustly enriched at the expense of the United States in an amount to be determined which, under the circumstances, in equity and good conscience, should be returned to the United States.

116. The United States claims the recovery of all monies by which defendants have been unjustly enriched.

PRAYER FOR RELIEF

WHEREFORE, the United States demands and prays that judgment be entered in its favor against defendants as follows:

1. On the First Count under the False Claims Act, for the amount of the United States' damages, trebled as required by law, and such civil penalties as are required by law.

2. On the Second Count under the False Claims Act, for the amount the United States was damaged, trebled as required by law, and such civil penalties as are required by law.

3. On the Third Count under the False Claims Act, for the amount of the United States' damages, trebled as required by law, and such civil penalties as are required by law.

4. On the Fourth Count for unjust enrichment, for the amounts by which defendants were unjustly enriched, plus interest, costs, and expenses.

5. On all Counts, such further relief as the Court deems just and proper.

Respectfully submitted,

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Dated: November 4, 2013

EXHIBIT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 14 1994

TRANSMITTED VIA FACSIMILE

[redacted]
Regulatory Affairs
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560-0200

RE: NDA# 20-272
Risperdal (risperidone) Tablets
MACMIS File ID# 2366

Dear [redacted]:

This letter is in response to Janssen Pharmaceutica's (Janssen) August 22, 1994, request for the Division of Drug Marketing, Advertising, and Communications (DDMAC) to review two marketing themes for Risperdal (risperidone) Tablets. DDMAC, in consultation with the Division of Neuropharmacological Drug Products, has reviewed these themes and offers the following comments.

The first proposed theme focuses on the promotion of Risperdal for psychotic disorders other than schizophrenia. Specifically, Janssen is proposing promoting Risperdal for disorders such as bipolar disease, psychotic depression, schizophrenic personality disorders, etc. Although the antipsychotic efficacy of Risperdal was established only in schizophrenic patients, Janssen notes that the indication is written in broader language, i.e. for the management of the manifestations of psychotic disorders. Therefore, Janssen is interested in encompassing other types of psychotic patients in their marketing campaigns.

We do not object to the inclusion of other disorders in the description of psychotic disorders in promotional materials for Risperdal. However, the description must be accompanied by the disclosure that Risperdal has only been studied in schizophrenic patients. Furthermore, a focused marketing campaign targeting specific non-schizophrenic psychoses would be misleading because it would suggest that Risperdal had been studied in that particular illness when, in fact, it has not.

The second proposed theme focuses on the promotion of Risperdal for use in the geriatric population. Although the approved product labeling does not specifically address efficacy in the

[redacted]
Janssen Pharmaceutica
NDA 20-272

elderly as it compares to the general population, Janssen notes that it does discuss this population in the Clinical Pharmacology and the Dosage and Administration sections.

DDMAC has significant concerns with this promotional theme. Precautions in the approved product labeling that state

> Clinical studies of Risperdal did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, a lower starting dose is recommended for an elderly patient reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and a greater tendency to postural hypotension.

This precaution reflects the lack of data to adequately address geriatric safety and efficacy. Only 83 patients greater than age 64 have been treated with Risperdal in the pre-marketing database (NDA plus safety update). Moreover, this precaution reflects the concern of postural hypotension, a potentially serious adverse event in the elderly.

Additional data from clinical trials would be required to support the promotion of geriatric use of Risperdal. Moreover, controlled trial data would be more informative than open-label data. Until this data is available, it would be misleading to suggest that the safety and efficacy of Risperdal has been established in the elderly when.

If you have any questions or comments, please contact me by telephone at (301) 594-6824, by facsimile (301) 594-6771 or by written communication at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, 5600 Fishers Lane, HFD-240, Rm. 17B-20, Rockville, MD 20857.

In all future correspondence regarding this matter, please refer to the MACMIS File ID# 2366, in addition to the NDA number.

Sincerely,

Sherry Danese

Sherry Danese, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

EXHIBIT 2

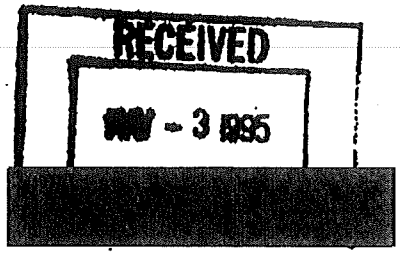
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 31,931

APR 28 1995



Janssen Research Foundation
Attention: [redacted]
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear [redacted]:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act for Risperdal (risperidone).

Reference is also made to your amendment (N-090) of February 10, 1995, and to protocol RIS-USA-63 entitled, "A Randomized, Double-Blind, Placebo-Controlled Study of Fixed Doses of Risperidone for Treatment of Behavioral Disturbances in Subjects with Dementia."

Your submission contains, among other documents, a cover letter in which you "invite ...[The Division's]... concurrence that this study [RIS-USA-63], should the results indicate efficacy, will serve as an adequate and well controlled assessment of the behavioral disturbances associated with dementia for the purpose of label revision."

While we have no safety objections to the conduct of your proposed study, we cannot provide assurance regarding your plans for label revision based on this study. Risperdal was developed as an antipsychotic drug in patients with schizophrenia and is currently approved only for the "management of the manifestations of psychotic disorders." If your interest had been in targeting another psychotic population, e.g., a subgroup of demented patients with associated psychotic symptoms, the labeling could be easily enhanced by simply describing the results of such a study, if positive, in the Clinical Trials subsection of Clinical Pharmacology. This would not really be an expansion of the basic claim for Risperdal, but rather, an extension of the population base supporting the claim. Such information would be potentially useful to clinicians and would improve labeling.

Alternatively, you appear to be exploring Risperdal's potential value for a much broader and more diffuse clinical target, namely "behavioral disturbances in demented patients." While this broad label would certainly include psychotic phenomena, e.g., delusional thinking, suspiciousness, and hallucinations; it would also encompass a range of other clinical findings, e.g., anxiety, depression, agitation, aggressiveness, verbal outbursts, wandering, etc., that would not necessarily be considered psychotic manifestations. Your entry criteria for this study would certainly not limit your sample to demented patients with associated psychotic symptoms. In addition, the BEHAVE-AD, your primary

outcome measure, includes a number of behavioral signs and symptoms that are not readily classified as manifestations of psychosis. Some of these findings, e.g., aggressiveness or verbal outbursts, might even be construed by some as appropriate responses to the deplorable conditions under which some demented patients are housed, thus raising an ethical question regarding the use of antipsychotic medications for inappropriate behavioral control. Nevertheless, the major concern we want to focus on is how any results from the study you are proposing might be incorporated into labeling in a way that is useful to clinicians and is not misleading.

The term "behavioral disturbances in demented patients" is so broad that it might be misinterpreted by clinicians to mean that a drug shown effective for such a target would be effective for all the various signs and symptoms that fall under such an umbrella, e.g., anxiety, depression, phobic fears, panic attacks, diurnal rhythm disturbances, etc. We would consider such a claim misleading in that sense, and consequently, we would not consider this broad claim, either as a new claim under Indications, or as an implied claim that would derive from permitting the description of your proposed study under Clinical Trials. Rather, we would suggest that you attempt to parcel out the various distinct clinical targets that are subsumed under the broad heading of "behavioral disturbances" and study these separately. Since risperidone is already approved for psychosis, an obvious initial target would be the subgroup referred to above, i.e., demented patients with associated psychotic symptoms.

There is a further difficulty. Even if agreement can be reached concerning the nature of the target signs and/or symptoms that will be treated, the linkage of those phenomena to dementia will remain problematic. The issue here involves the general problem of 'pseudospecificity' of labeling claims that occurs whenever a treatment for a symptom or sign that is common to several conditions is evaluated in only one of them. In such instances, it is impossible to discern when a beneficial treatment effect is found whether or not it is in any way linked to the diagnosis of the patients treated.

For example, assume that you were able to show by ordinary standards that risperidone does reduce agitation in a sample of patients with dementia. That finding, however, is not proof that the effect of risperidone is in any way specific to dementia. In fact, the only reason that a seeming link would exist in this situation between the demonstrated effect and dementia would arise from your decision to study risperidone in a sample of demented patients. Accordingly, such a result would not be sufficient to justify a dementia related claim.

You may, of course, our explanations of the issues affecting our views notwithstanding, still wish to pursue a claim for Risperdal in dementia. If so, you should understand that we are in no way opposed to such an effort; indeed, we would welcome one. In that case, however, you would have to demonstrate that the effects of Risperdal (and we would have to develop an explicit enumeration of the behaviors targeted) are in some way predicted by the diagnosis of dementia. Put another way, to gain a claim for

appropriate target behaviors associated with dementia, you would have to show that these behaviors are suppressed in dementia patients and not in patients with other conditions or diseases where they are also seen. The task, we acknowledge, is not easily accomplished, but without such evidence, you will not be able to assert a unique dementia related claim for an antipsychotic product.

Incidentally, the same general advice applies to any attempt to gain a specific disease related claim for a product that exerts a pharmacological action currently held to be more or less independent of the disease state in which it occurs, for example, disease specific claims for anxiolytics or analgesics.

In conclusion, the trial you propose cannot provide results that would, on their own, serve as a basis for expansion of the claimed indications for the use of Risperdal, nor would they be sufficient to serve as a basis for any other substantive modification of current product labeling. However, the results of the proposed study may well provide information critical to the planning and development of either 1) a program for further systematic evaluation of risperidone's use or uses in the management of one or more undesirable/untoward behaviors (e.g., agitation, seeming purposeless motor activity, etc.) that occur in a number of clinical conditions, including, but not limited to, dementia or 2) a program to define better the doses and regimens required to manage the psychotic manifestations exhibited by demented patients.

Should you have any further questions, please contact Steven D. Hardeman, R.Ph., Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

EXHIBIT 3

[redacted]

Aggression in Dementia

The Division is opposed to an indication for "aggression associated with dementia," due to the subjective nature of assessing the motivation for these symptoms, and the lack of a consensus within the medical community on a definition of "aggression." Thus, an indication would be misleading. The prescriber/caregiver would have to make a value judgment as to a patient's motivation for the behavior. For example, if a patient screams (one of the measured behaviors in the aggressive subscale of the BEHAVE -AD), is it because he/she is demented, or because he/she is trying to communicate displeasure or even pain? Many demented patients, particularly those included in our trials, have limited verbal skills. Therefore, an indication for "aggression" could allow a patient's limited capacity for self-expression to be reduced. In summary, Dr. Leber termed this type of indication an "enabling indication," due to its potential, unintended consequences indicating that just because it's being used for these purposes, does not mean it's medically appropriate. He did not dispute that we have demonstrated a treatment effect, but he questioned whether the effect was always a benefit. After reviewing the items we used to assess aggression, "physical threats or violence" was identified as, perhaps, a more objective item. Also, they will consider allowing the description of a treatment effect on behaviors that accompany the decrease in psychotic symptoms. While discussing our sub-group analysis excluding patients with somnolence, Dr. Leber expressed reservation about the appropriate definition and assessment of "somnolence" in this patient population.

[redacted]

EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FOI

JAN 5 1999

TRANSMITTED VIA FACSIMILE

Todd McIntyre, Ph.D.
Director, Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Rd.
Titusville, NJ 08560-0200

RE: NDA #20-272, 20-588
Risperdal (risperidone) Tablets
Risperdal (risperidone) Oral Solution
MACMIS #6908

Dear Dr. McIntyre:

This letter concerns Janssen Research Foundation's (Janssen) promotional materials and activities for the marketing of Risperdal (risperidone) Tablets that have been reviewed by the Division of Drug Marketing, Advertising and Communications (DDMAC) as part of its monitoring and surveillance program. In particular, DDMAC is concerned with a campaign that markets Risperdal for geriatric patients. These materials include, but are not limited to sales aids (ID# RS-420, RS-422, RS-473, RS-494), journal ads (ID# RS-470-1, RS-470-1-C, RS-470-1RB, RS-470-2, RS-470-2RB), a display panel (ID# RS-468), brochures (ID# RS-459, RS-469), and a letter (ID #RS-308). Other recent materials include journal ads (ID # RS-450-2, RS-451-2, RS-451-2A, RS-451-C, RS-470-1R, RS-470-2R), letters (ID # RS-462S, RS-477-1, RS-477-1R), a flashcard (ID # RS-518), a calendar (ID #RS-474), and a computer program (ID #RS-463). DDMAC has concluded that these materials are false, misleading, and/or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Specifically, DDMAC has the following objections:

Geriatric Campaign

1. Janssen is disseminating materials that state or imply that Risperdal has been determined to be safe and effective for the elderly population in particular. There is limited data on the use of Risperdal in the elderly, and the elderly population was not specifically studied in the clinical trials for Risperdal. Thus, presentations that focus on this population are

misleading in that they imply that the drug has been found to be specifically effective in the elderly population.

Also, according to the approved product labeling (PI), there are safety considerations for Risperdal in the elderly population. In healthy elderly subjects, the clearance of both risperidone and its active metabolite was decreased, and the elimination half-lives were prolonged. Hepatic impairment would further increase the mean free fraction of plasma risperidone. Risperdal should be used cautiously in healthy elderly individuals because of the potential for decreased clearance of drug, potential drug interactions, hepatic and renal dysfunction, and cardiovascular sensitivity. The safety of Risperdal in "fragile" individuals or individuals with concomitant illnesses has not been evaluated in adequate and well-controlled studies.

2. Risperdal is indicated for the management of the manifestations of psychotic disorders. However, Janssen is disseminating materials that imply, without adequate substantiation, that Risperdal is safe and effective in specifically treating hostility in the elderly.

Efficacy

Materials that claim that Risperdal is indicated "for psychotic symptoms associated with a broad range of disorders," including schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, and elderly psychosis, are false or misleading because the adequate and well-controlled clinical studies for Risperdal were not designed to examine the efficacy of Risperdal in this broad range of disorders.

Fair Balance

1. Janssen is disseminating materials that are lacking in fair balance because the risk information appears in pale and tiny font at the bottom or back of a journal ad or other presentation, or after the closing of a letter. Thus, the risk information is not presented with a prominence and readability that is reasonably comparable to the presentation of efficacy information.

2. Janssen is disseminating materials that are lacking in fair balance because they emphasize that Risperdal has a low incidence of certain side effects while minimizing or ignoring important risk information for Risperdal. For example, the sales aid ID# RS-420 has bolded headlines that state that Risperdal has a "low incidence of excessive sedation" and "low incidence of anticholinergic side effects," but the precaution concerning orthostatic hypertension is located in plain text in the "Dosing/Formulations" section, the ninth page of the ten-page piece. Further, the warning regarding tardive dyskinesia is minimized and the common adverse events, which occurred up to 34% of the time, have been reduced to a small paragraph with no quantification beneath a half-page table of common events associated with discontinuation (showing discontinuations were infrequent). Treatment-emergent extrapyramidal symptoms occurred 17-34% of patients on Risperdal (16% placebo). The dose-relationship of extrapyramidal symptoms is important risk information that is not included in many of the materials including this sales aid.

3. Materials that state or imply that Risperdal has a low incidence of movement disorders are false or misleading. According to the PI for Risperdal, adverse events that would cause movement disorders were common in the clinical studies for Risperdal and were often dose-related, as in the treatment-emergent extrapyramidal symptoms.

4. Materials that state or imply Risperdal has a low incidence of excessive sedation are false or misleading. According to the PI, the incidence of somnolence was 3% for 10 mg/day and 8% for 16 mg/day Risperdal (placebo = 1%). Sleepiness, increased duration of sleep, accommodation disturbances, asthenia, lassitude, and increased fatigability were all dose-related adverse events.

5. Materials that state or imply that Risperdal has a low incidence of anticholinergic effects are false or misleading. According to the PI, the incidence of constipation was 7% for the 10 mg/day and 13% for the 16 mg/day dose of Risperdal (placebo = 3%), and cognitive impairment (Precautions section of the PI) and reduced salivation are frequent adverse events. Furthermore, this claim is lacking in fair balance because there is no similar emphasis on adverse events that do occur with Risperdal.

6. Claims of low incidence of adverse events coupled with presentations of adverse events associated with discontinuation are false or misleading

because it implies that the events associated with discontinuation were the extent of the adverse events experienced with Risperdal.

Comparative Claims

1. Materials that state or imply that Risperdal has superior safety or efficacy to other antipsychotics due to its receptor antagonist profile are false or misleading because the mechanism of action of Risperdal is unknown, as is the correlation of the specific receptor antagonism to the clinical effectiveness and safety of the drug.

2. Presentations that compare the efficacy or safety of Risperdal to an active control make false and misleading superiority claims in the absence of substantiation from adequate and well-controlled comparative data (see for example, sales aid #RS-422).

Quality of Life Claims

1. Materials that claim that Risperdal can "enhance daily living" or that it offers "quality control of symptoms for daily living" are considered to be false or misleading in the absence of adequate and well-controlled studies using validated instruments to determine benefit to health-related quality of life.

2. The tagline "Quality control" is false or misleading because it is used out of context and can be interpreted to mean, without adequate substantiation, that Risperdal can control health-related quality of life.

The materials and promotional messages Janssen has disseminated contain false and/or misleading information about the safety and effectiveness of Risperdal. The violations discussed above do not necessarily constitute an exhaustive list. Accordingly, Janssen should immediately discontinue the use of all materials that state, suggest, or imply false, misleading, or unbalanced claims of the type discussed in this letter. Janssen should provide a written response to DDMAC stating its intent to comply with this request. The letter should also include a complete listing of the materials that Janssen will discontinue as a result of this letter, including the dates that the materials were discontinued, as well as a list of those materials that will remain in use.

Dr. Tod McIntyre
Janssen
NDA 20-272 (MACMIS 6908)

Janssen's response should be received no later than January 19, 1999. If Janssen has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm.17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS 6908 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

EXHIBIT 5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR - 9 1999

TRANSMITTED VIA FACSIMILE

[redacted] Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Rd.
Titusville, NJ 08560-0200

RE: NDA #20-272, 20-588
Risperdal (risperidone) Tablets
Risperdal (risperidone) Oral Solution
MACMIS #6908

Dear [redacted]:

Reference is made to the Division of Drug Marketing, Advertising and Communications' (DDMAC) January 5, 1999, letter regarding promotional materials for Risperdal that were determined to be false, misleading, or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act. These materials included a campaign directed towards the use of Risperdal specifically for geriatric patients (i.e., "Hostile Outside, Fragile Inside").

We also refer to Janssen Research Foundation's (Janssen) response dated January 18, 1999, and a follow-up communication dated February 16, 1999. In its response, Janssen stated that identified materials, as well as materials with the same or similar violative issues, would be immediately discontinued. Janssen requested an extension in DDMAC's imposed deadline for action because it was completing a comprehensive review of all materials that were not in compliance with DDMAC's notification. The results of Janssen's completed review were submitted in the follow-up communication.

We finally refer to Janssen's February 16, 1999, request to meet with DDMAC and members of the Division of Neuropharmacologic Drug Products (DNDP) to discuss issues in the untitled letter with which Janssen disagrees or for which Janssen requests further explanation.

Janssen has presented arguments to support the continuation of the geriatric campaign for Risperdal. DDMAC has considered Janssen's arguments and is not persuaded. DDMAC is aware that Risperdal may be used in the geriatric population, and that the approved product labeling (PI) includes instructions for dosage and administration in

[redacted]

this population. DDMAC has consulted DNDP on the geriatric campaign, as well as all other aspects of the untitled letter. Our concern is three-fold. First, the materials cited in our untitled letter are materials that focus on the geriatric population when, in fact, there is limited data on the use of Risperdal in the elderly and the group was not specifically studied in the clinical trials for the drug. Second, the campaign "Hostile Outside, Fragile Inside" implies, without adequate substantiation, that Risperdal has been specifically shown to be effective in treating psychotic elderly patients with hostility. Finally, the safety and efficacy of Risperdal in the elderly was not particularly examined in "fragile" individuals (i.e., individuals with particular hepatic or renal concerns, or other concomitant illnesses). In its January 18, 1999, letter Janssen notes that practitioners prescribe Risperdal to elderly patients "in the absence of controlled clinical trials."

Janssen argues that schizophreniform disorder, schizoaffective disorder, bipolar disorder, and elderly psychosis are all approved indications for Risperdal because DNDP has authorized "relatively broad indications for this particular class of drugs." DDMAC and DNDP disagree with Janssen's interpretation of Risperdal's indication. The Indications and Usage section of the PI for Risperdal states that Risperdal is indicated for the management of the manifestations of psychotic disorders...established in short-term (6 to 8-weeks) controlled trials of schizophrenic patients." The clinical trials for Risperdal were not designed to examine bipolar disorder. The clinical trials for Risperdal were not designed to examine efficacy for specific disorders, therefore it would be misleading to claim that Risperdal is effective in any of these particularly.

DDMAC has reviewed Janssen's discussion and arguments concerning fair balance and is not persuaded. Janssen has requested a specific list of promotional pieces that DDMAC finds lacking in prominence and readability. It was not DDMAC's intent to give an exhaustive list of citations for each violation to Janssen, however examples of poor prominence and readability would include journal ads JPI-RS-470-1, JPI-RS-470-1R, JPI-RS-470-1RB, JPI-RS-470-1-C, and JPI-RS-450-2. With regard to fair balance in letters, DDMAC maintains that letters with the risk information confined to the area after the closing are considered to lack fair balance.

DDMAC is not persuaded by Janssen's arguments regarding materials that emphasize that Risperdal has a low incidence of certain side effects (i.e., excessive sedation and anticholinergic side effects) while minimizing the side effects that Risperdal does have (i.e., orthostatic hypotension, tardive dyskinesia, treatment-emergent extrapyramidal symptoms). This is an issue of prominence and appropriate emphasis. For example, tardive dyskinesia is a warning and orthostatic hypotension is a precaution. These side effects require more prominence than a list of other adverse events. Balance for claims of reduced incidence of a particular side effect belongs on the same page as the claim,

and requires comparable prominence and readability in order to put the claim in the appropriate context. (e.g., claims of low incidence of excessive sedation require balance, with sleep/fatigue related adverse events and the rate of their occurrence; claims of low incidence of movement disorders requires balance with disclosure of the incidence of movement disorders and the fact that this is dose-related).

Janssen argues that audited IMS data indicate that the average daily dose of Risperdal, over a four-year period, was 4.6-4.8 mg/day. Moreover, Janssen argues that the FDA recommended dose is 4-6 mg/day, thus is "beyond the spirit of the fair balance requirements...[and] counterproductive" to require Risperdal promotional materials to disclose adverse events rates for doses above 6 mg/day (i.e., incidence rates for 16 mg/day Risperdal). DDMAC has considered Janssen's argument and is not convinced. DDMAC agrees that the Dosage and Administration section of the PI does not "generally recommend" doses 6 mg/day. However, the PI also states that "antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day," and stresses the dose-dependence of adverse events. Adverse events such as sedation, movement disorders, and anticholinergic effects are all dose-related, and, with the exception of extrapyramidal symptoms, are found to be 2-3 times greater than placebo even for Risperdal doses of ≤10 mg/day. For example, somnolence for Risperdal was 3% (vs. 1% for placebo), and constipation was 7% (vs. 3% for placebo). Extrapyramidal symptoms have a high incidence overall (even placebo), but are particularly problematic and were the symptoms most associated with discontinuation. Thus, it is important to stress these adverse events and provide their incidence. It is also important to disclose that these are dose-related risks. DDMAC also notes that the Adverse Reactions section of the PI lists adverse events at ≤10 mg/day and 16 mg/day Risperdal compared to placebo.

DDMAC notes Janssen's discussion of comparative claims. Whether or not Janssen believes that "the mechanism-of-action of most psychotropics have been fairly well established over the years," the correlation of specific receptor antagonism to the clinical effectiveness and safety of Risperdal has not been established in adequate and well-controlled trials. Furthermore, promotional materials for Risperdal must be consistent with its PI that states that the mechanism of action for Risperdal is unknown.

DDMAC notes Janssen's acknowledgement that DNDP did not consider comparative trials against the standard of therapy to be adequately designed. Accordingly, Janssen has agreed to discontinue the use of such comparative claims.

DDMAC also notes that Janssen will discontinue promotional claims implying that Risperdal can improve health-related quality of life in the absence of adequate and well-controlled studies using validated instruments.

[redacted]
Janssen
NDA 20-272 (MACMIS 6908)

Janssen has agreed to discontinue all promotional materials cited by DDMAC in our January 18, 1999, letter, including materials with the same or similar presentations and messages. Thus, DDMAC has no further objections and considers this matter closed.

DDMAC acknowledges Janssen's request to meet with DDMAC and DRUDP for clarification and discussion regarding future promotional materials for Risperdal. Janssen's letter has enumerated its concerns and views regarding DDMAC's untitled letter. In this letter, DDMAC has considered Janssen's arguments, and has provided further clarification and discussion on issues raised by Janssen. DDMAC believes that this clarification should make a meeting unnecessary. If Janssen wishes to request a meeting for further clarification, it should submit a written request of unresolved issues to DDMAC for consideration. The written request should include a proposed agenda, a listing of planned attendees representing Janssen, a listing of requested participants from CDER, and the appropriate time for which supporting documentation will be sent to DDMAC.

If Janssen has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm.17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS 6908 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

EXHIBIT 6

[redacted]

-----Original Message-----
From: [redacted]
Sent: Thursday, 22 March 2001 8:49
To: [redacted]
Cc:
Subject: RE: RIS-AUS-5: Presentation/Publication Plan

I am very reluctant to have these data in the public domain that soon.

You may have noticed in the topline results that there are substantially more CVD A.E.s in the Risperdal group. These are of substantial concern to us and we are reviewing all the narratives of these cases as well as CVD A.E. in our other dementia studies. It is crucial we have a better undersatanding of these data before we make the data public. I propose to keep this discussion and concern in house, though, untill we have better understanding.

So, I cannot endorse a rapid submission of an abstract end March.

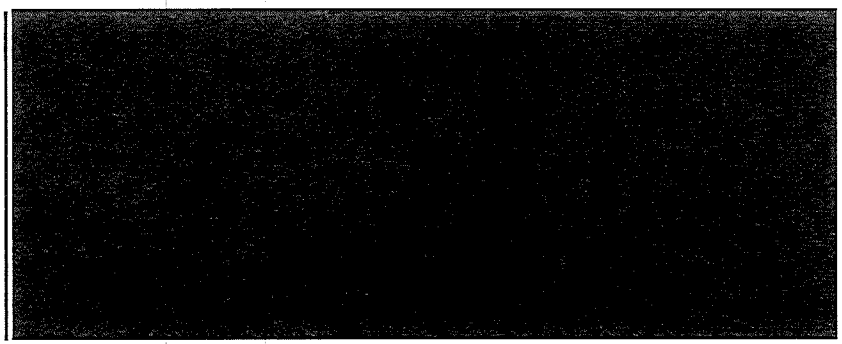
Ivo

[redacted]

EXHIBIT 7

Risperdal in BPSD

The BPSD project shall be terminated as ethically, legally and quickly as possible. The team should prepare a DCC presentation in the implications of exit.

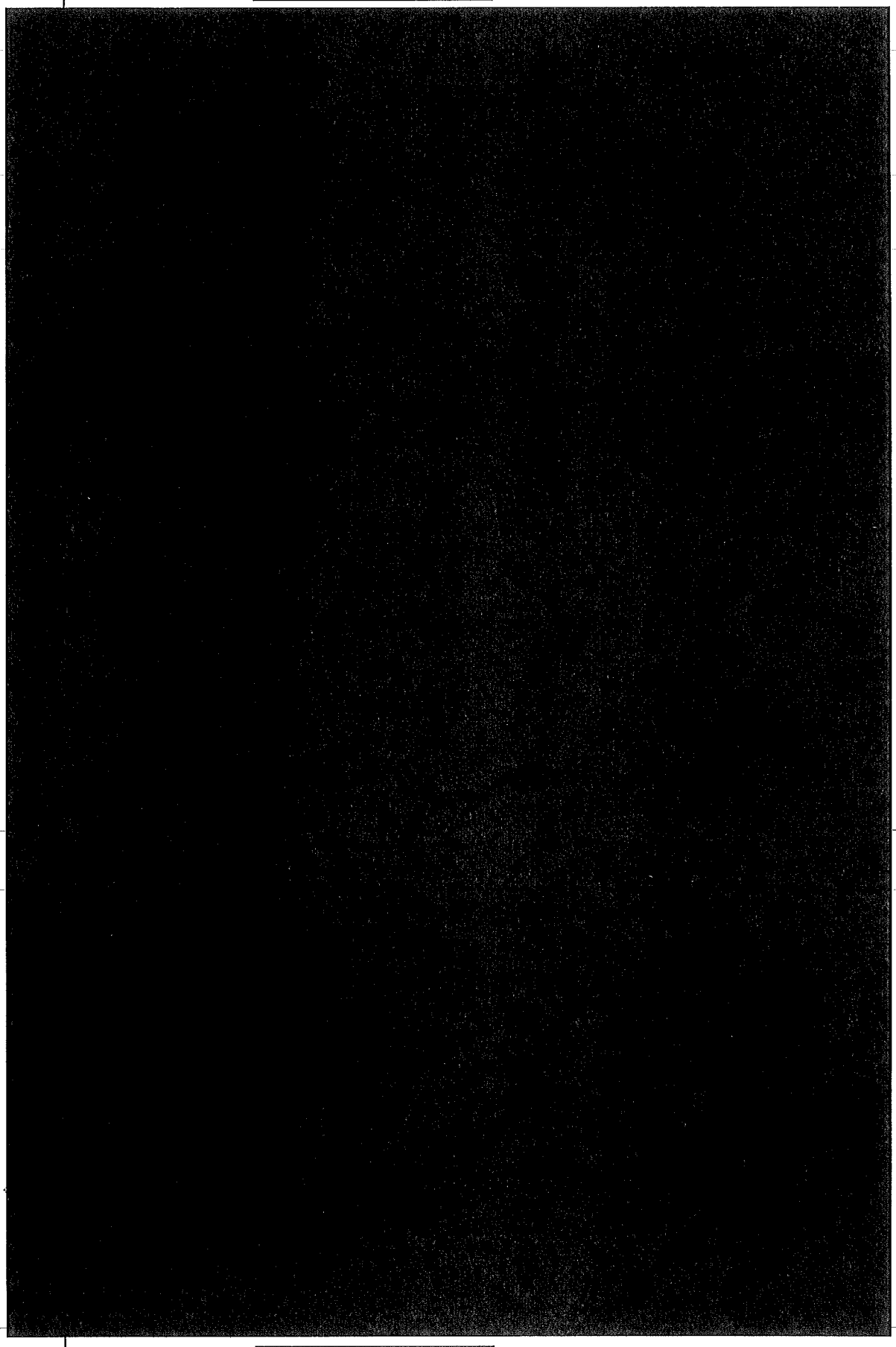


JANSSEN RESEARCH FOUNDATION

Risperdal in BPSD

Agenda

- Status of the project
- How we can terminate the program
- Ethical, regulatory and commercial implications
- Alternative proposal



Risperdal in BPSD - Regulatory status US

1Q99: FDA requests additional safety analysis for sNDA.

3Q99: Agreement with FDA to submit safety update once new controlled data available.

1-2Q00:
- FDA position : "Psychosis in Alzheimer's Disease" is valid diagnosis and claim; need 2 positive trials.
- USA-63 : accepted as positive trial, so 1 additional prospective positive study required.

  (Lilly/Astra will need 2 positive trials)

1Q01: FDAMA program accepted by FDA for RIS-USA-63 & 70

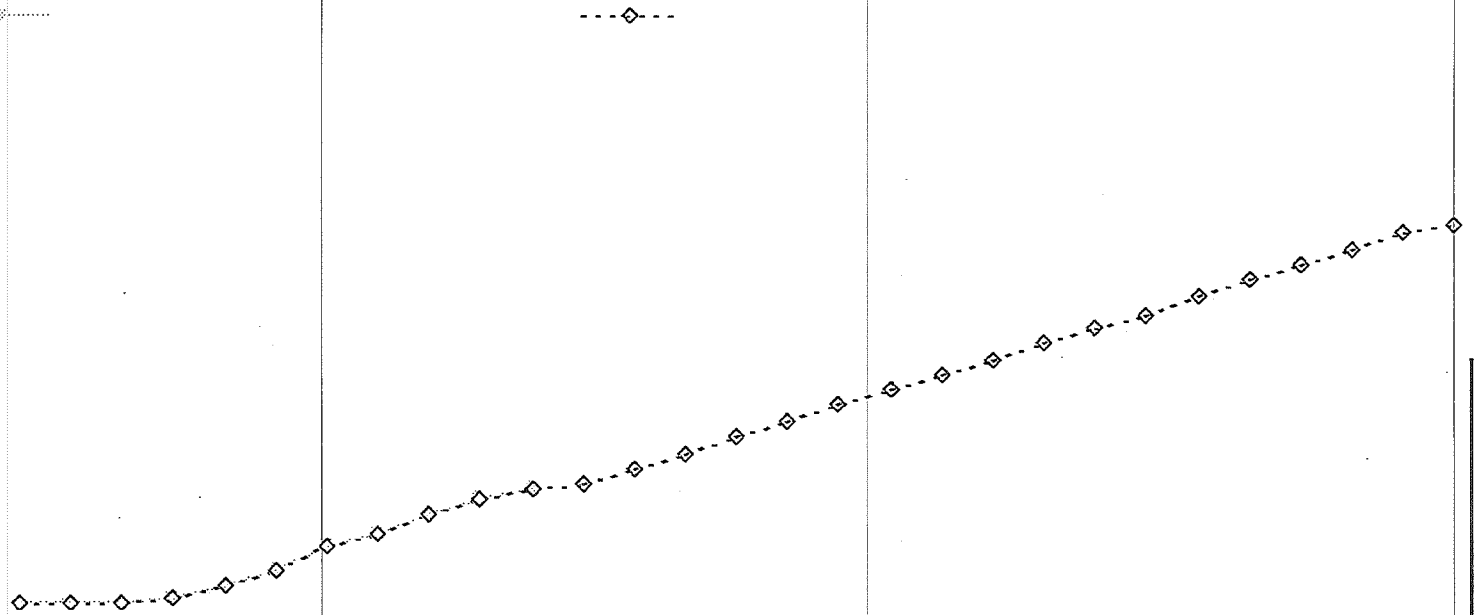
Aug 01: CVA document and proposed label change submitted to FDA

4Q01: Submission of safety update

Risperdal in BPSD - Present status of studies (Aug. 27)

	Active Sites	Pts Entered	Randomized	LPO	Filing
RIS-USA-63	-	-	462	Completed	-
RIS-USA-232	34	128	103 / 408	3 / 03	10 / 03
RIS-INT-83 (US + INT centers)	39	18	6 / 408	TBD	TBD

USA-232 Recruitment Rate



Risperdal in BPSD - How we can terminate the program

- Rationale towards investigators and medical community: "significant delays in recruitment and consequent approval"
- Included patients get final evaluation at next visit + provision for patients to be restabilized.
- Inform FDA and stop running FDAMA program (dissimination of publications RIS-USA-63 & 70)

Risperdal in BPSD - Financial savings ($MM)

	2001	2002	2003
RIS-USA-232	3.7	7.4	1.4
Spent + stopping costs	-2.4		
RIS-INT-83	4.0	7.5	1.5
Spent + stopping costs	-2.0		
Total savings ($ MM)	3.2	14.9	2.9

Risperdal in BPSD - Implications of Discontinuation

Ethical/Moral

- **Relinquish obligation to patients, caregivers & providers**
  - ➢ *Over one-half* of all antipsychotic-treated dementia patients are currently using Risperdal in US

[redacted]

  - ➢ Need to clarify significance of CVA signal
  - ➢ Concerns/misperceptions will be raised by Advocacy (NAMI & NMHA) and Opinion Leaders / Associations (IPA & NIMH), and healthcare providers

Risperdal in BPSD - Implications of Discontinuation

Regulatory

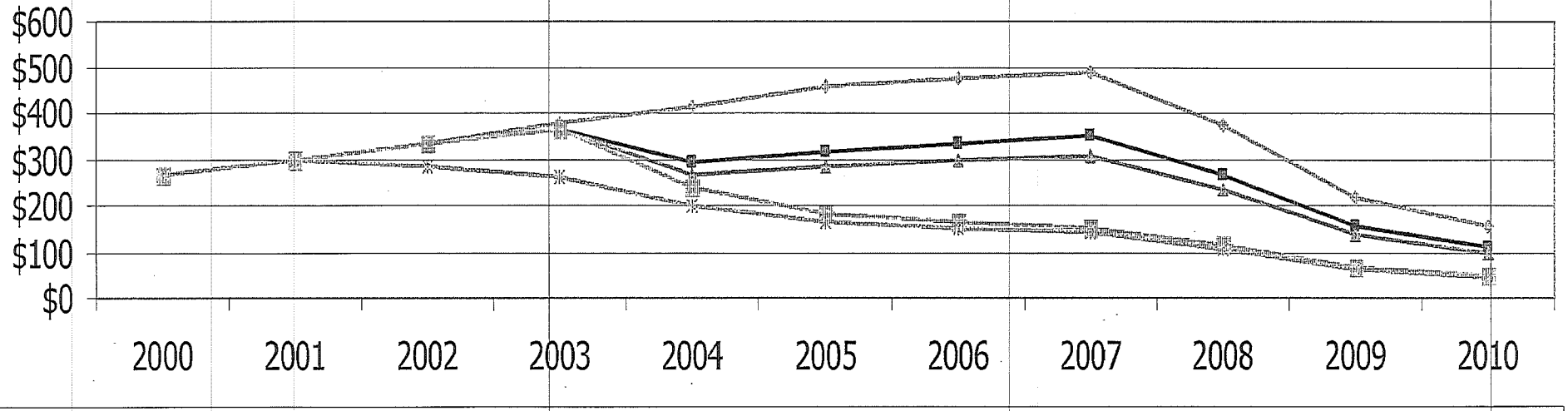
- **Credibility with FDA:** As the leader Janssen was 1st to file; prompted March Ad Board; led debate/discussion. Abrupt cancellation may be questioned.
- **Label at risk:** CVA observation remains unresolved with increased risk for unfavorable label that will impact entire brand.
- **FDAMA:** Must discontinue dissemination of USA-63 & 70 trials and may need to send 'Dear Prescriber' letter. FDAMA intentions may be questioned.
- Impact on EU/global (re)submission?

Risperdal in BPSD - Implications of Discontinuation

Commercial

- **Share loss will impact entire brand (not just dementia)**
  - Loss of ability to disseminate USA-63 & 70 data (competitive disadvantage)
  - Competition will mis-represent as a safety/efficacy 'concern'
  - Will initiate loss of formularly status and share
  - PCP opportunity is significantly compromised
- **Loss of Janssen strategic platform and goal to be #1 in ElderCare:**
  - Risperdal is the foundation of the J&J LTC portfolio
  - Will impact all Janssen growth brands: Risperdal (total), [redacted] (e.g., J&J contract leverage, ElderCare sales force justification, field retention, morale, etc.)
- **Trial enrollment/completion for Zyprexa, Seroquel and Abilitat will accelerate**

RISPERDAL DEMENTIA FORECAST COMPARISON
(US sales in millions)



Incremental Sales*:	$1.9B	$1.1B	$891MM	$230MM	-
NPV :	$475	$257	$197	$68	-

***Cumulative 2001-2010**

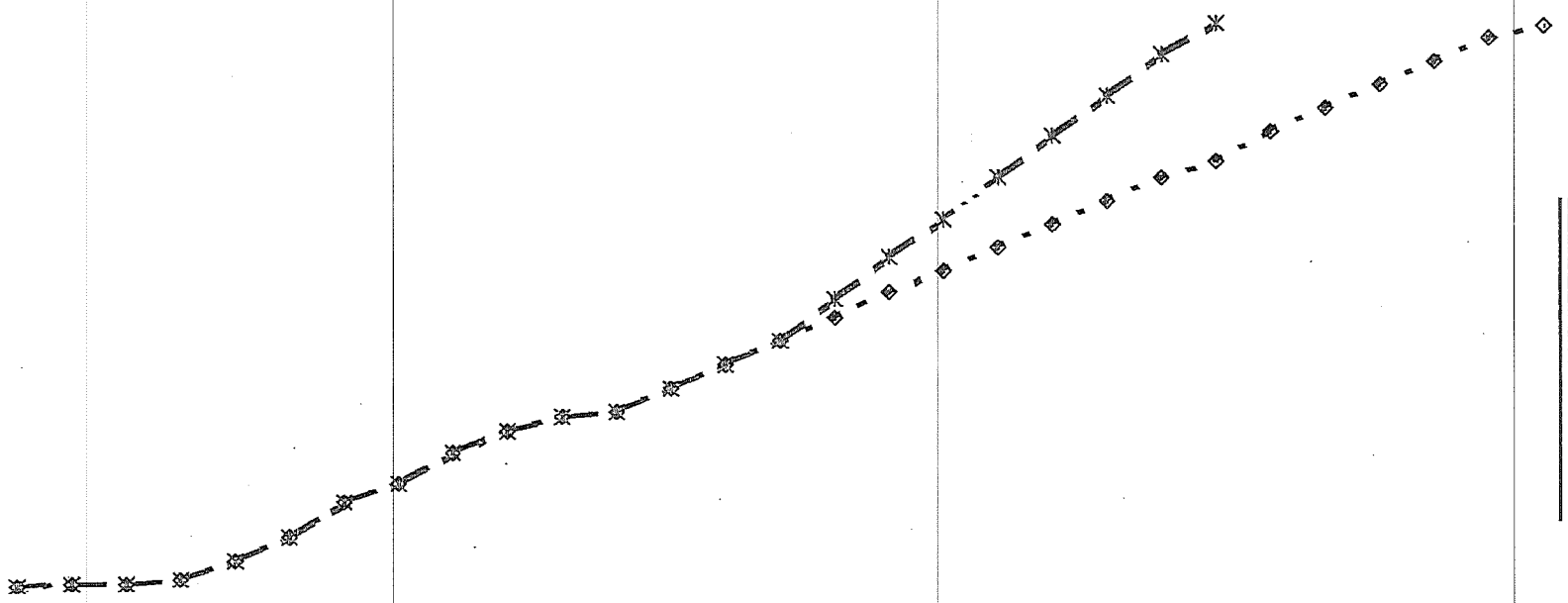
Risperdal in BPSD - Alternative proposal

- Continue RIS-USA-232 to obtain indication (at least to investigate the CVA signal)
- Stop RIS-INT-83 (too slow recruitment) and switch 10 best US sites to RIS-USA-232 => speed up RIS-USA-232
- File ≤ 10/03 if USA-232 is positive
- Savings: 2001 - $2.0MM
  2002 - $7.5MM
  2003 - $1.5MM
- $ 1.1 Billion incremental US Sales; $257 Million NPV*

* 1 year delay (2Q04 launch); 10 yr cumul. sales

BACK-UP

USA-232 Recruitment Rate



Current US Labeling

Identical 'Precautions' Section for CVA

PRECAUTIONS

General

Orthostatic Hypotension:

[Risperdal®/Zyprexa®/Geodon®] should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g....

Current US Label
Differences in CVA Labeling

Risperdal

ADVERSE REACTIONS *{nothing reported from registration trials}*

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causality) related to Risperdal® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated...

Zyprexa

ADVERSE REACTIONS *{as reported in registration trials}*

Cardiovascular System

Frequent: hypotension; *Infrequent*: bradycardia, cerebrovascular accident,....

Geodon

ADVERSE REACTIONS *{as reported in registration trials}*

Cardiovascular System

Frequent: hypertension; *Infrequent*: bradycardia, ...; *Rare*: first degree AV block, cerebral infarct, cerebrovascular accident,...

Note: Infrequent = 1/100 - 1/1000; Rare = <1/1000

Proposed US Label Change for Risperdal

ADVERSE REACTIONS

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causality) related to Risperdal® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, cerebrovascular accident, diabetes mellitus aggravated...

Worst Case Label for CVA Data

FDA mandates CVA inclusion in the geriatric sections (PK, use, dosing) of the label along with a description of the risk factors found in the analysis

e.g. "...higher risk of CVA in elderly patients with advanced age and prior history of vascular disease..."

Worst Case Impact of CVA Data

- Other drugs with serious AE label changes still demonstrated growth:

- Potential effect on Risperdal difficult to estimate, but *unlikely* to have significant financial impact. (-2% = $5.3MM; -5% = $13.3 MM; -10% impact = $27MM)*

*** Based on dementia sales forecast of $276MM**

EXHIBIT 8

To: [redacted]
Cc: [redacted]
Subject: RIS-232

August 31, 2003

Dear [redacted]

I have hesitated to write you this letter, hoping in part that you would have spoken to me.

I want to remind you that I was extensively involved in the design of the RIS-232 and RIS-82 trials. As you remember [redacted] had organized the consulting for these trials several years ago. Early on [redacted] and I worked with him both in meetings and in Titusville. In addition there were several meetings in Philadelphia. As the protocol developed I contributed substantial portions to it, and then to training, co-leading the 2 investigator meetings, and early trial consultation. Over this time I worked extensively with [redacted] initially and others.

As [redacted] and others can attest, I would not have done this simply to provide consultation but with the expectation of collegial collaboration and authorship.

Therefore you understand my concern when it turns out that the trial had been analyzed some time ago, presented to others, and then extensively discussed in unofficial ways at meetings.

Although I expressed these concerns to [redacted], and he did arrange a rather brief briefing on June 9 with [redacted] I thought I'd wait for you to actually contact me.

Respecting fully any confidentiality agreement that I have with Janssen, it is obvious to me and to others who may not be so bound and who have learned about the data that this trial is on its face nearly completely negative. Not because "psychosis of AD" was not a viable target but because a substantial proportion of subjects who were enrolled should not have been enrolled, and would not have been prescribed antipsychotics if they had been ordinary clinic patients. These were subjects who probably nominally fulfilled "psychosis" for entry into the trial, by having been rated on one or two delusion or hallucination items of the Behave-AD but who clearly had no severity of psychotic symptoms or associated behavioral disruption. Thus to a large extent this is a failed study because of inappropriate subject selection.

That you might find an effect when you sub-select more agitated patients will not get you a claim for "psychotic agitation" as some might be advocating.

As it was 4 years ago, FDA will clearly be concerned with the low psychosis scores on a rating scale not meant for this kind of clinical trial, not to mention the ongoing safety issues of CVAEs and deaths.

Entirely separately, Janssen has been sitting on the trial results for a long time. Yet it has a moral and ethical responsibility to publish results quickly and in a way that they can be understood and makes clinical sense. It has an obligation to publish not just the clinical efficacy data which could very well be informative and supportive of the use of risperidone if considered properly, but also the safety data, including events that have been labeled in the past as "cerbrovascular adverse events" and deaths.

This is my main reason for writing. Janssen had the opportunity to present this data, for example, at the IPA meeting in Chicago last week. It also has the opportunity to present it at the upcoming ACNP and ICGP meetings in San Juan, Puerto Rico and should do so.

The second matter of your excluding me from collegial collaboration in a trial that I was is one I would be happy to discuss with you or anyone else at Janssen.

Please note that all of what I wrote above was learned or inferred outside of any confidentiality agreement I have with Janssen. However, based on what was presented to me under the confidentiality agreement, it is clear that Janssen has not been able to consider the outcomes of Ris-232 properly, in a way to understand what the trial results do say, or to understand the clinical significance of the outcomes, and would benefit from crisp clinical and expert advice. Clearly psychotic agitation is not a helpful construct.

Regards

[redacted]

EXHIBIT 9

From: [redacted]
Sent: Friday, March 26, 2004 3:32 AM
To: [redacted]
Subject: FW: Pooled psychosis abstract for submission CINP
Importance: High

[redacted]

-----Original Message-----
From: [redacted]
Sent: donderdag 25 maart 2004 18:35
To: [redacted]
Subject: RE: Pooled psychosis abstract for submission CINP

At this point, so long after RIS 232 has been completed, I think it is wrong

to coninue to submit abstracts of the three pooled studies. At this point, we musr be concerned that this gives the strong appearance that Janssen is purposely witholding the findings from RIS 232.

Adverse effect findings from 232 are available on the web through the British government's regulatory site. It was also mentioned by someone from FDA at the AAGP annual meeting. It is not a secret that a fourth study has been conducted. As an investigator who is loyal to this program, I really do have

to speak out and urge that Janssen avoids embarrassment and accusations about suppressing information that is relevant to providers and consumers.

Please forward these concerns to the other coinvestigators and to the company.
I think the time has come when pooled analyses should include 232.

[redacted]

EXHIBIT 10

1999

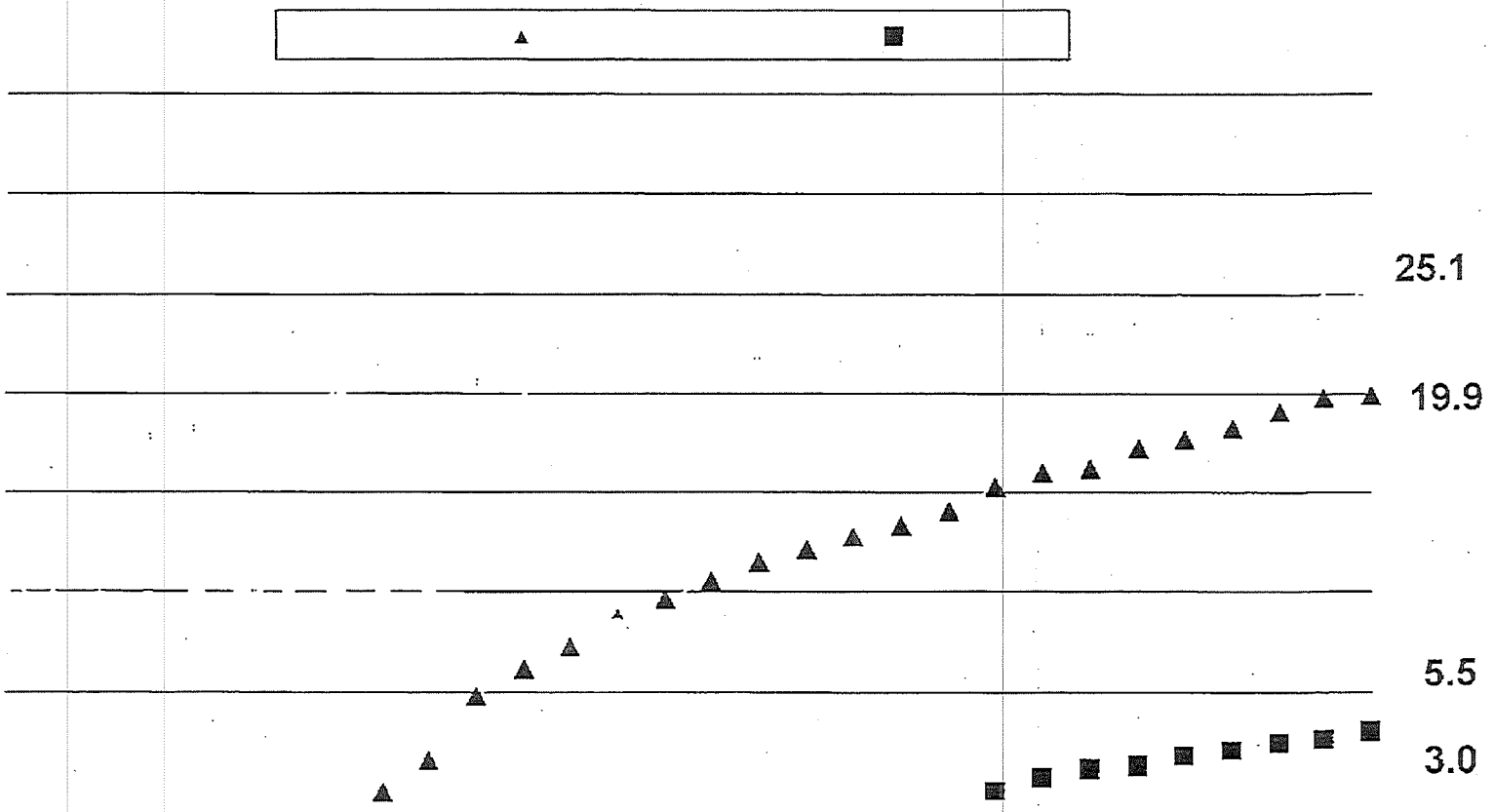
RISPERDAL

Strategic Business Plan

1998 Critical Success Factors

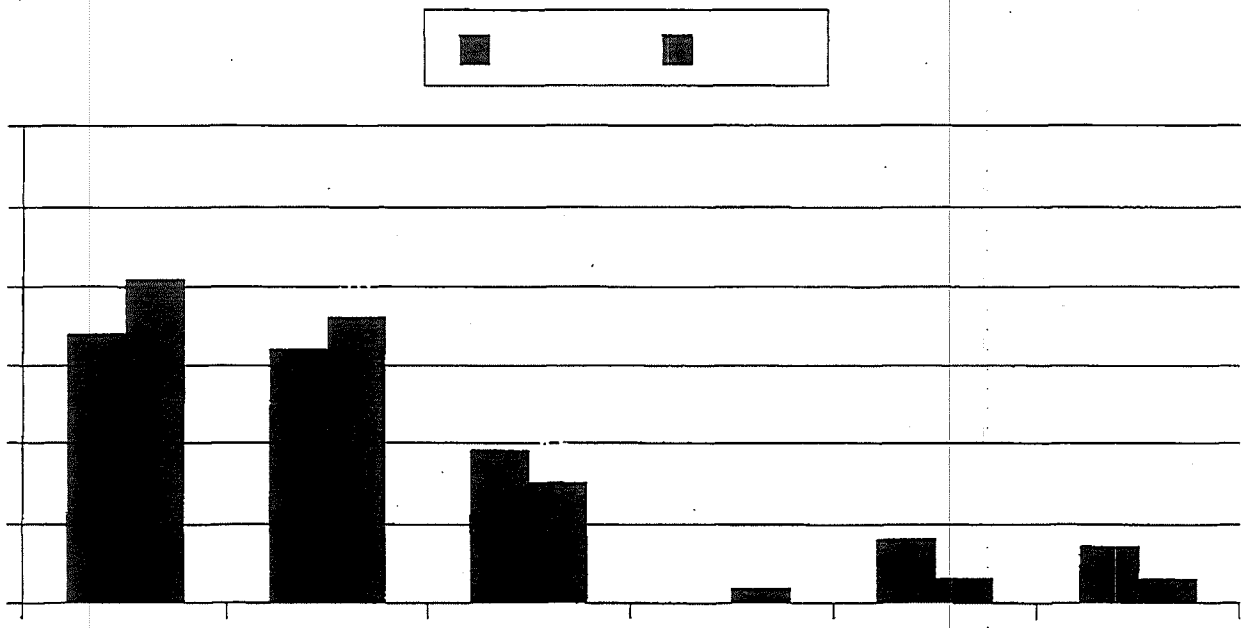
- Own Schizophrenia
- Stop the competition

Antipsychotic NRx Share



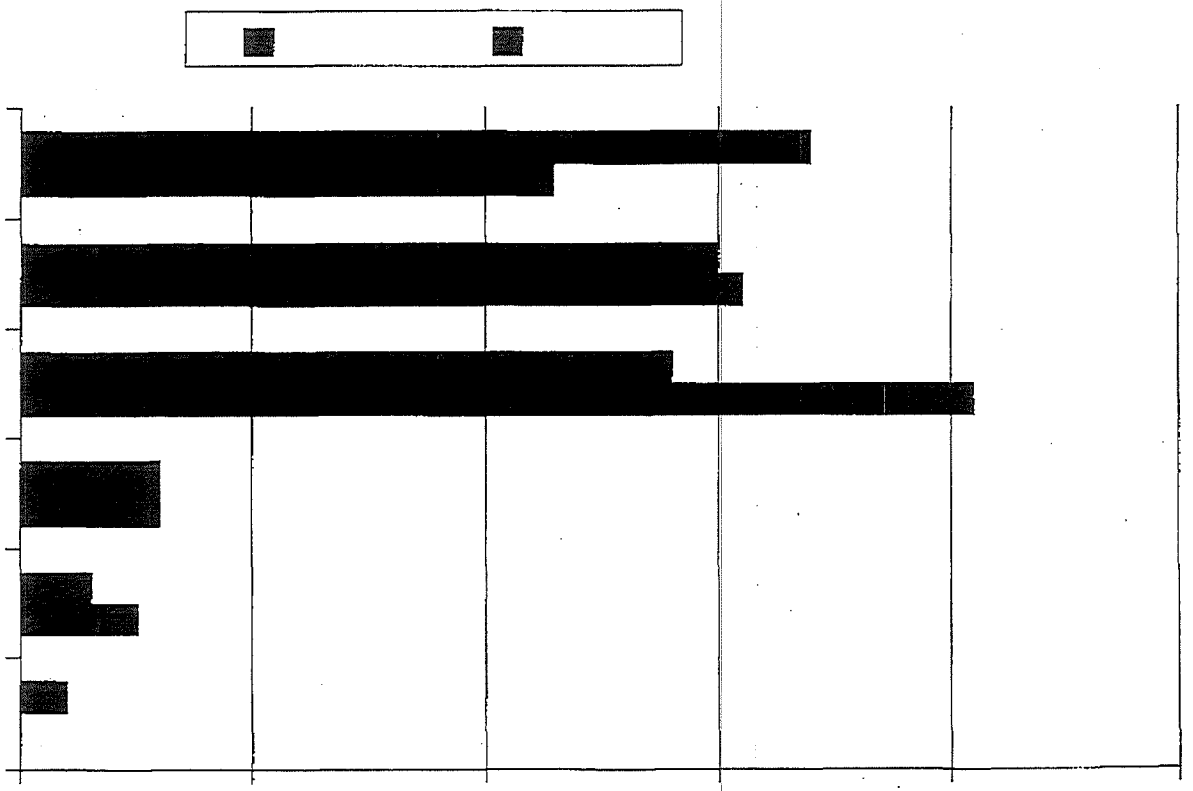
Source: NPA (IMS)

Most Preferred Agent - Schizophrenia



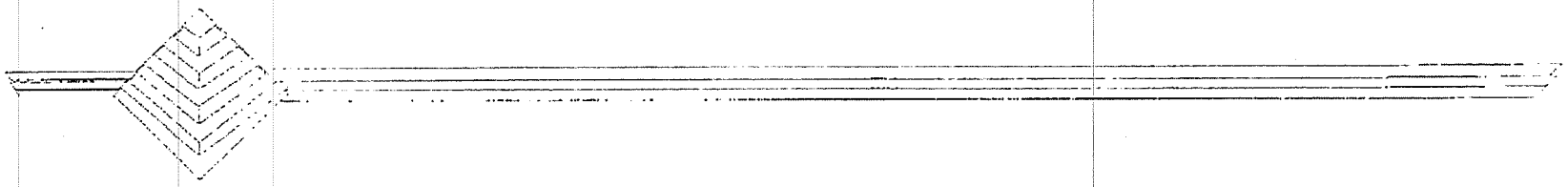
Source: 1998 Annual APA Survey, Hospital Research Associates

Switching Preference from Conventionals



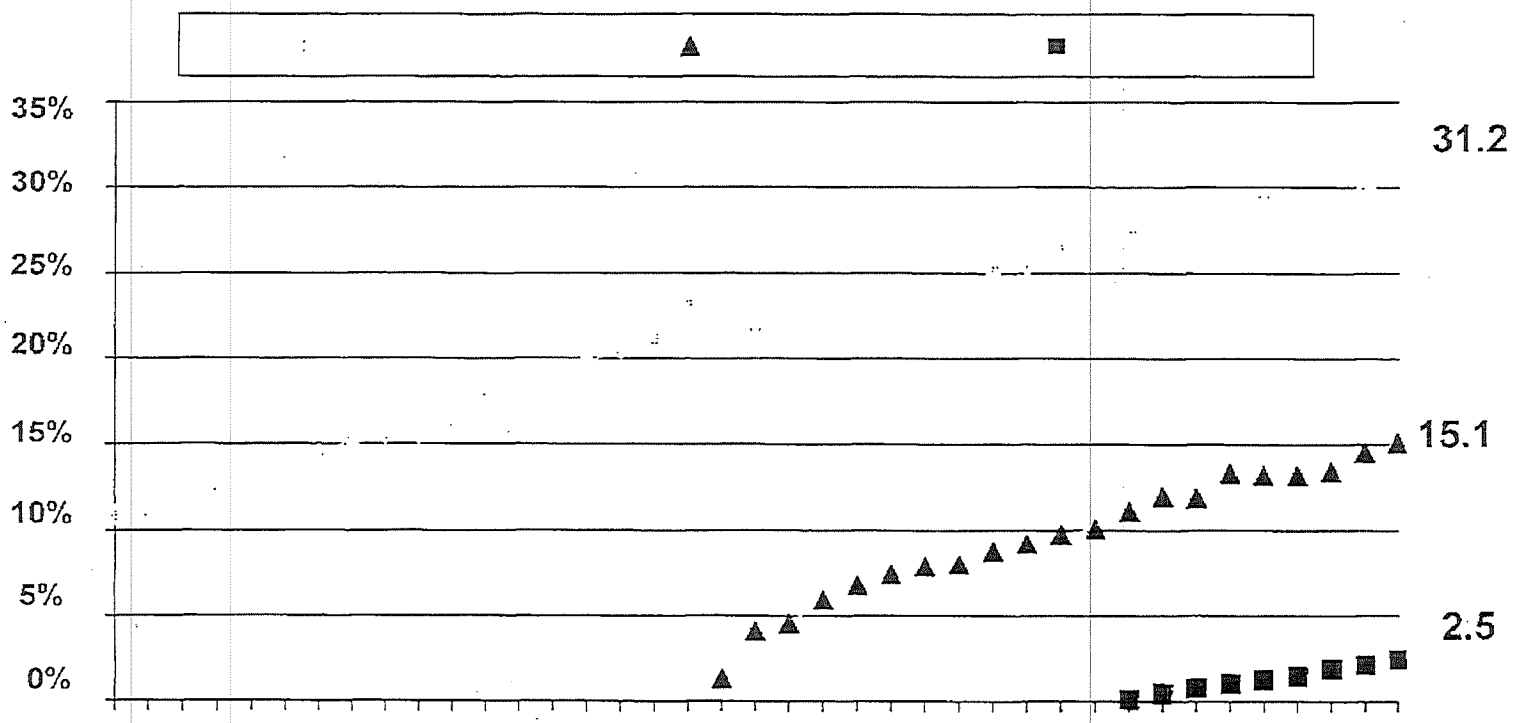
Source: 1998 Annual APA Survey, Hospital Research Associates

1998 Critical Success Factors



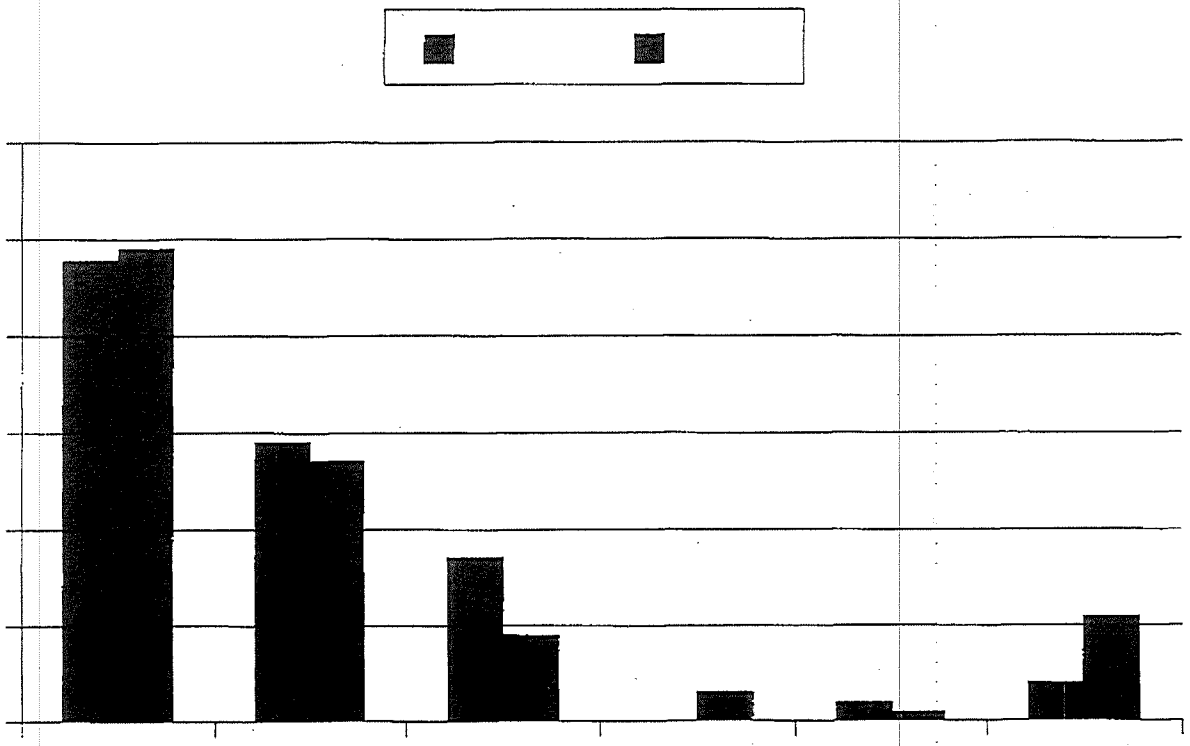
- Own Schizophrenia
- STOP the Competition
- Expand into New Markets

Antipsychotic NRx Share LTC Market



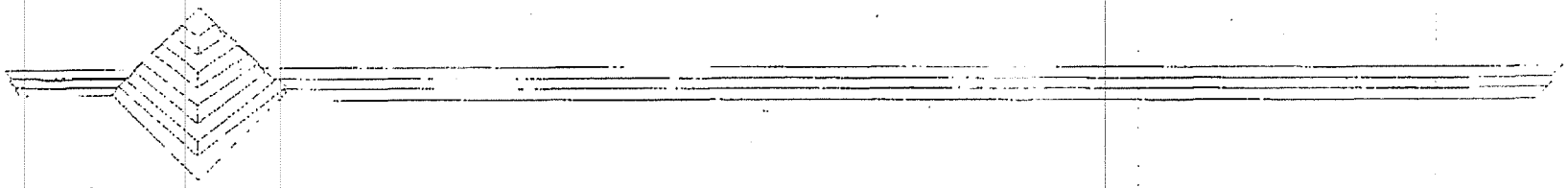
Source: NPA Plus (IMS)

Most Preferred Agent - Elderly

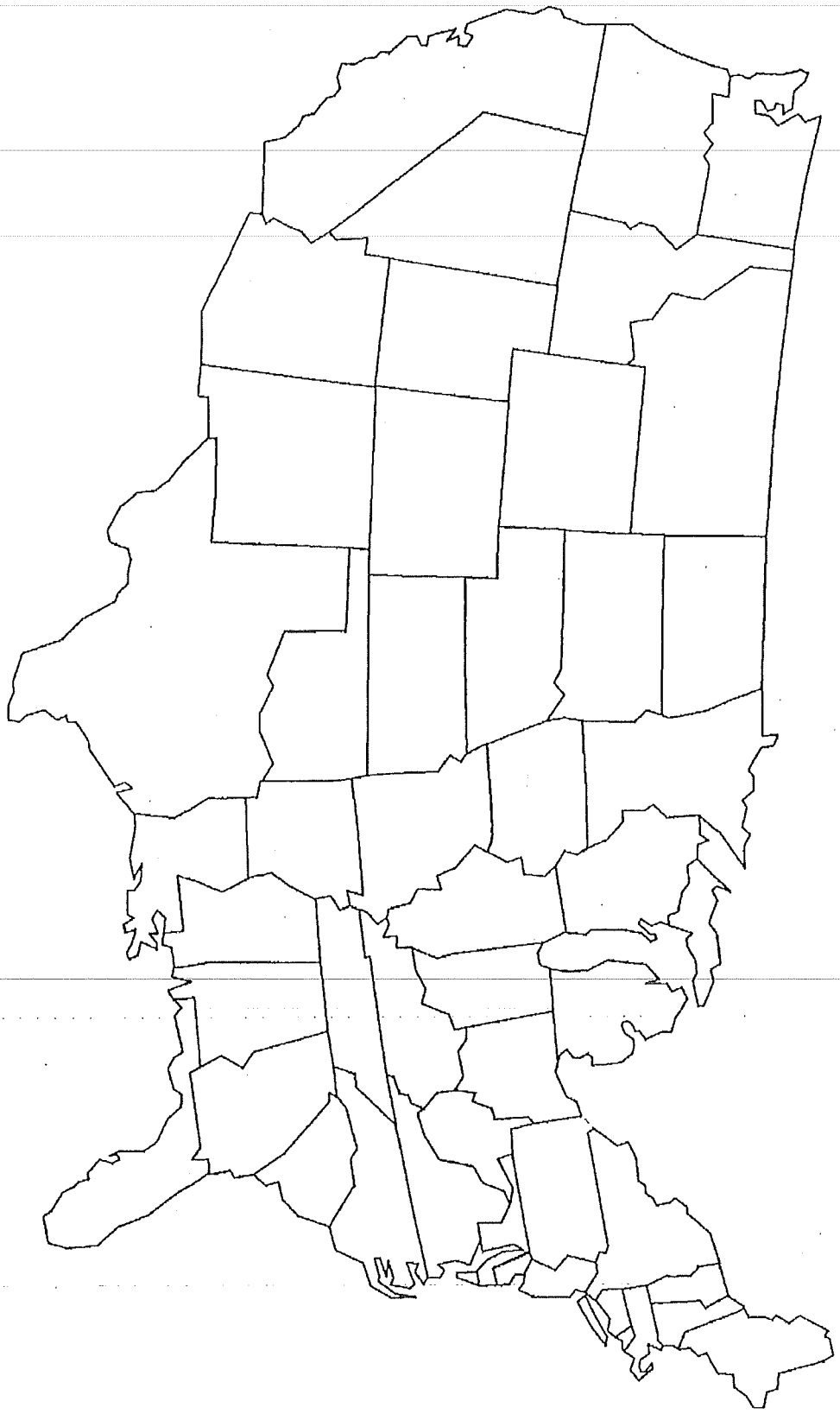


Source: 1998 Annual APA Survey, Hospital Research Associates

1998 Critical Success Factors

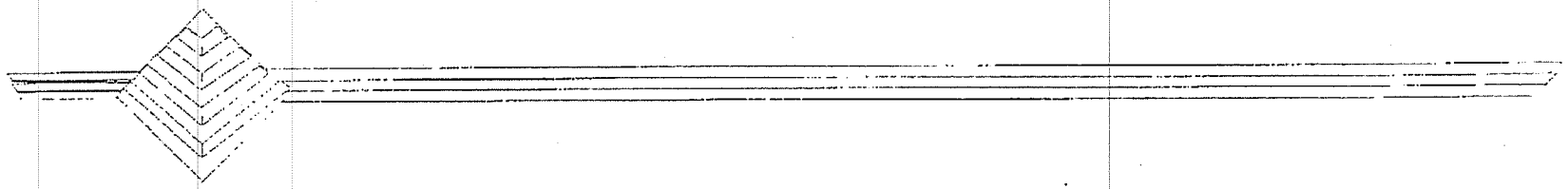


- Own Schizophrenia
- STOP the Competition
- Expand into New Markets
- Maximize Reimbursement Opportunities



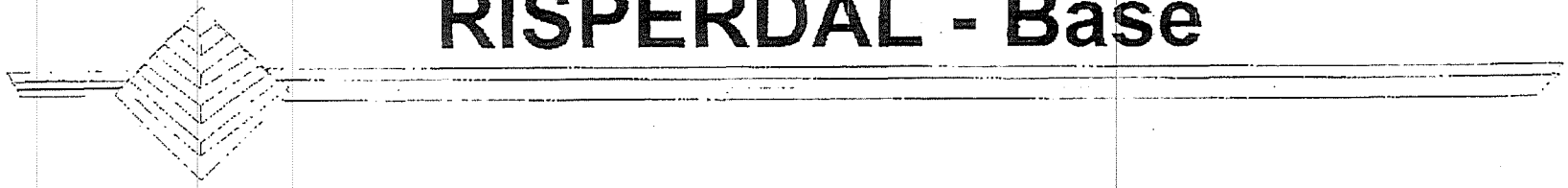
Reimbursement Key Wins

1998 Critical Success Factors



- Own Schizophrenia
- STOP the Competition
- Expand into New Markets
- Maximize Reimbursement Opportunities
- Optimize Teamwork

1998 Lessons Learned
RISPERDAL - Base

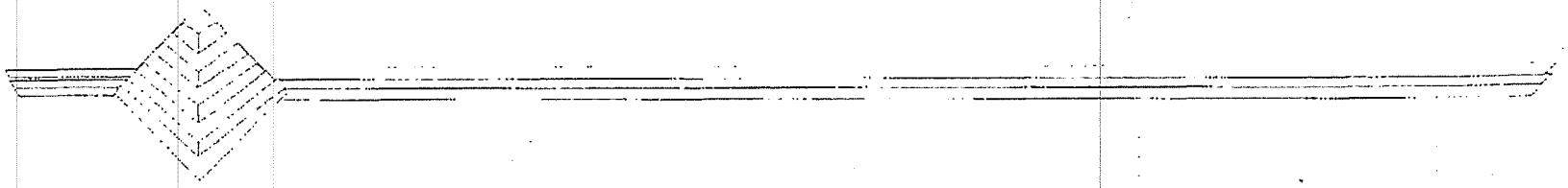


JANSSEN CAN WIN!!!

Strategic Vision
RISPERDAL - Base

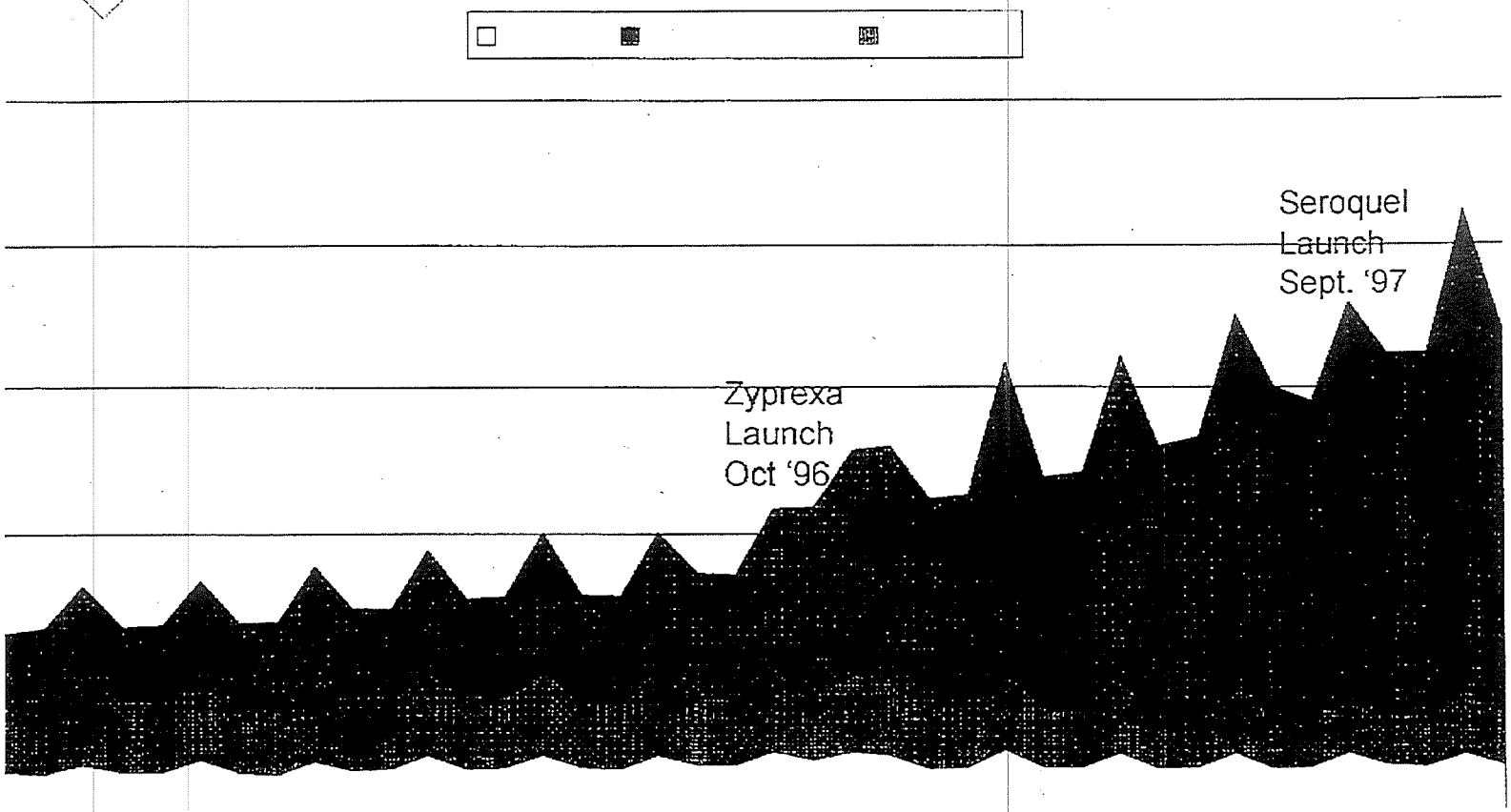
To be the first-line antipsychotic for the treatment of both psychotic and non-psychotic disorders

Strategic Vision
RISPERDAL - Geriatrics

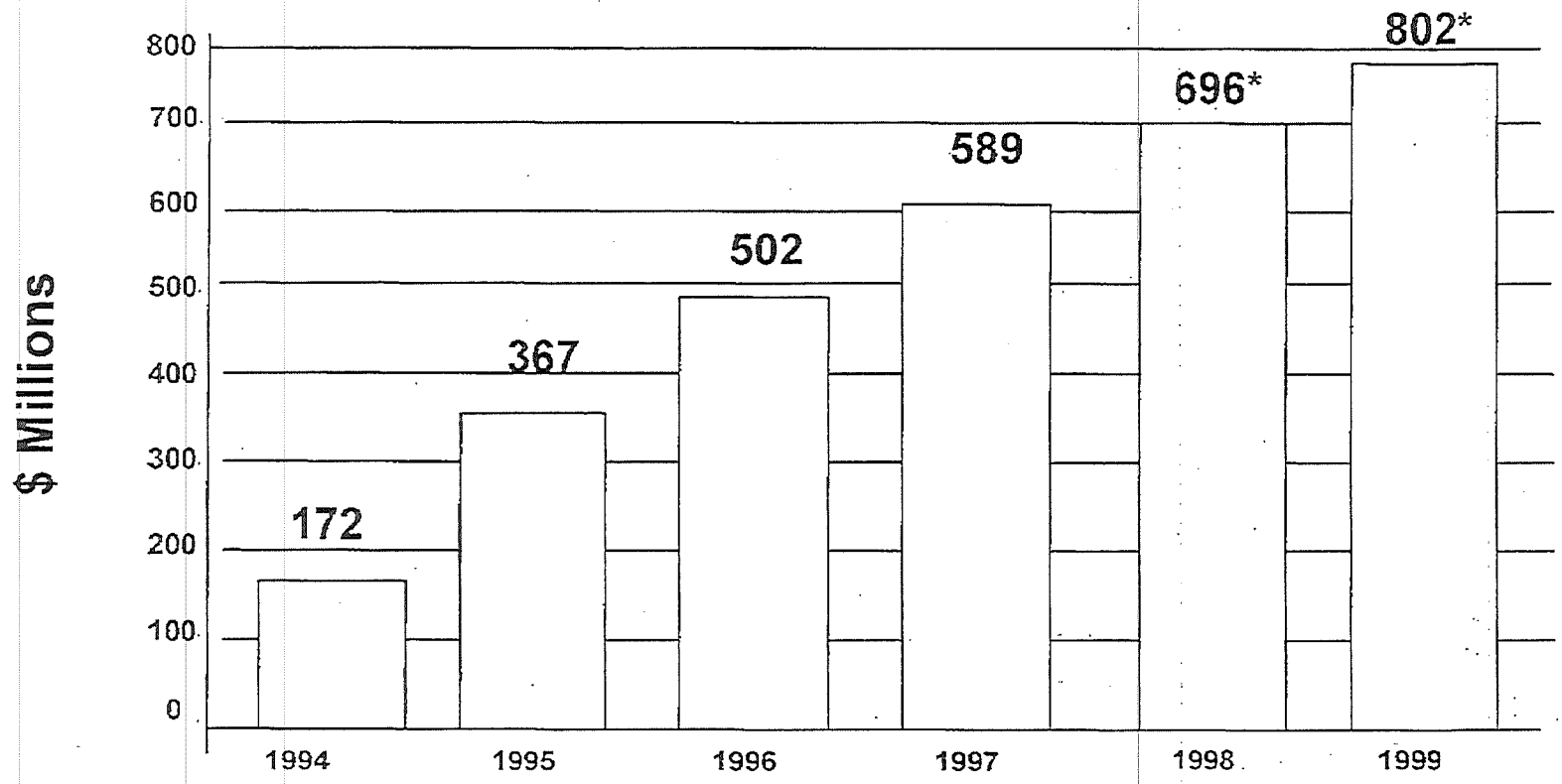


To be the product that healthcare professionals, families and caregivers rely on to treat late life mental disorders

APS Market Total Sales Volume



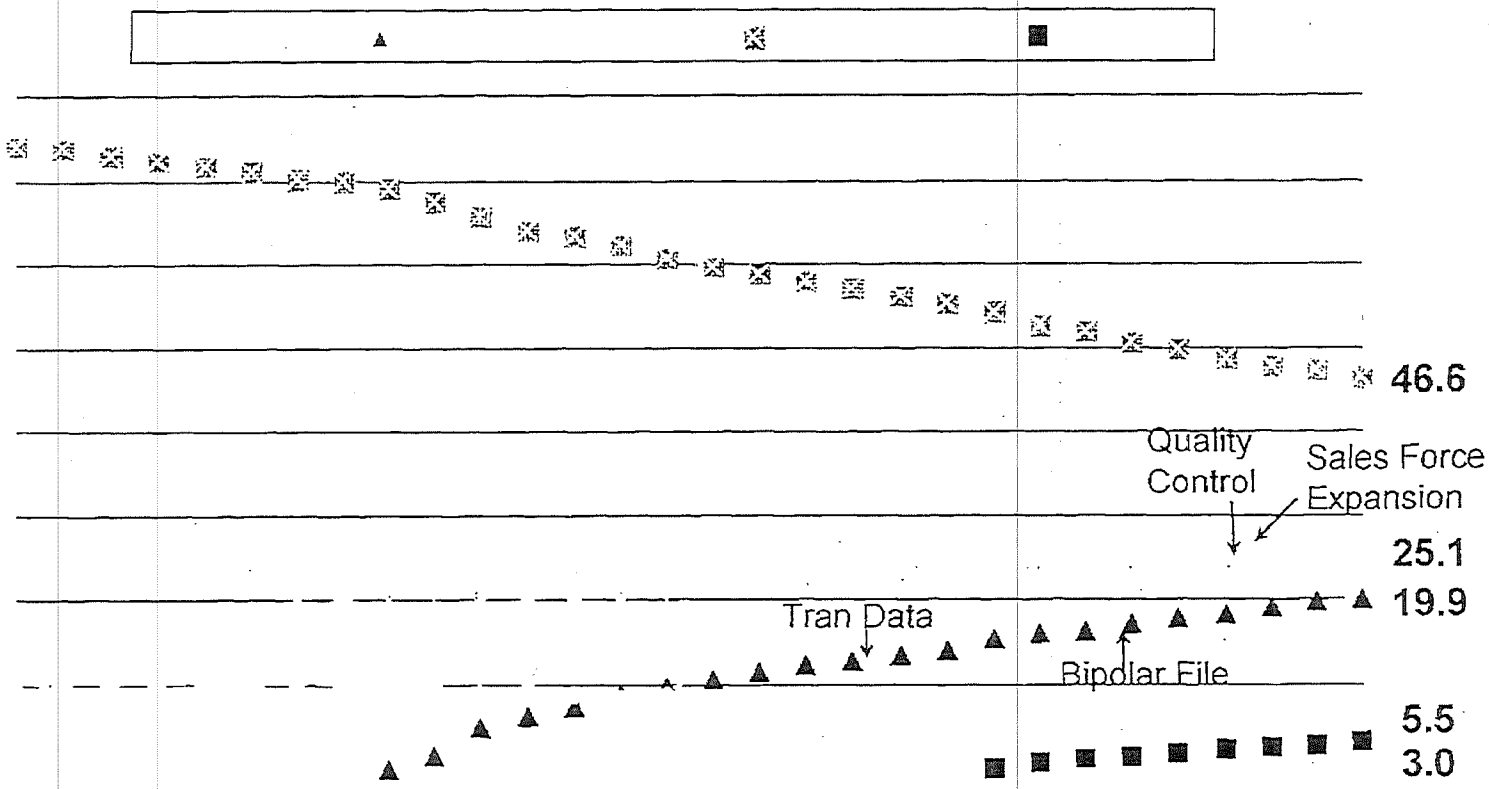
RISPERDAL Annual Sales



* Projected

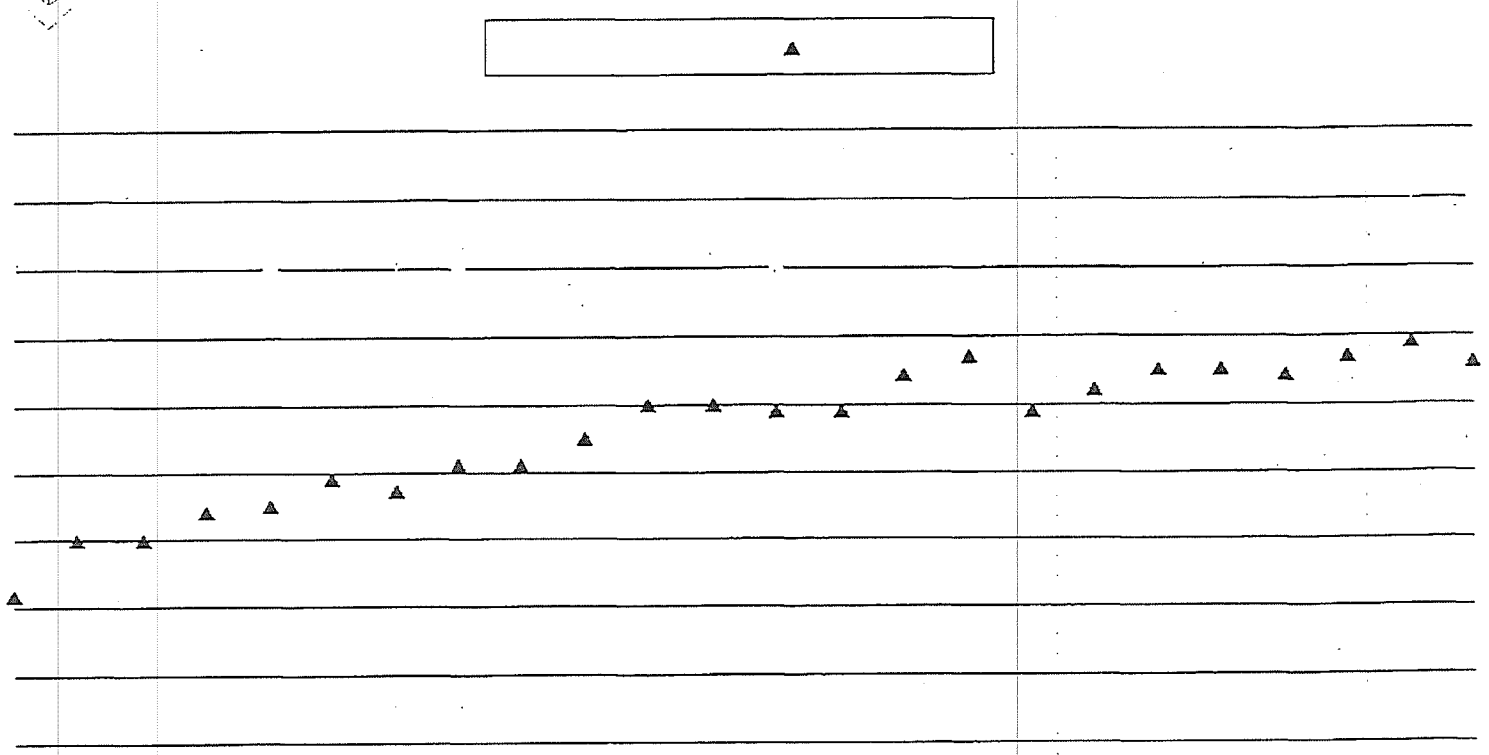
Source: Audit Sales

Antipsychotic NRx Share



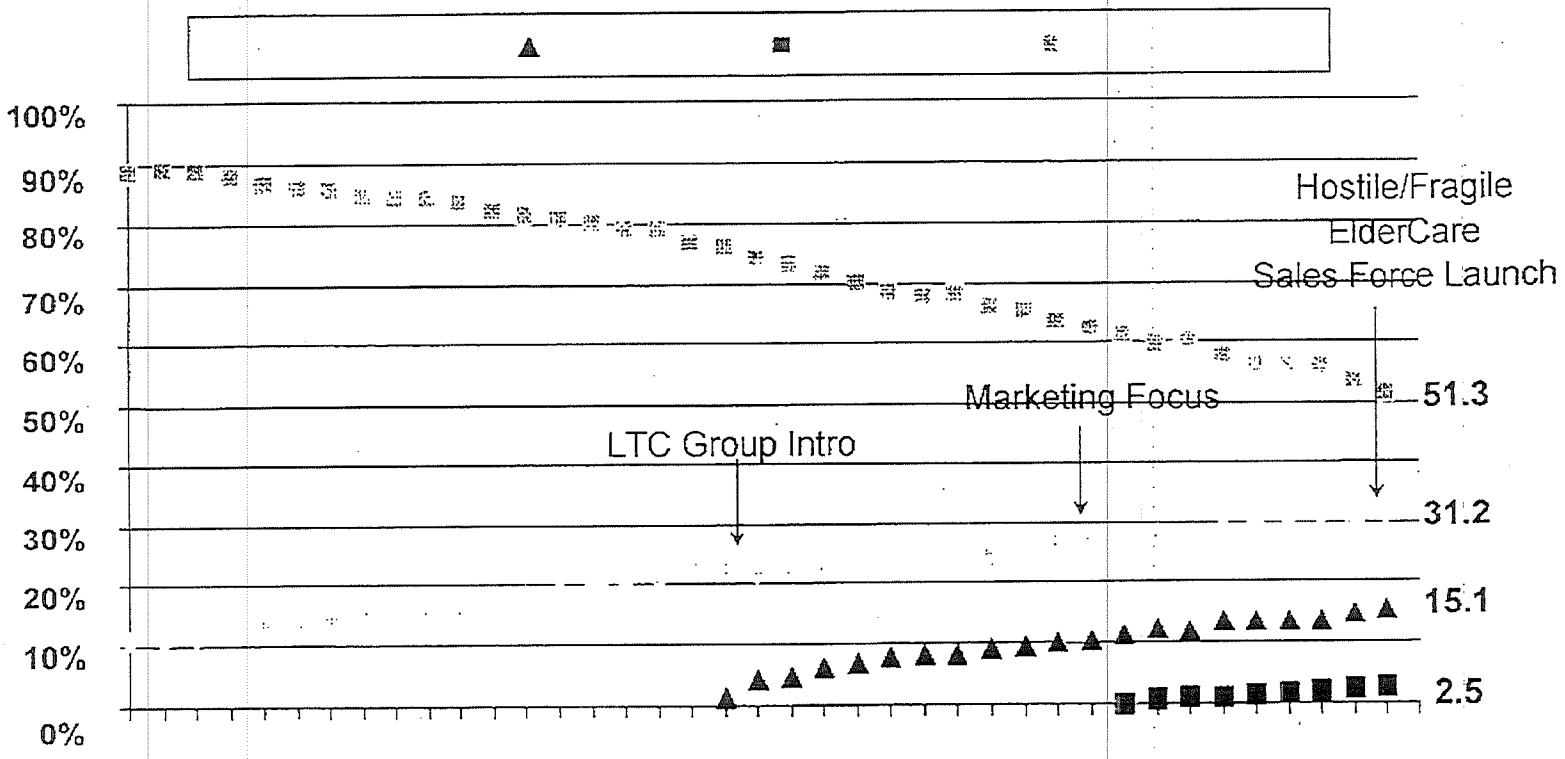
Source: NPA (IMS)

NRx Share - Weekly



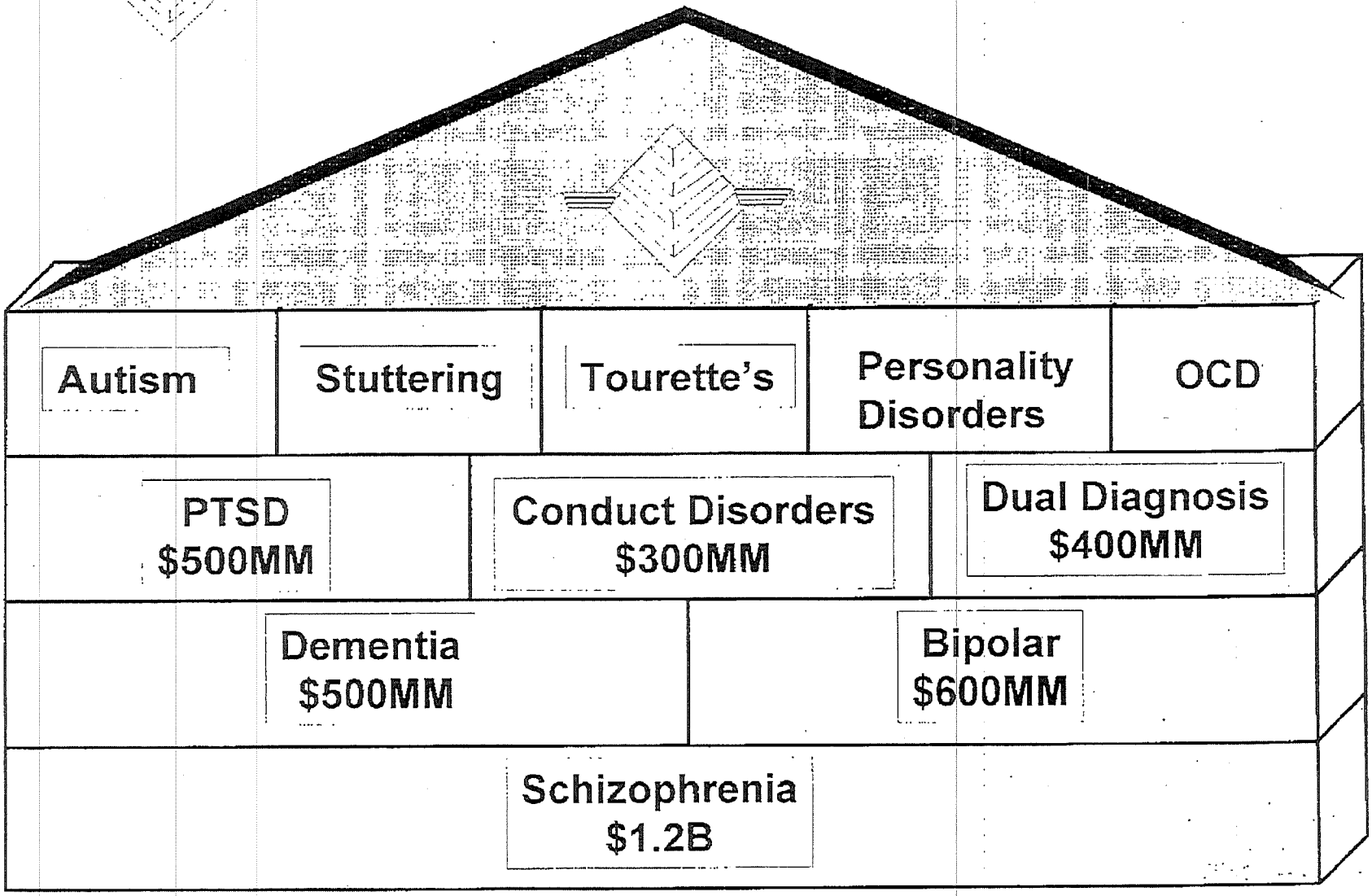
Source:: IMS Weekly (National) Market defined as USC5=64110 & 64190

Antipsychotic NRx Share LTC Market

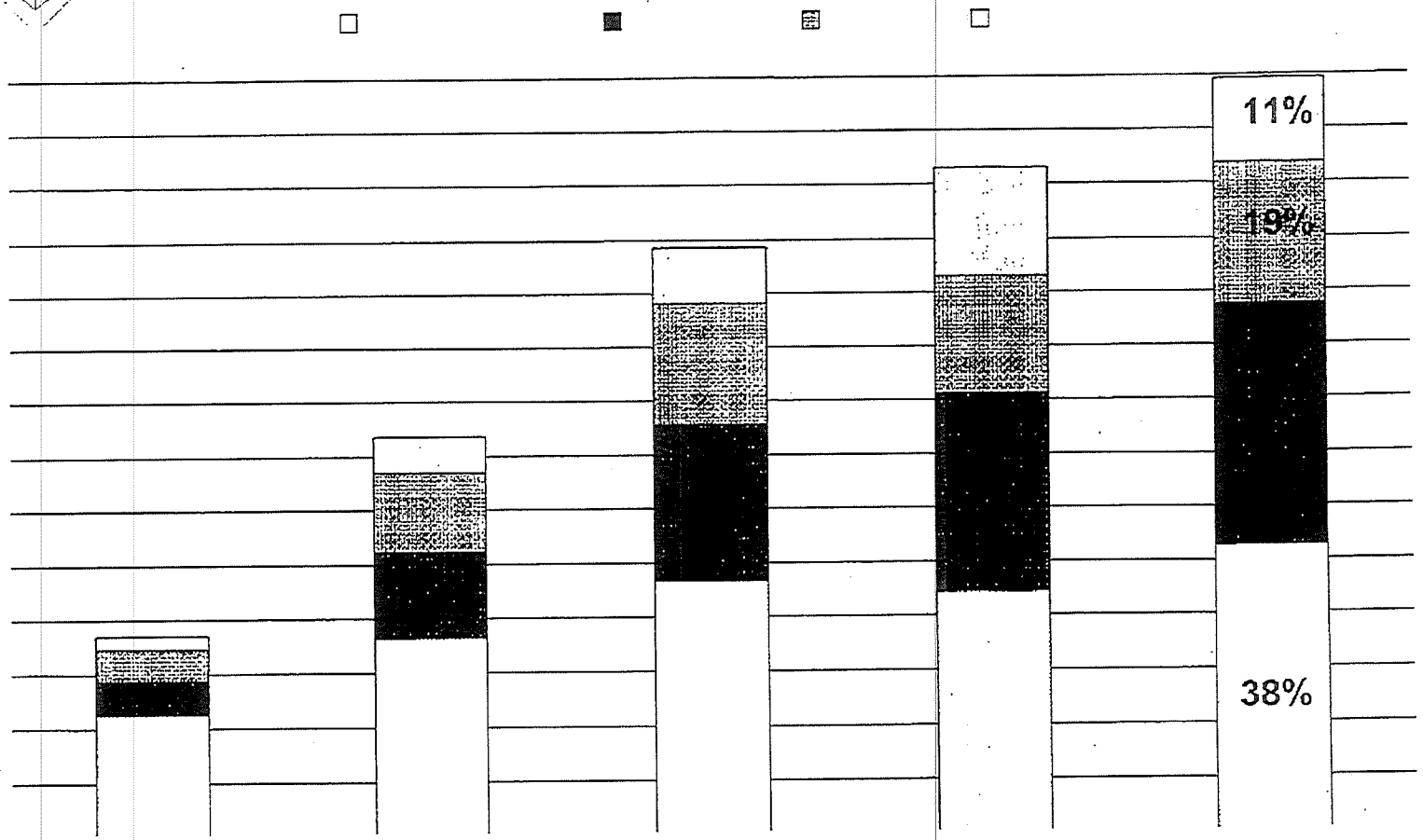


Source: NPA Plus (IMS)

Antipsychotic Potential

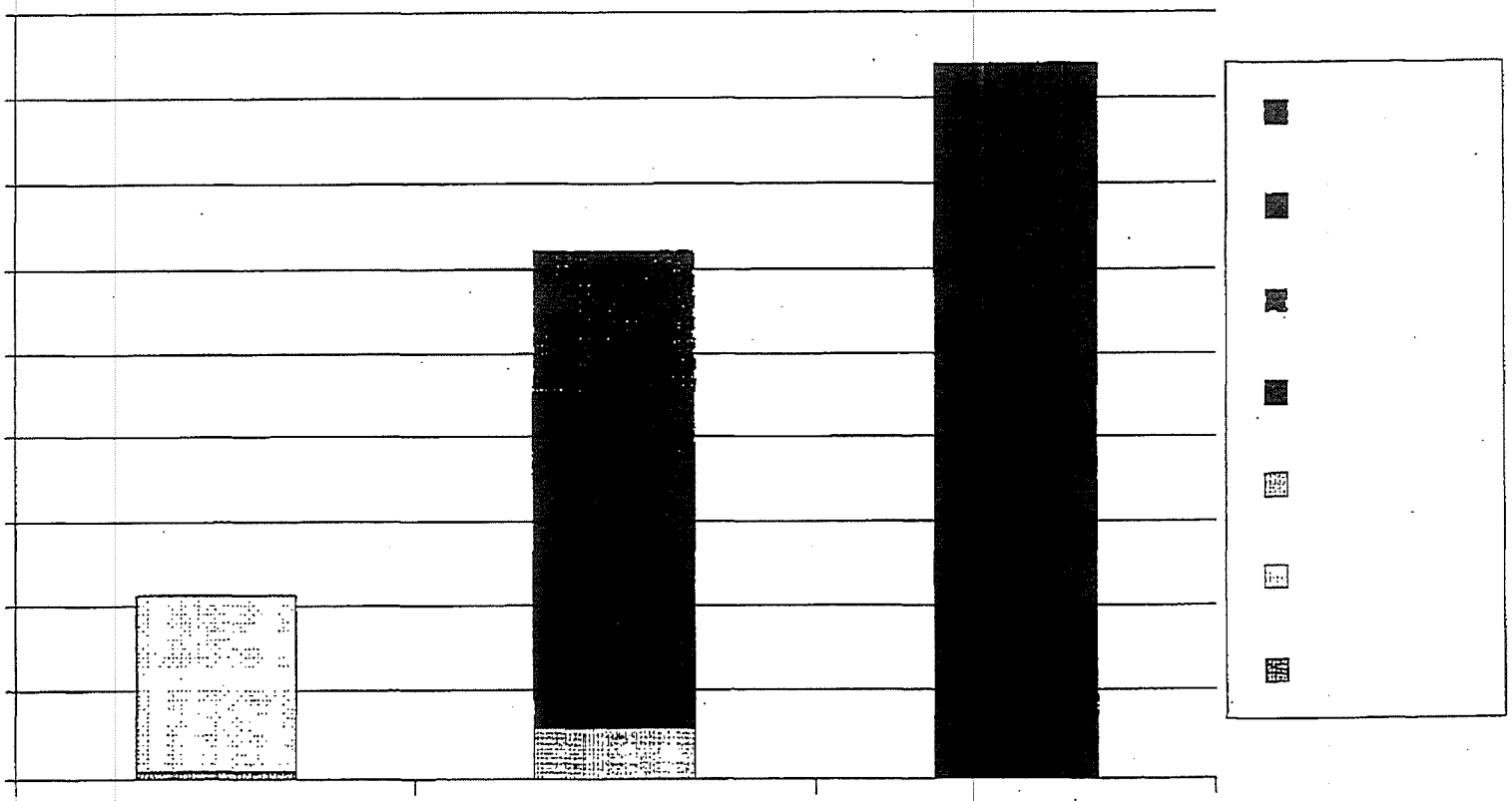


RISPERDAL Dollar Volume by Diagnosis



Source: IMS NDTI and NPA Plus Audits * YTD Sales

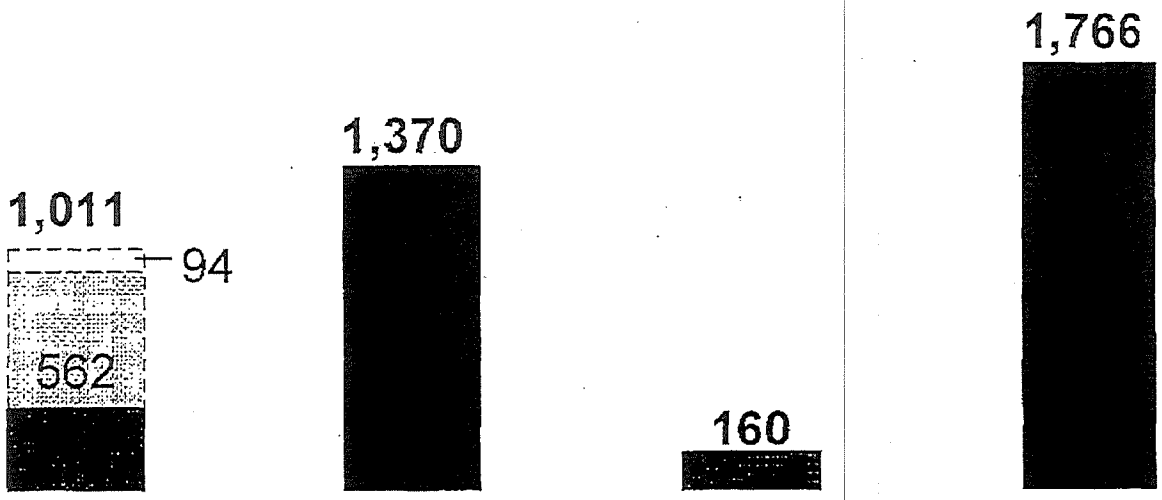
CNS Portfolios



*Estimated Sales - first 12 months

Source: IMS Retail and Provider Perspectives, 1997 US Audited Sales

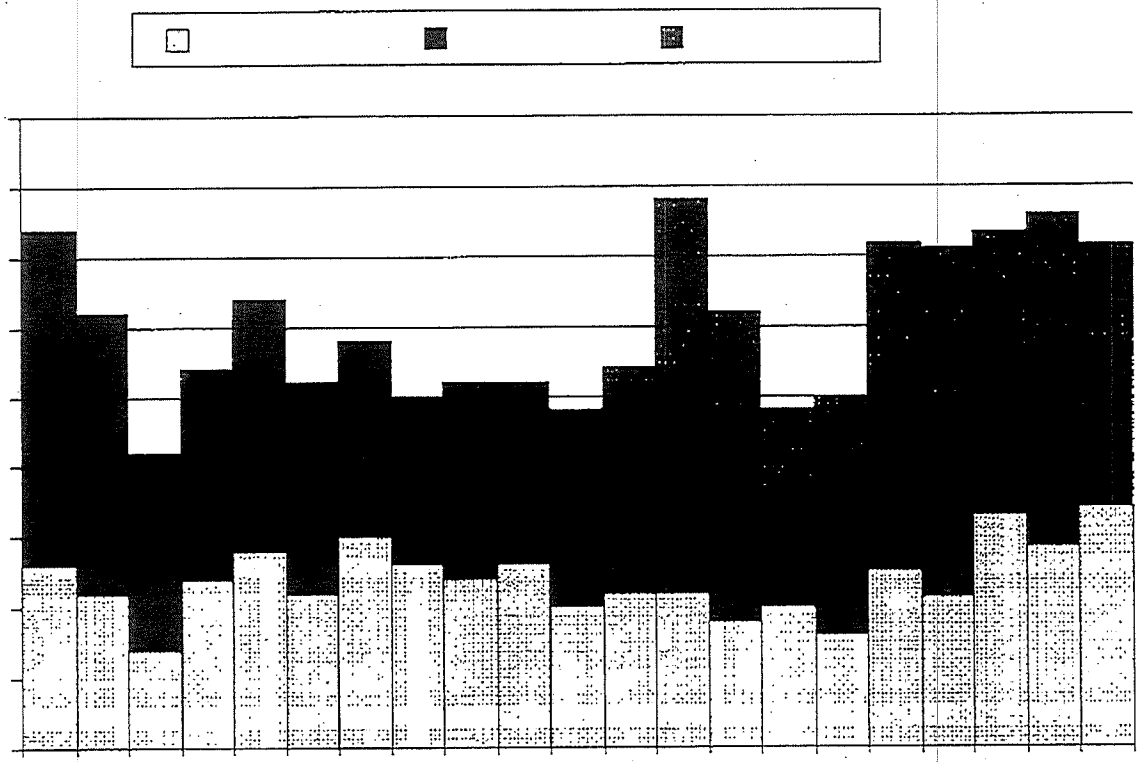
CNS Sales Force Capacities



Janssen = CNS, HSR, ElderCare
Plus SKB and Scios

Scott Levin 1997/98

Antipsychotic Detailing



Source: IMS IPS

Risperdal Detailing Includes Janssen, SKB, and Scios.

EXHIBIT 11

RISPERDAL®
2000 Business Plan Summary

OBJECTIVES:
RISPERDAL will be the antipsychotic treatment of choice for both psychotic and non-psychotic disorders. Average TRx share for 2000 will be 26.4% with sales of $1059.30 MM. The 2000 objectives by business segment are as follows:

Schizophrenia:
Accelerate growth to a schizophrenia market share of 20% and base sales of $583 MM.

Bipolar Disorder:
Differentiate RISPERDAL from other agents and establish a role in the treatment paradigm. Share will be 32% with sales of $175 MM.

Dementia:
Maximize and grow RISPERDAL's market leadership in geriatrics and long term care. Dementia share goal is 57% with sales of $302 MM.

FINANCIAL SUMMARY:

	Net Sales				Cost of Selling	% of Sales	PMEs	% of Sales
	$MM	% Chg	MM Units*	% Chg				
1998 Actual	695.4	18.1%	303.2	14.4%	12.9	1.9%	52.3	7.5%
1999 Aug Update	922.2	32.6%	389.8	28.6%	23.6	2.6%	66.5	7.2%
2000 Bus Plan	1059.3	14.9%	452.5	16.1%	25.0	2.4%	78.0	7.4%

*Includes tablets and oral solution

PME Breakdown:

	Total		Med Ed*		Samples/ Promotion		Journal Adv		PR		DTP/DTC		Agency	
	$MM	%Net Sales	$MM	%Net Sales	$MM	%Net Sales	$MM	%Net Sales	$MM	%Net Sales	$MM	%Net Sales	$MM	%Net Sales
1998 Actual	52.2	7.5%	32.9	4.7%	9.6	1.4%	4.0	.6%	3.4	.5%			2.3	.3%
1999 Aug Update	66.5	7.2%	43.5	4.7%	11.1	1.2%	3.9	.4%	5.6	.6%			2.4	.3%
2000 Bus Plan	78.0	7.4%	51.5	4.9%	14.3	1.3%	3.4	.3%	2.1	.2%	1.1	.1%	2.0	.2%

*Includes public relations, grants, sales support, and medical education programs

BplanDoc.doc

00360766 001

KEY BRAND FACTS:

	1998	1999 YTD (9/99)	2000
Market NRx	11,735	9,625	12,935
Market TRx	22,928	18,504	25,855
NRx Share (%)	25.0%	27.5%	30.0%
TRx Share (%)	23.7%	26.1%	27.6%
Dollar Share (%)	31.9%	32.1%	31.2%
Share of Business by Indication/Specialty (NRx%)			
Schizophrenia	18%	18%	20%
Bipolar Disorder	27%	25%	32%
Dementia	45%	50%	52%
Share of Business by Indication/Specialty ($%)			
Schizophrenia	37.1%	23.2%	21.3%
Bipolar Disorder	45.1%	33.1%	32.2%
Dementia	48.1%	55.3%	57.6%
# Sales Calls	378,000	363,000	707,500
Share of Detailing (%)	36.9%	35.8%	34.5%
Share of Samples (%)	39.6%	33.4%	29.5%
Share of Journal Advertising (%)	30.8%	37.3%	35.4%
Share of DTC Advertising (%)	N/A	N/A	N/A

STRATEGIES - Schizophrenia:

1. Differentiate RISPERDAL from the competition
2. Expand reach on key customer base
3. Solidify and expand opinion leader support
4. Explore compliance opportunities
5. Maximize cost and reimbursement opportunities

STRATEGIES - Dementia:

1. Optimize efficacy and safety positioning
2. Rapidly drive market penetration
3. Expand reach with key customers
4. Develop advocacy and opinion leader support
5. Strengthen data generation and dissemination

STRATEGIES - Bipolar Disorder:

1. Differentiate RISPERDAL and disseminate benefits for appropriate patients
2. Strengthen opinion leader and advocacy support for RISPERDAL
3. Improve compliance and optimize patient management
4. Develop comprehensive clinical program (Medical Affairs Group)

I. RISPERDAL® (risperidone)

A. Strategic Vision

The vision of the RISPERDAL franchise is to reinforce the position of RISPERDAL as the antipsychotic of choice and to further establish Janssen as a leader in the CNS marketplace. Our focus in 2000 will be to enhance the leadership of RISPERDAL as the most effective atypical antipsychotic for first-line treatment of both psychotic and non-psychotic disorders. These disorders include schizophrenia, schizoaffective disorder, bipolar disorder, dementia and conduct disorders. RISPERDAL will also be building a foundation to launch future CNS products such as VESTRA, REMINYL, TOPAMAX-Bipolar and other future CNS compounds.

B. Market Overview/Situation Analysis

The antipsychotic market is valued at approximately $2.9 billion ($3.4 billion in RISPERDAL dollars), representing a dollar increase of over 23% from last year. It is projected that this increase in dollar volume will continue as the market rapidly converts from conventional antipsychotics (declining at about 10 share points per year) to more expensive atypical antipsychotics.

RISPERDAL has remained the #1 most prescribed antipsychotic in the United States for over 3 years. The current NRx share of 28.8% (Oct 99) represents an all time high.

In 2000, schizophrenia will remain a critical area of focus for RISPERDAL. Schizophrenia is the foundation for antipsychotic use and represents the greatest dollar potential (~$1.3 billion in RISPERDAL dollars). RISPERDAL currently has 18.0% share (MAT Sept 99) of the schizophrenia market, compared to 25.1% for Zyprexa. In 2000, our objective will be to accelerate RISPERDAL share growth, and ultimately retake the lead in this critical market.

The geriatric market represents RISPERDAL's second wave of growth. The incidence of dementia in the U.S. is about 3 MM people and demographic trends suggest the aging population will continue to drive market growth well into the next century. With one-half of all nursing home residents suffering from dementia (650 K), the long-term care (LTC) segment is a significant opportunity for RISPERDAL. In addition, many patients still live at home so prescriptions are being generated in the retail market as well. RISPERDAL LTC NRx is growing at a rate of 26% versus last year. In addition, YTD LTC segment sales exceed $120 MM, an increase of 11.5% over 1997. This solid sales growth has been facilitated by the introduction of 0.25mg and 0.5mg tablets, which are parity-priced with 1mg tablets. The parity pricing has helped to maintain sales despite a declining average daily dose. In fact, RISPERDAL continues to be the number one prescribed antipsychotic in LTC in terms of both market share and dollars. Increasing competition from Zyprexa and Seroquel is making this a much more competitive segment than in the past.

Bipolar disorder represents about one-fifth of the prescriptions for RISPERDAL, with a market potential estimated at nearly $600 MM. RISPERDAL has experienced significant growth in this market with a 25.2% share (MAT Sept 99), down from 26.8% in December 1998. Zyprexa has a current market share of 34.7%. Lilly's recent FDA "approvable letter" for Zyprexa bipolar labeling appears to have overcome an earlier setback in September 1998. A critical success factor for RISPERDAL will be effective positioning of the efficacy of RISPERDAL as adjunctive therapy without the significant weight gain liability of Zyprexa.

The continued publication of data supporting the efficacy and safety of RISPERDAL will drive the use of this product in a variety of psychotic conditions. Specifically, future developing markets for RISPERDAL include stuttering, conduct disorders in children and adolescents, post traumatic stress disorder and dual diagnosis.

In 2000, three major market forces will affect the overall antipsychotic marketplace:

- Increasing competitive intensity among existing atypical antipsychotics.
- Continued demand for new data and additional formulations of atypical antipsychotics.
- Changing reimbursement environment.

Competitive Intensity in Differentiating Atypical Compounds

The competitive environment of the atypical antipsychotic marketplace has intensified with a corresponding increase in the total dollar value of the market (an increase of 23% over last year). All pharmaceutical companies invested in the atypical antipsychotic marketplace have increased promotional intensity substantially. Most noteworthy have been Eli Lilly's expansion of LTC and bipolar-focused sales forces, AstraZeneca's increase by 100 LTC representatives, and significant spend by Pfizer in medical education programs and opinion leader focus in preparation for Pfizer's Zeldox. RISPERDAL must position itself as the antipsychotic with superior efficacy in order to differentiate from the other atypicals in 2000.

Continued Demand for New Data and Additional Formulations of Atypical Antipsychotics

Because of the importance of Zyprexa to the growth of Eli Lilly, a significant amount of resources—both human and financial—are devoted to their clinical development program. In addition to an extensive schizophrenia clinical program, Lilly has an advanced program for bipolar disorder which has resulted in an 'approvable letter' from the FDA. Lilly is also pursuing indications for dementia and Parkinson's dementia. In addition, new formulations including Zydis (a QuickSolv-like formulation), a patch, and a long-acting (depot) injection are also being aggressively developed. It is anticipated that Pfizer will re-file an NDA for ziprasidone in 1Q'00 with oral tablets, an IM formulation, and a claim for relapse prevention. Other schizophrenia products in development include aripiprazole (an Otsuka compound co-licensed with Bristol Myers Squibb - NDA late 2001) and Zomaril (Novartis - NDA mid-2001). RISPERDAL is significantly behind Zyprexa in terms of published clinical data as well as clinical research programs. Clearly, a major challenge for the CNS Franchise will be in providing resources to adequately support the development of new clinical data and formulations for RISPERDAL.

Changing Reimbursement Environment

The superior efficacy and safety profile of the atypicals has increased the NRx volume growth, and has dramatically increased the total dollar volume within the antipsychotic class. Atypical antipsychotics represent nearly two-thirds of NRx volume and over 90% of the existing dollars.

With the rapid shift towards the more expensive agents, it is anticipated that payors will continue to focus more attention on the use of atypical antipsychotics. Such changes will offer challenges and provide opportunities for RISPERDAL. In addition, there is a potential for change in the Medicaid reimbursement system. In 1998, the Prospective Payment System (PPS) was introduced in the Medicare nursing home population. PPS transfers the financial risk from Medicare to nursing home providers. Depending on the success of Medicare PPS, Medicaid may implement it's own version of capitated payment. With over 80% of RISPERDAL sales distributed via the public sector, this could have a significant impact on our business. Thus, the need to quickly expand and solidify RISPERDAL use becomes even more important.

C. Life Cycle Analysis – Schizophrenia/Geriatrics/Bipolar/Conduct Disorder

The atypical antipsychotic market is becoming increasingly competitive. The need to differentiate RISPERDAL from the competition with clinical data, new indications and additional formulations is critical. The primary focus will be to leverage our competitive advantage in schizophrenia, followed by expanding use in geriatric psychosis, bipolar disease, and conduct disorders. The potential of these markets is noted below:

Disease	Yearly Patient Population	$ Potential
Schizophrenia	2,500,000	$1.3 B
Bipolar Disorder	3,500,000	$640 MM
Dementia	2,900,000	$500 MM
Conduct Disorders	6,800,000	$300 MM

Schizophrenia:
The reanalysis of the RIS-112 data (RISPERDAL vs. Zyprexa) provides us with a strong opportunity to differentiate RISPERDAL from Zyprexa in the Schizophrenia market. In order to maximize these data, Medical Affairs will be analyzing the data to support several poster presentations and at least two manuscripts. RIS-79 (relapse prevention), is another important data set with regard to the schizophrenia market. Long term data is essential in this market. While the initial results of RIS-79 were released in 1999, several additional analyses are planned for 2000, as it is a robust data set. In addition, RIS-79 will be the key study to go for a long-term maintenance sNDA and potentially a superiority claim over Haldol for positive symptoms.

Dementia:
In order to maximize our competitive position and support our growth in dementia, a label change is critical. It is essential to co-operate with the FDA and opinion leaders in preparation for the Advisory Committee meeting scheduled for spring 2000.

With the increasing number of atypical antipsychotics on the market, the need to differentiate RISPERDAL from the competition on both efficacy and safety will be critical. The focus will be on expanding the data and supply of published literature on RISPERDAL in dementia patients with Alzheimer's Disease suffering from psychotic symptoms and behavioral problems. We have a large database with RIS-USA-63/RIS-USA-70 and RIS-INT-24/26, which could provide a wealth of data for years to come if analyzed effectively. It will also be important for us to

conduct head-to-head studies vs Zyprexa to combat the results of the Lilly sponsored RISPERDAL vs Zyprexa trial in dementia.

As we develop new formulations for RISPERDAL with depot we will need to ensure that appropriate low dose formulations for dementia patients are developed at the same time as doses for schizophrenic patients.

In order to maximize our CNS portfolio in geriatrics it will be critical to conduct studies with RISPERDAL and REMINYL regarding safety interactions and enhanced efficacy for both memory enhancement and behavioral control.

Bipolar:
The bipolar program includes RIS-102 and INT-46, both of which are critical for 2000 in order for us to remain competitive within the bipolar market. Both studies are acute mania, add-on studies and will form the basis for a bipolar sNDA to be submitted in June 2000. Acute mania monotherapy studies are expected to start 2Q'00.

Conduct Disorders:
RIS-USA-93 and the long-term extension RIS-USA-97 will provide us with data on the safety and efficacy of RISPERDAL in children with conduct disorders. These data will help us extend RISPERDAL use within the pediatric market and will potentially extend our patient with an additional 6 months.

The consistent practice of performing additional analysis on existing data sets is critical to maximizing the data, and therefore our publication exposure in the marketplace. However, with increasing competition, the need for new clinical data supporting the use of RISPERDAL in each strategic areas is also essential.

The long-term development plan for RISPERDAL is prioritized according to market potential. Our number one priority is the development of a RISPERDAL depot formulation. Several other new formulations, indications and line extensions are planned for launch within the next 1-5 years. A summary timeline of the new developments for RISPERDAL are summarized below:

	2000	2001	2002	2003	2004
Brand Introductions		QuickSolv Approval	Depot (2-wk formulation)	Bipolar Monotherapy	Depot (4-wk formulation)
		POC Approval			
Label Changes New Indications	Dementia Labeling	Acute Mania Bipolar (adjunctive therapy Labeling)	Conduct Disorders		Palmitate
New Data	Stuttering Data Dual Diagnosis Data Glucose Metabolism Data Long-term Conduct Disorder	Maintenance Label			

	Data				
Key Publications	Comparative Data (RIS-112)	First-Break Data			
	Relapse Prevention (RIS-079) Bipolar – Acute (RIS-102/46) Conduct Disorder (RIS-93/RIS-97)				

D. RISPERDAL- Schizophrenia 1999 Accomplishments and Lessons Learned

Accomplishments

- Overall NRx market share reached an all-time high seven out of eight months in 1999
- RISPERDAL sustained double-digit sales growth for the fifth consecutive year
- Zyprexa posted its first NRx share decline since launch
- The Janssen booth at the 1999 APA was rated Number One by attendees
- The CNS Summit has become a highly regarded meeting among opinion leaders

Lessons Learned

We need to focus on a specific promotional schizophrenia message

Since the launch of RISPERDAL in 1994, the base promotional message has focused on efficacy in "psychosis." This broadly defined message has been effective in diversifying the range of diagnoses for which RISPERDAL has been prescribed, but has also diluted the core message for schizophrenia. Zyprexa surpassed RISPERDAL in schizophrenia market share in May of 1998, and while RISPERDAL has remained flat at an NRx share of 18.2%, Zyprexa has grown its NRx share in schizophrenia to a new all-time high of 25.1%. In 2000, our promotional and medical education activities will need to focus on driving a strong evidence-based message for the efficacy of RISPERDAL in the treatment of schizophrenia.

Seroquel (quetiapine) cannot be ignored

In spite of the fact that the psychiatric community continues to question the efficacy of Seroquel, it currently has a NRx share of 7.1%. In addition, Seroquel has shown consistent growth that has actually outpaced growth rates for both RISPERDAL and Zyprexa in the last year. Zyprexa is and will remain the main competitor for RISPERDAL, but it will be important to make sure that we maximize every opportunity to blunt the continued growth of Seroquel.

Weight gain is a defensive issue for Zyprexa, and an offensive issue for ziprasidone

Lilly is now defensively addressing the issue of weight gain in their sales materials, but Pfizer is quickly trying to pre-position ziprasidone as weight neutral. There is also further evidence that Zyprexa may be associated with causing Type II diabetes in some patients. We will need to explore this further, as this would have significant impact on the medical community. Until we know further, we need to continue to firmly position RISPERDAL as the most effective first-line atypical, while differentiating on weight gain as a secondary message.

The antipsychotic marketplace is still price inelastic

Despite the fact that Zyprexa is typically priced 40% higher per prescription than RISPERDAL, the market still remains slow to react to this difference in terms of formulary positioning.

Publication opportunities have not been fully leveraged

Janssen is significantly behind Eli Lilly in terms of studies and related publication volume. There have been few new studies since launch in 1994, and the data sets we do have are not fully leveraged to produce multiple publications.

E. SWOT Analysis - Schizophrenia

The SWOT analysis is the basis for RISPERDAL-Base promotional activity in 1999:

Strengths	Weaknesses
Superiority in positive and negative symptoms over Haldol Relapse prevention data (RIS-79) New data Vs Zyprexa (RIS-112) Rapid onset of action Low weight gain QD dosing Low TD Low anticholinergic effects Low sedation	Publication Volume Dose-Dependent EPS Perceived TD liability (EPS) Prolactin elevation Perception of more complex dosing Breadth/number of speakers
Opportunities	**Threats**
Acute care setting Psychiatric Residents Low cost/changing reimbursement environment Opinion leaders	WLF ruling Zeldox (ziprasidone launch) tablets and IM formulations Zyprexa "Zydis" (quick-solv) and IM formulations Growth trend of Seroquel Zyprexa bipolar approval

F. Key Issues - Schizophrenia

Increasing Competitive Intensity

1) *Decreasing share of voice*
   In the year 2000, there will be four atypicals on the market which are actively promoted, with a fifth due to be approved by year-end (ziprasidone). While this increases the "noise level" for the atypicals overall, it also creates more fierce competition. There will be more representatives promoting each drug, either from corporate mergers (Astra-Zeneca), sales force expansions (Janssen and Lilly), or a new drug launch (Pfizer). From a promotional standpoint, representatives then face more competition for physician time. At a different level, there will be increased competition for opinion leader relationships. Medical education will also be more challenging, with five companies actively pursuing the antipsychotic market, and therefore competing for physician time at major meeting symposia, and representative delivered programs. To be successful in 2000, we will need to ensure that promotional messages are solid in content, and that they are consistent from rep-to-rep and program-to-program. We will also need to continue to strengthen our existing relationships with key opinion leaders, and strive to further widen our circle of key contacts.
2) *Existing perception gap*
   To regain market share in the treatment of schizophrenia, we must address current perceptual gaps relating to the product profile of RISPERDAL. Market research has shown that prescribers feel that Zyprexa is superior to RISPERDAL in the treatment of negative symptoms, and that it has a superior EPS profile. In contrast, however, the large evidence

of clinical data demonstrates both drugs to be equal. In addition, weight gain and diabetes were not listed as part of the top 10 attributes of importance to physicians, although both were rated strongly in favor of RISPERDAL. Our current promotional message focuses on efficacy, low weight gain and appropriate dosing. We will need to continue to drive this core message, and work to close the existing perceptual gaps versus Zyprexa. We also need to raise the overall importance of weight gain and diabetes with key prescribers.

3) *Sub-optimal physician targeting*
In the interest of pursuing high volume prescribers, Janssen has not devoted a great deal of selling time to psychiatric residency programs, acute setting psychiatrists, or psychiatric nurses. We now have a dedicated sales force in institutional settings that will allow us more time with these important customers. Promoting RISPERDAL to all of these key customers (in addition to high volume physicians) will allow our representatives cover the continuum of patient care.

Poor Compliance
Similar to other atypicals, market research has shown that for every 100 patients, who begin RISPERDAL treatment, only 15 will remain on RISPERDAL one year later. The reason for this alarmingly high rate is complex, stemming partly from the diagnosis itself and compounded by a very fragmented mental healthcare system. Countless programs have been put in place from various organizations, all aiming to correct the problem. While this is a key issue for RISPERDAL, any tactics aimed at addressing poor compliance must be carefully considered as to their projected impact.

Low Cost and Challenging Reimbursement Environment
In spite of the fact that RISPERDAL is 40% less expensive per patient than Zyprexa, and approximately 30% less expensive than Seroquel, we have not yet seen payors move toward preferring one atypical over another on formularies to any significant degree. We must first differentiate the efficacy and safety product profile of RISPERDAL with payors. This message can then be combined with a strong cost-effective message to move toward gaining preferred formulary status.

Secondarily, the JanssenCares patient assistance program has experienced some blatant misuse in certain states. Some counties have decided to implement this patient assistance program as a chief source of funding for RISPERDAL medication, instead of paying for the drug based upon county budgets. We will need to evaluate whether this "misuse" is part of the cost of doing business, or if we should redesign the program at the risk of alienating key customers.

Timing and Scale of Clinical Development Plan
The role of our clinical data development is crucial for maximizing RISPERDAL's potential in Bipolar Disorder. Clinical data is essential to support our strategy of differentiation. Positive data to show RISPERDAL's superior properties of rapid onset of action and low weight gain in relation to Zyprexa, Depakote, and Lithium will be important for success in 2000.

Aggressive Competition
Zyprexa is RISPERDAL's main competitor in Bipolar Disorder. Lilly has recently received a FDA approvable letter for bipolar mania for Zyprexa. This letter was issued in October 1999 and formal approval should occur during the last quarter of 1999. Lilly will be able to promote Zyprexa for Bipolar Disorder in 2000, which makes the timing of our clinical development plan even more crucial, as it will determine our capacity to promote RISPERDAL in Bipolar Disorder.

G. 2000 Business Objectives - Schizophrenia

Quantitative:
Base business sales: $583 MM
December Schizophrenia share: 20.0%

Qualitative:
To accelerate share growth in schizophrenia, with the ultimate goal of recapturing the lead position in the treatment of schizophrenia. With the introduction of the RISPERDAL relapse prevention study in schizophrenia, as well as the competitive trial versus Zyprexa, we will have the evidence we need to reclaim the number one position.

H. Key Strategies with New Tactics for 2000 - Schizophrenia

Strategy #1: **Differentiate RISPERDAL from the competition**
- RISPERDAL.com
- Influence Network Marketing dinner meetings
- Field-Based Psychiatry Advisory Forums
- Ziprasidone Blocking Kit
- Sales Training Motivational Tapes

Strategy #2: **Expand Reach on Key Customer Base**
- Janssen Resident of the Year Award
- Residency to Practice Management Seminars
- Virtual Hallucinations Education Endeavor
- ER education pack
- Psychiatric Nurse Home Office Advisory Forum
- APNA Newsletter

Strategy #3: **Solidify and Expand Opinion Leader Support**
- Speaker Intranet/Slide Updates

Strategy #4: **Explore Compliance Opportunities**
- Compeer Program
- Discharge Planning Kit
- DTP Pharmacy Intervention

Strategy #5: **Maximize Cost and Reimbursement Opportunities**
- Leveraging Economic/Clinical Competitive Advantages
- Public Sector Forums

I. Sales Force Requirements - Schizophrenia

Call activity and capacity are as follows:

Sales Force	Annual Call Capacity	RIS 1st	RIS 2nd	VESTRA 1st	VESTRA 2nd
S (165)	254,100	254,100			192,693
I (52)	114,400	114,400			71,500
T (121)	199,650	33,275	124,780	166,375	
Total	568,150	401,775	124,780	166,375	264,193
Scios (94)	50,000	50,000			

Message:
The sales force message for 2000 will be:

- **Differentiate on efficacy in schizophrenia**
  - significantly superior: positive and negative symptoms
  - improvement as soon as week one
  - sustained improvement
- **Discuss low weight gain**
  - 5.7 lbs. after one year
  - consider the short term/long term effect of weight gain
- **Stress appropriate dosing**
  - starting dose 2 mg QD
  - target 4-6 mg in schizophrenia

Specialty "S" and Target "T" reps will co-promote RISPERDAL in community office-based settings. Institutional reps will be asked to spend time with their key customers in the ER, to promote the use of RISPERDAL in the acutely agitated patients. They will also be asked to spend more selling time with psychiatric residents so that these important customers of the future can begin to build positive experience with the use of RISPERDAL. It will also be important for institutional reps to interact with and promote the benefits of RISPERDAL to psychiatric nurses, because these customers are highly influential in generating medication switches.

Programs:
All medical education program topics will be designed to discuss the same three key communication points.

- Teletopics
- Distance Learning Network Satellite Programs
- Peer to Peer Meetings
- Speaker Programs
- Symposia
- Audiotapes

See attachment 5a for complete listing

J. Business Imperatives - Schizophrenia

Publication of Relapse Prevention and RISPERDAL vs Zyprexa Studies
These two studies provide solid evidence of the superior efficacy of RISPERDAL in the treatment of schizophrenia. The data strongly reinforce our sales message in schizophrenia and publication will significantly aid us in regaining lost market share in schizophrenia. Once published, we will submit these studies to internal review, with the ultimate goal of having the sales force distribute them under Washington Legal Foundation guidelines.

Lessen the Perceptual Gap Between RISPERDAL and Zyprexa in Negative Symptoms and EPS; Elevate Importance of Weight Gain and Diabetes
We will conduct another perceptual map survey with 300 key customers in 1Q'00. We will minimize the gap between RISPERDAL and Zyprexa on these two attributes, utilizing the 1999 survey for baseline results. We will also shift the overall importance of weight gain into the top ten categories, and raise awareness of diabetes risk with competitors.

Implement Ziprasidone Blocking Strategy with Sales Force Prior to Launch
We will provide the sales force with a thorough review of Pfizer as a company, their strategies for ziprasidone, and an overview of the clinical data with thorough commentary and interpretation. We will also provide the sales force with specific lists of physicians who are likely to prescribe ziprasidone at launch. It will be imperative that 100% of the sales force is fully trained and understands how to position RISPERDAL versus ziprasidone by August of 2000.

Establish Productive Working Relationships within Public Sector Markets
Timely identification and management of RISPERDAL business opportunities, threats and vulnerabilities will be essential. Reimbursement managers will establish productive working relationships with payers in Medicaid, State Mental Health, CMHCs, Counties, VAs, Department of Corrections and Behavioral Health Organizations leveraging clinical and pharmacoeconomic advantages.

Manage Public Sector Market Trends such as Budget Limitations (Diminishing Elasticity, Zyprexa Expenditures), Medicaid Managed Care and State DUR Threats
We will design and implement CME public sector forums, maximize our Performance Guarantee Program, and DUE forms with targeted top level decision makers and institutions. Each reimbursement manager will be responsible for multiple programs and selected participation in advisory boards (Corrections, VA, Medicaid and State Mental Health) with the overall goal of maximizing RISPERDAL's formulary position and business growth.

D. RISPERDAL- Geriatrics 1999 Accomplishments and Lessons Learned

Accomplishments

- Increased RISPERDAL market share in dementia from 43.0% in Sept. 1998 to 51.1% in Sept. 1999 for a total increase of over 8 share points.
- Launch of the .25 mg and .5 mg tablets.
- Doubled use of teletopics to over 500.
- Increased attendance at nurse programs by 30%.
- Enhanced relationships with key associations including AMDA, ASCP, and AAGP.
- Better understanding of dosing by physicians. All called on physicians are primarily using low doses in the elderly in the .25 - 2 mg range.

Lessons Learned

- In the geriatric market it is vitally important to balance our safety and efficacy messages. Market research has indicated efficacy is the most important attribute a physician looks for in gaining control of agitated and/or aggressive behaviors. Our physicians believe this is a clear Risperdal strength. While no single safety parameter is more important than efficacy, it is also clear safety is extremely important, i.e., EPS, TD, sedation, anticholinergic profile, etc. We have the most robust data available and we intend to continue to leverage this data stressing, in parallel, our unsurpassed efficacy and safety messages.
- Without proper education PPS and OBRA regulations could negatively impact antipsychotic prescriptions in the nursing home. PPS has more fully impacted nursing homes, as the 3 year staged national rollout is nearly complete. This has caused some nursing homes to increase pressure on physicians to prescribe less expensive drugs such as conventionals. Proper education on overall health care cost reductions and improved patient care with RISPERDAL is important in this environment.
- Nurses are key influencers over switching and diagnoses. Physicians are very open to taking advice from director's of nursing and other nurses since they are with the patients, observing symptoms and side effects for such a great amount of time.
- Important to stress proper dosing or physicians will switch because of EPS. EPS with RISPERDAL is dose dependent and when used at 2 mg or greater in geriatric patients there is far greater risk of EPS. Currently, the dosing in our package insert does not indicate the truly appropriate range for patients.
- Target audiences are still interested in treating behavioral symptoms more than "psychotic" symptoms. Physicians will treat psychotic symptoms such as paranoia, delusions, and hallucinations when they involve aggression or agitation that becomes problematic for the patient and staff.
- The LTC market is very responsive to promotion, however it is becoming increasingly more competitive as Eli Lilly and AstraZeneca both have launched sales forces in the LTC market.

E. SWOT Analysis - Geriatrics

Strengths	Weaknesses
Efficacy/safety data (RIS-63 & RIS-70) Market leadership Performance based contracts J&J LTCM/ElderCare team Availability of dosing options	EPS at ≥ 2mg/day Physician/customer targeting due to data Delay in label change for RISPERDAL No switching or 'head-to-head' data Dosing confusion OBRA Orthostatic hypotension
Opportunities	**Threats**
RIS-OLZ Dementia Trial Additional 'pull-through' programs REMINYL synergy OL/association relationships WLF AUS-5 Study	Dementia label for Zyprexa Dementia label denied for RISPERDAL Competitive sales force expansions Zeldox/Aricept/Zoloft synergy Seroquel geriatric focus AChE, AC & ADP use PPS Lilly comparative trial

F. Key Issues - Geriatrics

Increasing Competitive Intensity
As the competition grows among the atypical antipsychotics and our competitors add 'ElderCare-like' sales forces it becomes more important for us to maintain our share of voice. Our competitors are also publishing off-label data prolifically and these may dilute the impact of our few small Phase IV studies in geriatric patients. In addition, both Lilly and Zeneca have increased their share of voice at national conventions and with national and regional CME education.

Increased Focus on Opinion Leaders
Competitive intensity is increasing for share of voice with the opinion leaders as well. In geriatrics there is a small number of really top tier opinion leaders. These individuals are all being strongly pursued by both Eli Lilly and AstraZeneca. We will need to ensure coverage of these opinion leaders in order to build and maintain the relationships we have already established. We should also leverage our REMINYL position when maximizing our relationships with the opinion leaders.

Perceptual Gap
A perceptual gap exists between RISPERDAL's clinical data in geriatrics and the perception physicians hold who treat geriatric patients. RISPERDAL is perceived as having a worse safety profile that the drug actually has, often because physicians are using inappropriately high doses. In addition, most physicians do not recognize that RISPERDAL is the only drug with proven data on efficacy in geriatric patients.

Sub-optimal Customer Targeting
Sub-optimal customer targeting exists as a result of lack of decile data on physicians who treat geriatric patients in nursing homes and hospitals. A broad number of health care professionals, with a varied understanding of antipsychotics, influence patient treatment and switching. It takes a great deal of time and education to ensure that all of the members of the treatment team understand the impact of using RISPERDAL in their geriatric patients or any one "weak link" in the treatment team can negatively impact the business. The primary care audience needs additional education and coverage. This will be substantially increased in 2000, with over half of the antipsychotic decile 4-9 primary care physicians called on. Our coverage will increase to almost 75% after the sales force expansion.

Reimbursement "Window of Opportunity"
We have a reimbursement window of opportunity that is beginning to close as the Prospective Payment System (PPS) more fully impacts nursing homes. By the end of 2000 PPS should be fully implemented nationwide. PPS encourages nursing homes to manage total drug costs downward and thus encourages the use of conventionals vs. atypicals. It will be important for RISPERDAL to capture as much share as possible in order to prevent possible erosion of market share and to insure there is a better understanding of the overall treatment cost savings with RISPERDAL. In addition, the cost gap between RISPERDAL and other atypicals is narrowing in patients diagnosed with dementia. Zyprexa's dosing size continues to decline which makes it only slightly more expensive than RISPERDAL and the newest atypical, Seroquel appears to be priced at a slight discount to RISPERDAL although the data is fairly thin to determine the average dose and cost in dementia patients.

FDA Changing Position
The FDA has recently developed some hesitation on granting specific indications on the use of antipsychotics in Alzheimer's patients with psychotic symptoms. Previously, the FDA had indicated it was very likely RISPERDAL would be granted this label change. The FDA has declined approval for Zyprexa and has announced it will hold an advisory committee meeting in the spring of 2000 to discuss all the issues before granting any approvals.

G. 2000 Business Goals & Objectives - Geriatrics

Quantitative:
Geriatric Sales: $302 MM
December Share: 57%

Qualitative:
Maximize and grow RISPERDAL's market leadership in geriatrics and LTC

H. Key Strategies and Tactics - Geriatrics

Strategy #1: **Optimize safety and efficacy positioning**

- CNS Advisory Forums
- Dementia labeling change preparation (FDA advisory committee meeting) and Dementia launch promotion and PR preparation
- Dementia IPT CD-ROM
- CME speaker's bureau

Strategy #2: **Rapidly drive market penetration**

- Nursing home team education
- PPS video and symposia
- TeleTopics

Strategy #3: **Expand reach to key customers**

- PCP CME teleconferences
- Nurse collegia
- Patient/caregiver educational brochures

Strategy #4: **Develop advocacy and opinion leader support**

- PCP Advisory boards co-sponsored by RISPERDAL and REMINYL brand teams
- Advisory boards with geriatric psych residency training directors
- Advisory boards with Directors of Assisted Living Facilities
- Advisory boards with key Nurse Practitioners
- Educational program development with AAGP, AMDA, AGS, NADONA, ASCP

Strategy #5: **Strengthen data generation and dissemination**

- Analyze RIS-63 and RIS-70 data
- Increase number of small, investigator initiated studies in geriatric patients
- Increase body of peer reviewed published data for use under WLF

I. Sales Force Requirements - Geriatrics

Calls – ElderCare, with the expansion to 136 representatives by March, should provide a total of 65,500 calls for RISPERDAL - geriatrics for 2000.

Message –
- RISPERDAL has proven efficacy in treating geriatric patients
- RISPERDAL has an excellent safety and tolerability profile in geriatric patients
- RISPERDAL is easy to dose with our flexibility of formulations and easy titration

Programs -

ElderCare

- Speaker's bureau
- TeleTopics
- PCP teleconferences
- Videos
- Case workbooks
- Nurse Collegia
- Advisory Forums
- SLU Preceptorship
- Giveaways
- Backgrounder
- Patient/caregiver brochure
- Patient pill box
- New campaign materials
- Safety fact sheets
- Dementia launch
- Advisory Forums
- SLU Preceptorship
- IPT CD-ROM

LTC Business Management Team

It is increasingly important to work closely with this team and we will continue to support their efforts with their primary customers the pharmacy providers (Omnicare, PharMerica, NCS and NeighborCare). We have set aside specific programs and budgets for this team.

- Speaker's bureau
- TeleTopics
- Videos
- GNC education program
- Advisory Forums
- Giveaways
- Backgrounder
- Safety fact sheets
- Dementia launch
- Advisory Forums
- SLU Preceptorship

J. Business Imperatives - Geriatrics

Expand Reach with PCPs

The ElderCare initial expansion will increase the size of the sales force from 86 to 136 representatives. This will enable the sales force to increase reach and frequency of antipsychotic decile 4-9 primary care physicians from 2,600 in January to 4,500 by March. It is imperative that we reach all 8,000 decile 4-9 physicians with Risperdal promotional items at least twice in 2000. This will be done through direct mail and teleconferences where we do not have coverage of physicians. In addition, we will achieve 2 calls per quarter on at least 90% of the 4,500 primary care physicians we are calling on with ElderCare.

Implement a Successful Plan for the FDA Advisory Committee

A white paper will be developed which will effectively summarize RISPERDAL's efficacy and safety data in geriatrics. Data will be compiled from key Janssen studies such as RIS-USA-63, RIS-USA-70, RIS-INT-24 and RIS-INT-26. This will be disseminated prior to the FDA Advisory Committee meeting on the use of antipsychotics in the elderly. We will also leverage the behavioral data contained in our REMINYL Phase III trials.

In addition, a complete backgrounder on the FDA advisory committee members will be disseminated to internal Janssen personnel. The backgrounder will include publication histories, and other appropriate information and this will assist our regulatory group in negotiating a favorable outcome for RISPERDAL regarding label changes in geriatrics.

Generate/Disseminate Clinical Data

It will be critical to generate publications in 2000 through additional analysis of the large RIS-USA-63 and RIS-USA-70 databases. Preliminary analysis should be complete by Q3'00 and pursuit of publications, where applicable, should be sought by end of year.

We will also begin comparative studies with RISPERDAL vs. Zyprexa by end of Q2'00 to assess primarily anticholinergic side effects with other secondary measures in place. A RISPERDAL/REMINYL combination use study should be assessed by end of Q2'00 and if it is determined that it is in the best interest of both products the study should begin, at the latest, by the beginning of Q4'00. The RISP/REM study will likely primarily focus on pK and safety issues with efficacy a secondary measure.

Increase Focus on Opinion Leaders

Opinion leader development is an important strategy for us in 2000 and as such it will be very important for us to ensure both MSL and representative coverage of at least the top 30 opinion leaders in geriatrics. MSL capacity will be assessed to determine if they will be able to call on additional opinion leaders. The representatives will call on the top 100 opinion leaders in geriatrics at least 10 times.

D. 1999 Bipolar Accomplishments and Lessons Learned

Accomplishments

- Focused marketing effort to maximize synergies between RISPERDAL and TOPAMAX
- Organized brand team and developed strategic and tactical plans for 2000
- Initiated Bipolar opinion leader development in conjunction with TOPAMAX

Lessons Learned

RISPERDAL used as add on agent for antipsychotic effects in bipolar disorder
The norm in the treatment of bipolar disorder is to combine therapies. Market research shows that 73% of patients are treated by a combination of therapies. In this context RISPERDAL is not an exception and has been prescribed as an add-on therapy for its antipsychotic effects.

Need data in bipolar disorder to further differentiate RISPERDAL from Zyprexa
In order to differentiate RISPERDAL from Zyprexa, we need to generate clinical data in bipolar disorder and communicate positive results effectively to the psychiatric community. Market research indicates that physicians perceive RISPERDAL as stronger on "improving quality of life" and "reduced risk of weight gain". We must generate clinical data to show that. Positive data from clinical studies will be the foundation for growth in the bipolar segment.

Patients change therapy due to weight gain
The importance of the weight gain side effect is evident. Weight gain affects compliance. Market research shows that one third of the patient population changes therapy due to weight gain. In this way, weight gain is a major obstacle for compliance in the treatment of bipolar disorder. Market research indicates that at least 50% of prescribers associate the use of Zyprexa, Depakote, or Lithium with weight gain. While low weight gain is an important property for patients and prescribers, Zyprexa, Depakote, and Lithium are not associated with this attribute according to the physicians' perception.

Effectiveness and weight gain are 'differentiating' factors
Effectiveness, including rapid onset of action and low weight gain are key properties that may become important differentiating factors for RISPERDAL in bipolar disorder. The psychiatric community considers these attributes important as they improve compliance and patients' quality of life. As we generate and disseminate positive clinical data to support those attributes for RISPERDAL, we will have a strong competitive advantage in relation to Zyprexa, Depakote, and Lithium.

E. SWOT Analysis - Bipolar

The SWOT analysis is the basis for RISPERDAL Bipolar promotional activity in 2000:

Strengths	Weaknesses
Familiar APS profile Low weight gain Cost advantage vs. Zyprexa Faster onset of action vs. mood stabilizers "Improves quality of life" RIS-USA-112 Data (Anxiety/Depression)	Dose-dependent EPS risk Conventional agents perceived as faster acting in mania Perceived mania induction
Opportunities	**Threats**
RIS-USA-102 Unsatisfied Market & RIS-INT-46 Data Leverage Topiramate interest into RISPERDAL support BD depression & maintenance Improve compliance	Zyprexa BD mono-therapy label change: Acute indication (4Q'99), Depression (4Q'01), Maintenance (4Q'02), Zyprexa vs Depakote data Zeldox launch Seroquel fast growing market share

F. Key Issues - Bipolar

Large Dissatisfied Market

The diagnosis, and treatment and management of bipolar disorder is very complex. Market research indicates that the psychiatric community is not satisfied with the available choices for treatment of bipolar disorder. 98% of specialists want to make adjustment in treatment. This dissatisfied population of physicians and patients represents a major opportunity for RISPERDAL given its superior attributes of rapid onset of action and low weight gain.

Timing and Scale of Clinical Development Plan

The role of our clinical data development is crucial for maximizing RISPERDAL's potential in Bipolar Disorder. Positive data to show RISPERDAL's superior properties of effectiveness, rapid onset of action and low weight gain in relation to Zyprexa, Depakote, and Lithium will be important for successful differentiation.

Aggressive Competition

Lilly has recently received a FDA approvable letter for acute bipolar mania for Zyprexa. This letter was issued in October 1999 and formal approval is expected in December. Lilly will be able to promote Zyprexa for Bipolar Disorder in 2000, which makes the timing of our clinical development plan critical.

Weak Opinion Leader Support Base

A key factor for RISPERDAL's success in bipolar is opinion leader support. Few programs were developed to enhance RISPERDAL's opinion leader support in the past. Consequently, few opinion leaders supported the use of RISPERDAL bipolar disorder. Opinion leader support is essential for obtaining expert endorsement for use in bipolar disorder. These same expert

endorsement for use in bipolar disorder. These same experts also conduct seminars and dinner meetings, etc., at which they endorse RISPERDAL.

Poor Patient Compliance and Management
The poor patient compliance and management in bipolar represents a major opportunity for RISPERDAL. Many bipolar patients are non-compliant with their medications for a variety of reasons. Side effects from mood stabilizers, such as weight gain, tremor, hair loss causes 50% of patients to discontinue therapy at some time during treatment. In fact they average length of therapy is only 70 days, in a disease which daily therapy is recommended. Non-compliance increases the chance of an acute bipolar episode and also reduces the sales of drugs used to treat bipolar disorder. Improvement in patient compliance and management will enhance RISPERDAL usage and strength its position as the treatment of choice in bipolar disorder.

G. 2000 Business Goals & Objectives - Bipolar

Quantitative:
Bipolar business sales: $175 MM
December TRx: 32.0%

Qualitative:
Differentiate RISPERDAL from other agents in Bipolar Disorder capitalizing on RISPERDAL's effectiveness as add-on therapy, fast onset of action, and low weight gain.

H. Key Strategies and Major Tactics - Bipolar

Strategy #1: **Differentiate RISPERDAL & Disseminate Benefits for Appropriate Patients**

- RIS-102/46/112 Dissemination Program
- Regional CME Programs: 3 Tracks
- RISPERDAL Evolution
- Publication Program
- Bipolar Sales Training and Targeting Program

Stragegy #2: **Strengthen Opinion Leader and Advocacy Support**

- Millennium Leaders
- RISPERDAL BD Symposia
- CME Casexchange BD Meetings
- MSL Program
- Janssen Resident of the Year Award

Strategy #3: **Improve Compliance and Optimize Patient Management**

- NDMDA Ultra-Care & Patient Max Programs: Diagnostic Kit and Patient Treatment Guide
- NIMH Educational Program: "New Developments in the Diagnosis and Management of BD for Community Psychiatry"

I. Sales Force Requirements - Bipolar

Programs:
The sales force will be involved in three medical educational programs and one training program, as follows:

RIS-102/46/112 Dissemination Program
The sales force will disseminate a sealed reprint pack to physicians with the results of the RIS-102, 46, and 112 studies. We expect to have the sealed reprint packs by the end of the first cycle for RIS-112 and third and fourth quarters for RIS-102 and RIS-46.

CME Casexchange Programs
All sales representatives will be involved in this program. Each sales representative will invite 10 to 12 psychiatrists to each dinner. A logistics agency will be utilized to assist in the organization of this program. Janssen will sponsor a series of 320 CME accredited dinner meetings in 2000.

Regional CME Programs: 3 Tracks
These 60 one-day CME programs will be held in the top 25 markets across the country. Each meeting will have at least 50 community psychiatrists attending. Our sales force will be able to deliver invitations during the recruitment process. We recommend the attendance of sales representatives and district managers to each meeting.

Bipolar Sales Training Program
The sales representatives will be trained on bipolar disorder. We are planning presentations at the district meetings and sales training classes. Didactic materials will also be provided to sales representatives. Training videotape on bipolar disorder is expected to be completed by the end of the first quarter.

Targeting
Treatment of bipolar disorder, and consequently the use of drugs to treat the disease, is concentrated among minority of psychiatrist. Approximately 3500 physicians are responsible for half of the prescriptions for mood stabilizers. Similarly, 7000 psychiatrist are responsible for 80% of the total volume and 10,000 for 90% of volume. Cross-mating decile 8,9, 10 mood stabilizers and antipsychotics identify 3600 high volume target psychiatrists. Approximately 67% are currently called on by the Janssen sales organization. Targeted lists by territory will be available for use in 2000.

J. Business Imperatives - Bipolar

In order to achieve the presented business goals and objectives, the following deliverables are critical:

Use appropriate data to blunt Zyprexa launch
It is mandatory to utilize onset of action, effectiveness, and weight gain data currently available to blunt the Zyprexa launch. All data about RISPERDAL's superior attributes must be well disseminated to the psychiatric community.

- Regional CME programs completed – 20 per quarter 2Q'00 through 4Q'00
- 300 CME case exchange (dinner meeting) programs completed
- 4 posters, 2 journal articles, and 1 supplement in each quarter of 2000

Quality and timing of studies

The quality and timing of RIS-USA-102 and RIS-INT-46 studies are crucial in order to achieve the 2000 qualitative and quantitative objectives. Positive and timely data will help to differentiate RISPERDAL from Zyprexa.

- RIS-USA-102 Manuscript completed and submitted 1Q'00
- Accepted for publication and published 2Q'00
- Field force sealed reprint distributed 2Q'00
- RIS-INT-46 sealed reprint distributed 4Q'00

Strengthen Opinion Leader Support

It will mandatory to strengthen bipolar opinion leader support. Existing relationships should be reinforced and new relationships established. Support from Bipolar opinion leaders will be crucial to success in 2000.

Opinion Leader Support

- Develop individual relationship plans for top 100 opinion leaders and MSL call plan
- Conduct 1 regional advisory board per quarter and 2 national advisory boards in 2000
- Sponsor 1 national preceptor program per quarter in 2000
- Sponsor 5 visiting professors programs per quarter in 2000

EXHIBIT 12

LTC/GERIATRICS

2001 Business Plan

RISPERDAL - LTC/GERIATRIC
2001 BUSINESS PLAN SUMMARY

I. EXECUTIVE SUMMARY:

Atypical antipsychotics are commonly prescribed for elderly patients who exhibit psychotic symptoms (delusions, paranoia, and hallucinations) as well as disruptive behaviors that interfere with needed care. The atypicals are a more attractive option particularly in the vulnerable elderly compared to the conventionals, whose side effect profiles are very problematic. The brand's pre-launch marketing focus has been to prepare for the new indication in psychotic symptoms of Alzheimer's dementia. There are other opportunities in 2001 to effectively and appropriately expand into serious mental illnesses of the elderly, such as psychosis w/o dementia, schizophrenia, management of psychosis accompanying Parkinson's Disease and others.

There are diverse treatment settings within the geriatrics market – nursing homes, Assisted Living, Community Mental Health Centers as well as home-based care. Within each setting a different mix of prescribers and influencers are involved; including psychiatrists, primary care physicians, geriatricians, neurologists and nurse practitioners. Influencers in the market include consultant pharmacists, Directors of Nursing, nursing staff, caregivers, and regulators. The needs of all segments must be considered and will be addressed in our strategic and tactical plan for 2001.

In LTC/Geriatrics market RISPERDAL is the market leader with more than one third of all antipsychotic prescriptions written for RISPERDAL. It should be noted our competition is aggressively expanding into this market. Eli Lilly and Astra-Zeneca have had a strong presence at medical meetings and have increased their promotional activity and spend during the past year and have made market share gains. Pfizer, a recognized leader in LTC (Aricept, Zoloft) will introduce Zeldox in 1Q'01 and we will prepare for the potential impact of Zeldox despite recognized limitations due to its cardiac safety profile.

Our goals for 2001 are to increase RISPERDAL leadership in LTC/Geriatrics. The brand will achieve its goals by implementing tactics against 4 key strategies: 1) strengthen our efficacy/safety positioning and prepare for approval of our new indication; 2) expand effectively and appropriately into additional elderly markets, 3) expand reach and educate our key customer audiences, and 4) effectively position and maximize RISPERDAL [redacted]

The brand has several significant initiatives in its 2001 tactical plan. There will be a focus on broadening the appropriate use and benefits of RISPERDAL in serious mental illnesses that effect the elderly; implementation of appropriate non-rep mediated tactics to expand our reach to broad customer audiences as well as work with the FSF and LTC team to re-enforce messages to current called on clinicians. We will appropriately and effectively introduce RISPERDAL to new customers – such as Neurologists, Family Practice Residents, and Nurse Practitioners. We will conduct regional advisory boards to target and more effectively penetrate key markets. These are just a few of the specific programs and tactics outlined in this plan and available in more detail in our expanded tactical plan.

Several success predictors must be driven to optimized RISPERDAL LTC/Geriatrics business in 2001.

1) Execution of new studies & dissemination of clinical data that at a minimum match the output of our competitors;
2) Psychosis in Alzheimer's disease indication trials (RIS-232/INT-83) must remain on timelines;
3) Drive alignment and focus around our key issues, strategies and tactics among EC, CNS I-Reps, LTC, MSLs, OMP SLs, Medical Affairs, Sales Training, & JRF;

4) Strengthen label related to geriatrics;
5) Maximize FDAMA opportunity; and
6) Maximize RISPERDAL/REMINYL positioning & synergies.

II. SITUATION DIAGNOSTIC/ANALYSIS:

There has been significant growth in the use of atypical antipsychotics in LTC/Geriatrics. Several factors are driving this growth, including:

- Demographic trends shifting toward an aging population
- Use of antipsychotics, particularly atypicals, which are increasingly recognized as the standard of care for patients struggling with behaviors and symptoms associated with psychosis
- Declining use of conventionals due to concerns about their safety, particularly EPS and TD

Use of conventional antipsychotics continues, however it is declining more rapidly in geriatrics (~25% share in elderly population) compared to the market overall.

The brand's promotional efforts have been to focus on the appropriate use of antipsychotics in the elderly for the management of psychotic symptoms and behaviors. We believe opportunities exist in 2001 to appropriately and effectively use our clinical data to continue to expand use of RISPERDAL in serious mental illnesses in the elderly, such as psychosis w/o dementia, schizophrenia, psychosis associated with Parkinson's Disease and others.

Many elderly are placed in nursing homes and other extended care facilities due to their psychotic illnesses and/or associated behavioral disorders so these facilities and the clinicians that deliver care within them remain important targets for RISPERDAL. Within the nursing home setting, the important prescribers are the consulting psychiatrists, medical directors, attending physicians and nurse practitioners. Other influencers we will appropriately interact with include consultant pharmacists, Directors of Nursing and the nursing staff. Many nursing homes are struggling to survive within a highly structured regulatory and reimbursement environment. Organizations that survive are often plagued with reduced reimbursement, low census and a high turnover among an often inadequately trained staff.

Assisted Living Facilities, Community Mental Heath centers and even home-based care are emerging as alternatives to nursing homes and are important target segments for RISPERDAL. There is an opportunity for RISPERDAL to strengthen its focus to deliver appropriate information to those serving within the outpatient setting and to more effectively and appropriately target family practice, geriatricians, nurse practitioners, neurology and psychiatry.

Both family caregivers and professional caregivers (for example, the certified nurse assistant in a nursing home) are on the front line in dealing with resident's symptoms. They often communicate the symptoms and behaviors of a patient to the prescriber. Caregivers are an important audience to appropriately educate on issues of symptom recognition and how to effectively manage symptoms using both pharmacological and non-pharmacological treatments.

Our primary competitors, Zyprexa and Seroquel continue to make inroads in the LTC/Geriatric market.
Zyprexa has been very active:

- Zyprexa's second double-blind placebo controlled study in patients with dementia authored by Street et. al. was published (Archives of General Psychiatry, October 2000 issue) and is being used aggressively by Lilly via WLF with prescribers and influencers.

- Lilly has recently expanded its field force to a total of 160 LTC representatives and is recruiting consultant pharmacists. They have redirected up to 1300 PCP representatives in support of Zyprexa that has expanded Zyprexa's reach into this community of prescribers.
- Lilly is actively pursuing a claim for Zyprexa in the psychosis associated with Alzheimer's Disease and our market intelligence indicates they may be up to 6 or more months ahead of our timelines.

Seroquel has been also been aggressive in the elderly market.

- They are making significant efforts via posters and presentations of re-analyzed data. Astra is promotionally using this data in sales brochures and other vehicles delivering this information via its sales representatives.
- Astra is having an impact among prescribers by focusing and leveraging the sedating properties of Seroquel, which is viewed by some as an advantage.
- Seroquel has only minimal efficacy data and therefore focus on an overall perceived better safety profile - this has made it an attractive agent.
- Among neurologists, Astra has created support for Seroquel's use in the management of psychosis associated with Parkinson's Disease and raised general concerns about movement disorders. OMP's Neuroscience representatives have been calling on a core group of neurologists since early October and this will blunt this impact and maximize our RISPERDAL opportunity with neurologists. Additional tactics with OMP are planned for 2001.

Zeldox most likely will enter the market in 1Q'01 with an indication for the manifestation of psychosis in schizophrenia.

- To date, clinical data on Zeldox in geriatrics has neither been postered or published.
- Since the product is associated with QTc interval prolongation this safety precaution will likely be a significant deterrent to its usage in the vulnerable elderly patient population.

III. PRODUCT PERFORMANCE SUMMARY:

RISPERDAL remains the #1 prescribed antipsychotic in the LTC/Geriatrics market with a current TRx share of 34%. RISPERDAL in LTC/Geriatrics is the #2 market for the molecule and is expected to maintain this position in 2001. With the possible addition of other uses to our mix in 2001 the importance of the elderly market to RISPERDAL will continue to be significant.

The RIS-63 (Katz) study (published in February 1999) has been a powerful and convincing study supporting RISPERDAL efficacy and safety. In July of 2000 the long-term extension to RIS-63, RIS-70 (Jeste) was published. Both articles have been approved via FDAMA and we begin dissemination in February 2001. These two studies and others will form a significant foundation for our brand's medical education programs.

The launch of the J&J LTC group has been an effective way to partner with the LTC pharmacy providers. Our ElderCare sales force has been effective despite its limited reach among our target audiences. Both teams have consistently and effectively delivered critical messages on the benefits of RISPERDAL to our target audiences - nursing homes, consultant pharmacists, primary care physicians and psychiatrists.

Astra and Lilly have recognized the importance of this market and increased their promotional activities toward prescribers/influencers within it and are deploying significant resources against it.

2000 Critical Success Factors

- Close the Perception Gap on safety with Zyprexa and Seroquel;

- Expand reach and frequency and grow market share with PCPs;
- Disseminate clinical data under WLF
- Rep and MSL coverage of top Opinion Leaders

IV. SWOT ANALYSIS, KEY ISSUES:

An assessment of RISPERDAL's strengths and weaknesses in the current market reveals the following:

Strengths

- ElderCare: Janssen's #1 strategic objective
- Efficacy/safety data (RIS-63 & RIS-70)
- Continued market leadership
- J & J LTC/ElderCare team
- Performance based contracts
- Dosing flexibility and cost advantage

Weaknesses

- EPS liability
- Sub-optimal deployment against emerging customers (PCPs, Neuros, NPs)
- Lack of geriatrics/dementia data in label
  - Limitations in use of our clinical data and lack of comparative data

Opportunities

- New geriatrics markets (e.g., elderly psychosis)
- Residency Programs, Training Centers,
- Professional & Family Caregivers, State
- Surveyors & other influencers
- New LTCPP Market Share Tier Programs
- Clinical/outcomes data
- Accelerate conversion of conventionals
- RIS/REM position/synergies
- e-business
- FDAMA dissemination of RIS-63 & 70

Threats

- Seroquel/Zyprexa: expanding geriatric focus
  - sales force, marketing & clinical
- Zeldox geriatric focus?
- ACHEIs/AC/AD positioning in behaviors
- Reimbursement environment:
- PPS/Medicare; Medicaid?
- RIS not first with indication

KEY ISSUES

- Increased competition from atypicals and other drug classes, i.e., ACHEIs, AC, and AD.
- Untapped market opportunities (e.g. elderly psychosis)
- Educational needs on appropriate use and benefits of atypicals not being met across diverse customer base
- Current labeling unfavorable
- RISPERDAL & REMINYL co-positioning

V. 2001 STRATEGIC OBJECTIVES:

Grow RISPERDAL leadership position in LTC/Geriatrics market and prepare for approval of the new indication.

Our positioning in the LTC/Geriatric market has remained consistent: RISPERDAL has the best combination of efficacy and safety while providing needed dosing flexibility.

Our support for this positioning has been strengthened with the launch of a new effective and appropriate promotional platform and the wide acceptance of lower dosage strengths (0.25mg and 0.5mg)

Our core messages in the 2001 are:

Outstanding Efficacy

- Significant improvement in psychotic symptoms and behaviors
- Improvement as soon as one week

- Efficacy maintained for one year

Excellent Safety Experience

- Low incidence of excessive sedation
- Benign anticholinergic profile
- Minimal EPS at recommended low doses

Custom-Tailored Dosing

- Available in 0.25 and 0.5mg dosage strengths as well as oral liquid formulation

VI. KEY BUSINESS STRATEGIES:

1. Strengthen efficacy/safety positioning vs. the competition and grow our leadership dominance in LTC/Geriatrics and prepare for approval of the new indication.
2. Expand effectively and appropriately into additional geriatrics market opportunities.
3. Expand reach/educate a diverse audience:
   - PCPs, Neurologists, NP
   - Training Centers (ADRC, GRECC/VA, Residency Programs)
   - State Surveyors
   - Professional and Family Caregivers
4. Effectively position and maximize RISPERDAL/ REMINYL

VII. KEY PROGRAMS AND TACTICS:

Strategy #1: Strengthen efficacy/safety positioning vs. the competition and prepare for approval of the new indication

Program	Volume/Description
Advisory Boards (Home Office)	9 programs
Regional Advisory Boards	9 programs
Speaker Training	250 physicians
CME Senior Care Seminars	1100 Programs (5 / Rep)
CME Distance Learning Network	1 Program
CME Teletopics	2 Programs (16 dates each)
Quality Indicator Program	Multiple tactics (symposia, SCS, Promotion)
LTC Pull-through	Market share targets

Other tactics include:

- Promotional platform
- Publications
- Medical Meetings/Symposia
- Medical Affairs
- FDAMA: Dissemination of published studies in dementia
- Label changes in dosing/precautions section of PI

Strategy #2: Expand effectively and appropriately into additional geriatrics market opportunities

Program	Volume/Description
Elderly Psychosis Program/ Parkinson's	Multiple tactics: DLN, CME web-based program, GMR website, posters, symposia

Strategy #3: Expand reach/educate a diverse audience

Program	Volume/Description
Primary Care Outreach	Multiple tactics: Target Prozac writers; SCS audiotape; Direct mail; AAFP Symposium, NP/PA Symposium; Journal supplement
Nurse Education	Magic pen/training for CNAs
Neurology	Multiple tactics: OMP Neuroscience reps, promo materials, SCS, Ad boards, NIH consensus conference

Other tactics:

- CNS Summit
- Keystone 3
- AAGP Stepping Stones
- AAGP Training Directors Program
- Summer Research Institute
- Education initiatives: state surveyors, nurse practitioners, caregivers, nurses
- Residency Program (Primary Care/Geriatrics)
- AMDA Futures Program
- ADRC/GREC/VA Program
- Adopt-a-doc
- Assisted Living Pilot (Alterra)

Strategy #4: Effectively position and maximize RISPERDAL/ REMINYL

- SCS
- Advisory Boards
- Speaker Bureaus and Training
- Symposia/Enduring Materials
- Caregiver Education
- Sales Training/Preceptorships

VIII. SUCCESS PREDICTORS:

To be successful in this marketplace, certain things must happen. The brand team will play a key role in driving each of these success predictors:

- Execution of new studies & dissemination of clinical data that at a minimum matches the output of our competitors
- Psychosis in Alzheimer's disease indication trials must remain on timelines
- Drive alignment and focus around the key issues, strategies and tactics by EC/CNS I-Reps/ LTC/ MSL/OMP SL/ Medical Affairs, Sales Training & JRF
- Strengthen label related to geriatrics
- Maximize FDAMA
- Maximize RISPERDAL/REMINYL positioning & synergies

Sales Plan Summary - Long-Term Care / Janssen-ElderCare 2001 Business Plan - Highlights
After a very successful 2000, the LTC/EC teams are poised for another outstanding year in 2001. The expansion of the EC sales force to 135 representatives with the addition of 50 EC specialists will allow us to stay competitive in this market and regain our leadership position as the number one company in ElderCare.

The expansion and training is scheduled for completion by end of March 2001. This will expand our reach to 73% of the PCP APS 3 - 9 from 2,700 to 5,090. The call average is targeted for 7 per day, with a frequency of 12 calls per year on 90% of the key targets. RISPERDAL call activity by customer segment is summarized as follows:

	#Targets	Frequency
PC/IM	5,090	12.0
Med. Dir. & Attending Phys.	9,000	6.0
Psych Consultants	2,250	6.0
Psychs	2,932	12.0
VA NH Facilities	62	6.0
LTC Facilities NH	4,500	6.0

Working closely with the brand team the EC/LTC team will be utilizing among others - CME/CE accredited speaker programs, teletopics and advisory boards to accelerate growth for our key strategic brands.

Our efforts will be focussed on harnessing the power of technology to expand our reach and give us a distinct competitive advantage. Two major initiatives are the Dr to Patient web hosting program and the launch of Janssen-ElderCare.com. Differentiating the EC/LTC teams from competitors will continue to be the focus throughout 2001.

Human resources development and improving the standards of performance to ensure that over 65% of the sales force is in stage II of the standards of leadership will be a priority for the management team.

To stay competitive in this market place the LTC group will work on creative contracting programs to curtail the intense competitive activities and stay ahead.

EXHIBIT 13

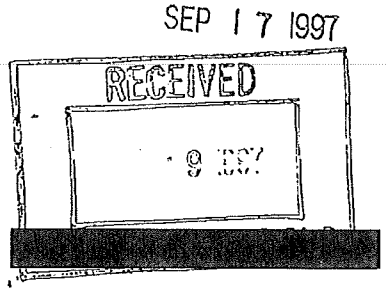
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272 / SLR-006
NDA 20-588 / SLR-001

Janssen Research Foundation
Attention: [redacted]
1125 Trenton-Harbourton Road
Post Office Box 200
Titusville, NJ 08560-0200



Dear [redacted]

Please refer to your supplemental new drug applications dated August 15, 1996, received August 21, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) 1mg, 2mg, 3mg, 4mg tablets and Risperdal (risperidone) 1mg/mL oral solution.

These supplemental applications provide for a change in the labeling with the addition of a new section for pediatric use.

We have completed our review and find the information presented is inadequate, and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

Your supplement proposes the expansion of Risperdal use into pediatric patients, however, you never state for what child or adolescent psychiatric disorders Risperdal would be intended. Indeed, you acknowledge that you have not provided substantial evidence from adequate and well-controlled trials to support any pediatric indications nor developed a rationale to extend the results of studies conducted in adults to children. Your rationale for proposing this supplement appears to be simply that, since Risperdal is being used in pediatric patients, this use should be acknowledged in some way in labeling.

We note that labeling changes proposed are nonspecific:

1. Under the Pharmacokinetic subsection of Clinical Pharmacology, you propose acknowledging that no systematically collected PK data are available, but you refer nevertheless to the Dosage and Administration section.

2. Under the Pediatric Use subsection of Precautions, you refer to "limited evidence regarding the safety and effectiveness of risperidone in the pediatric population," and again refer to the Dosage and Administration section.

3. Finally, in the Dosage and Administration section, you again suggest that there is limited evidence of safety and effectiveness from "small clinical studies, literature reports, and spontaneously reported adverse events." As noted, you never state in this language what indications are supported by these data. Regarding safety, you simply suggest that the safety profile for Risperdal appears to be similar in pediatric patients to that observed in adults. Nevertheless, you advise caution, i.e., avoidance of prescribing in neonates and infants, and cautious titration, beginning with 0.25 mg/day in children and adolescents.

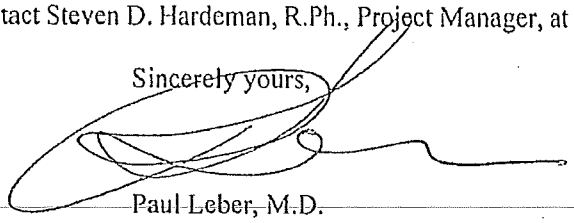
You have provided very little information to support these proposed labeling changes. You acknowledge that the supplements provide no i nterpretable efficacy data. The safety data submitted were also very limited, including data for n=14 pediatric patients exposed to Risperdal in Janssen-sponsored studies, n=29 pediatric patients exposed to Risperdal in studies reported in the published literature, and n=186 spontaneous reports involving pediatric patients exposed to Risperdal. None of these data were suggestive of any unusual or unexpected adverse events occurring specifically in association with the use of Risperdal in the pediatric age group.

Accordingly, we must conclude that there is inadequate support for the changes sought. As noted, you have not identified any pediatric indications for which you believe Risperdal could be approved and you have provided no data from adequate and well controlled trials to support any such approvals. There were no specific safety findings of sufficient concern among the meager safety data submitted to justify adding any information to labeling about the safety experience with this drug in the pediatric age group. To permit the inclusion of the proposed vague references to the safety and effectiveness of Risperdal in pediatric patients and the nonspecific cautionary advice about how to prescribe Risperdal for the unspecified target indications would serve only to promote the use of this drug in pediatric patients without any justification. Consequently, this supplement is not approved.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw these supplemental applications. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,



Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

EXHIBIT 14

JANSSEN · PHARMACEUTICA · RESEARCH FOUNDATION ·

RECORD OF FDA CONTACT

PRODUCT IDENTIFICATION: RISPERDAL® (risperidone) tablets and oral solution	
ORIGINATOR/SIGNATURE: [redacted]	DATE: 03 March 2000
NDA NUMBER: IND NUMBER: 31,931	INITIATED BY: JANSSEN X BY TELEPHONE FDA IN PERSON X
FDA PERSONNEL: See below	DIVISION: Neuropharmacological Drug Products TELEPHONE: (301) 594-5533
SUBJECT: Minutes of March 3rd Meeting to Discuss RISPERDAL Pediatric Exclusivity and Development Program for Conduct Disorder	

Meeting Attendees:

FDA *Janssen Research Foundation (JRF)*

[redacted]

Summary: The objectives of this meeting were to discuss the requirements to obtain an additional six months market exclusivity as permitted under the FDA Modernization Act of 1997 and to discuss the clinical development plan for an indication in conduct disorder. The key issues discussed were:

Pediatric Exclusivity

- Pediatric exclusivity is not possible based on safety and PK alone (as proposed). Exclusivity must be based on the approved indication.
- FDA will issue a written request that contains a controlled trial in schizophrenia. JRF will submit a proposal for this controlled trial in adolescents (>13 years old); younger children will not need to be studied.
- The proposed PK trial was acceptable and if needed, JRF could enroll a mixed diagnosis (conduct disorder, schizophrenia) population.

Conduct Disorder (CD) as an Indication

- FDA questioned the validity of CD as a diagnosis and even the concept of CD as a disorder.
- They stated that even though CD is in DSM-IV that does not mean it is a disorder warranting an indication in the label.
- FDA feels a public hearing is needed to define how to look at CD. Their main concern is that RISPERDAL or any other product would be used as a chemical straight jacket. This is the reason the issue needs to be publicly debated.
- FDA believes aggression is synonymous with CD.
- We could proceed with the two trials proposed (RIS-USA-161, RIS-USA-222). However, even if these trials are positive, they would want a consensus advisory committee meeting to confirm the disorder exists. This advisory committee meeting would be triggered by the review of our supplemental application.
- The Division is willing to work with us to define scales for CD and would like to see our data to show their validity and reliability.

Details: A briefing package was submitted on February 10, 2000 (Serial No. 237) in which background information was provided to address questions proposed by Janssen. The questions were divided into two sections, pediatric exclusivity and registration strategy for conduct disorder, and served as the agenda for the meeting. Although we did not discuss each question individually, the issues raised in the questions were discussed in general. The questions and associated discussion points are provided below.

Pediatric Exclusivity

- *Is RIS-USA-160 adequately designed to provide sufficient pK/safety data for inclusion in the labeling for a pediatric population?*
- *Will a written request be issued based on the pharmacokinetic data from the proposed trial RIS-USA-160, as well as the safety data from trials RIS-USA-93, RIS-CAN-19, RIS-USA-97, RIS-CAN-20 and RIS-INT-41?*

[redacted] indicated that they want to see at least 1 controlled trial in the indication we already have approved in order to obtain pediatric exclusivity. They don't believe that submitting only PK and safety data is in the spirit of the pediatric exclusivity provision, unless we can prove schizophrenia is the same in pediatric and adults. So far they have not seen a credible argument that the two populations are the same and did not think it was a worth while endeavor for us to try to prove. Because the safety data proposed is not from a schizophrenic population, it can not be handled appropriately in the label since it would be considered an implied claim. The safety and PK data for pediatrics may be useful, but there are other ways to convey this information to physicians.

For the controlled trial, FDA thought the appropriate pediatric subgroup to study in schizophrenia would be adolescents 13 to 16 years old. Although there are some schizophrenic patients as young as 10 years old, they did not think it would be possible to enroll enough patients in this younger age group. FDA felt they had enough information to issue a written request, however, we suggested that we submit a proposal for the study for them to base the written request on. FDA agreed this would be helpful.

In regards to the proposed PK trial, FDA did not have any specific comments and believed it would provide useful information. They did not have any concerns that the age groups being proposed were younger (5-16 years old), as long as this information was being generated to support an indication in younger patients. FDA also indicated that it is acceptable to study a mixed diagnosis (conduct disorder, schizophrenia) population in the PK trial.

Registration Strategy for Conduct Spectrum Disorder

- *Does the Division support the use of the term "conduct spectrum disorder" to describe conduct disorder, oppositional defiant disorder and disruptive behavior disorder not otherwise specified, in children?*
- *As a follow-up to the letter from the Division on January 22, 1997, does the Division agree with our proposed clinical development plan to support the indication of Conduct Spectrum Disorder, including Conduct Disorder (312.8), Oppositional Defiant Disorder (313.81) and Disruptive Behavior Disorder Not Otherwise Specified (312.9), in children ages 5-16 without mental retardation?*
- *In studies RIS-USA-161 and RIS-USA-222, the Nisonger Child Behavior Rating Form - modified version (N-CBRF), will be used to assess efficacy. The Conduct Problem subscale of the N-CBRF will be the primary outcome variable of these trials. Secondary efficacy parameters will be based on the Conners Parent Rating Scale (CPRS) and Clinical Global Impression (CGI). Does the Division agree that these are the appropriate parameters for evaluating non-mentally retarded children with conduct spectrum disorder?*

- *Are the proposed studies RIS-USA-161 and RIS-USA-222 adequately designed to evaluate the safety and efficacy of risperidone in non-mentally retarded children with conduct spectrum disorder?*
- *Are the available data and data from the proposed trials adequate to support a new indication for risperidone for the treatment of conduct spectrum disorder in pediatric patients (ages 5-16) without mental retardation?*

FDA questioned the validity of conduct disorder (CD) as a diagnosis and even the concept of CD as a disorder. They don't believe it is well accepted outside the child psychiatrist community. FDA acknowledged CD as a valid clinical entity as it is included in DSM-IV, however elevation of a disorder to permanent status in DSM does not make it a disorder warranting an indication in the label.

FDA believes CD is synonymous with aggression and thinks we are trying to get approval of aggression under the guise of CD. Although we strongly disagreed, FDA indicated that they feel the problem is in the nature of the diagnosis because it is just a "list of behaviors", mainly aggressive behaviors that annoy others. If CD is just a form of aggressive behavior, they recommended that we study this from a symptom approach and look at aggression straight on. If the symptom approach were taken, FDA would expect us to look at the effects of RISPERDAL in three models. The suggested populations to examine were dementia, mental retardation, and conduct disorder. However, the first step in looking at aggression would be to get agreement publicly (e.g., an advisory committee meeting) on how to define aggression and the best way to measure it. FDA acknowledged it would take time to get public agreement and that this approach may not be the easiest way to get approval.

FDA commented that they do not often question a diagnosis, but in the case of CD they are. They feel a public hearing is needed to define how to look at CD and if it is an indication that society is willing to treat. Their main concern is that RISPERDAL or any other product would be used as a chemical straight jacket. Although CD has been discussed publicly at several conferences, the conference audiences have been only child psychiatrists. FDA would require this type of issue to be discussed by a wider scope of psychiatrists, so that the entire psychiatric community can weigh in on the decision, similar to discussions regarding behavioral disturbances in dementia at the March 9, 2000 Psychopharmacological Drug Advisory Committee meeting.

In the absence of a public hearing, either on aggression or CD itself, FDA could not assure us that we would be able to get an indication in the label, even with two positive trials. They emphasized again that they are uncertain whether CD is a diagnosis that merits treatment.

In regards to the two trials proposed (RIS-USA-161, RIS-USA-222), the FDA commented that they have no experience with the scale selected (Nisonger Behavior Rating Form). Based on the information we provided, (Attachment 1), they did not feel the subscale of the Nisonger mapped well to CD, and it was more of a combination of Oppositional Defiant Disorder and CD. This is based on the questions "talks back to teacher, parents, or other adults," "stubborn, has to do things own way," and "disobedient". We commented that we have experience with the Nisonger scale and believe it has a better CD subscale than the Conners rating scale does.

FDA asked about the validity and reliability of the Nisonger scale. We provided an article by Aman, et al (Attachment 2) to demonstrate validation in a mental retardation (MR) population. FDA indicated that they would not extrapolate from the MR population to the non-MR, and that we would have to validate the use of the scale in the non-MR population as well. We informed them we are in the process of doing the validation in the non-MR population. To address reliability, we offered to send the available clinical data we have generated along with any literature references. FDA requested that the clinical data provided include an item analysis.

Until FDA reviews the validation and reliability data, they can not accept the use of the Nisonger scale as the primary endpoint. We asked if they preferred us to use another scale (i.e., Conners), but they

indicated they did not have an alternative scale for us to use. The subscales of the Conners rating scale was provided to FDA for their review as well (Attachment 3).

We talked briefly about the length of the proposed trials. Although 6 weeks is short, they thought it is an acceptable duration for the trials. In chronic conditions, they would like to see that the drug effect persists, and that may not be accomplished in a 6 week trial. If we decide to do 6 week trials, they requested that we provide a rationale as to why trials of longer duration are not possible (e.g., because of a high drop out rate).

With regards to safety, we pointed out that our long-term data in pediatrics would be in a MR population. FDA did not think this would taint the non-MR safety data, but we would need to address how the MR data is relevant in any application. The number of pediatric patients with long-term exposure to RISPERDAL (>300) is not robust, but is generally the exposure numbers the Division is used to seeing. FDA commented on the high rate of somnolence (50%) presented in the background package for RIS-USA-93 and pointed out that this will be a problem if it is a chronic effect. We explained that additional analyses of the data have been performed which showed that this effect was not tied into efficacy.

It was emphasized in conclusion, that if we choose to proceed with the two proposed trials, even if they are positive, FDA would want a consensus advisory committee meeting to confirm that CD is a disorder worthy of treatment and requires a separate indication in the label.

Action Item: Submit available clinical data on the reliability of Nisonger scale.

g:\wpdocs\cns\risperdal\filenotes.all\030300_minutes.doc

EXHIBIT 15

JANSSEN PHARMACEUTICA
FIELD CONFERENCE REPORT

Rep Name:	[redacted]	D.M. Name:	[redacted]	Start Date:	8/19/03	End Date:	8/20/03	# of Field Days:	2	# of Field Days YTD	10

I - OBJECTIVE/ACTIONS FROM PREVIOUS FCR

COMPLETE		Y	N	COMPLETE		Y	N
Previous Objective				Previous Objective	Selling effectiveness	x	
Action 1				Action 1	Increase assertiveness with product agenda during calls	x	
Action 2				Action 2	Deliver a more complete sales message	x	

II - SALES RESULTS

Month: 5/03

		RISP	ZYP	SER	ABL	REM	EXE	DUR
TRx	Share	22.77	29.50	22.28	2.24	13.50	23.09	18.20
	Growth	-1.20	-1.43	+2.44	+1.02	+2.16	-.53	+2.40
DDD	Share	30.09	NA	NA	NA	11.74	NA	44.97
	Growth	-.82	NA	NA	NA	+2.94	NA	-.79

				Nation	Region	District
TPQ	District	101.5	Rank	140/283	42/61	6/11
	Territory	97.68				

Comments

Your May TPQ is 97.68%, ranking you 6/11 in district, 42/61 in region, and 140/283 in the nation. From a retail standpoint, your PQ is 100% and while you have grown both Reminyl (+2.16) and Duragesic (+2.40), you are trending down with Risperdal (-1.20). For Reminyl, you are gaining ground on Exelon, and are currently within 10 share points of becoming the second most Rx'd AChEI in your territory. While you are growing share with Reminyl overall, you are actually losing share in your decile 90 Neurologists, -2.58% (worth $67K). Remain focused on your top Neurologists to turn this trend around and drive overall share even further. For Risperdal you are losing the most share in PCP decile 80 ([redacted], down –3.60% (worth $156K). You have set some action plans specific to Dr. Tadros and I'm confident that these will turn his trends around. From a DDD standpoint, our team is currently ranked 11/28 in the nation with a PQ of 106%. While we are growing Reminyl (+2.94), we are losing share with Risperdal (-.82). To turn this around we must focus on our NH's and the larger ALZ unit facilities.

III - PRODUCT & MARKET KNOWLEDGE

OBSERVED	Y	N	CONSISTENT
Janssen Products	X		Choose One
LTC	X		Choose One
Proof Sources	X		Choose One

Comments

Your overall product knowledge continues to develop and after 8 months in the field, you are tracking well. In past work sessions your focus in this area has been displaying a "working" product knowledge by using your knowledge of the products during calls. During our work session I observed you to have progressed well in this regard. For example, during our call on [redacted] you showed a strong working product knowledge using the Blesa Reprint and explained that, "In the Blesa analysis, patients were selected from 4 trials with ADAS-Cog scores of 30, and MMSE scores of >14, indicating moderate to severe dementia."

Competition	X		Choose One	"Reminyl effectively treated the moderate to later stage patients maintaining them above baseline for 12 months." [redacted] responded by telling you that the results are impressive, and that the patients included in the trial were more severe in nature and that she would use more Reminyl as a result. From an ElderCare market knowledge standpoint you are also developing and you have been active within your pharmacy accounts working very closely with the consultants and pharmacy owners. During our work session we made a call on [redacted] (the districts #3 ranked APS pharmacy at $5.1M) and were able to meet with [redacted] (reimbursement manager) to discuss M-Tab strategies and how [redacted] can help us drive share. [redacted] were open to switching Risperdal oral solution patients over to M-Tab and even entertained new Zydis switches. Your follow up on this will be instrumental. We did not have the opportunity to make any nursing home calls during our work session and you'll want to make sure you are working them with the consistency you're working your pharmacy accounts as this will help pull through your own efforts at the pharmacy and physician level.

IV – SELLING EFFECTIVENESS

OBSERVED	*Y*	*N*	*CONSISTENT*
Approach (Social Style sensitive?)	X		Choose One
Interview (Open-ended questions?)	X		Choose One
Demonstrate (Solution oriented?)	X		Choose One
Validate (Visually reinforced?)	X		Choose One
Negotiate (Six magic words?)	X		Choose One
Close (Script or Action?)	X		Choose One

Comments

You continue to show particular strength in your approach and building strong rapport with your customers and you are now at a product knowledge level to handle objections as they come up. Developmentally in this area you have been focusing on sticking with your pre-call agenda, and delivering a more complete product message. You have progressed well in both areas. For example, in our call on [redacted] you accomplished your call objectives of 1) using head-to-head data to sell against Aricept, 2) find out how he compares Reminyl and Aricept in terms of cognition, 3) close him for increased Reminyl business. You were successful in this call because you set a clear objective, and stuck to it without compromising [redacted] schedule, and as a result, [redacted] told you he would continue to use Reminyl in his practice. During our call on [redacted] you delivered a complete message as well, as you covered Reminyl efficacy, safety, and dosing. As a result, [redacted] knows how Reminyl compares to Aricept from an efficacy standpoint, and Exelon from a tolerability standpoint leaving nothing to question as she makes her decision.

Pre – Call / Post – Call Analysis : You are conducting both pre and post call analysis

V - TERRITORY MANAGEMENT

Month:	8/3/03	
	Rep	*Nation*
Total CPA%	42%	59%
NH/Day	1.29	1.33
Calls/Day	3.5	6.1
Pres/Call	2.1	2.1

Comments

During our work session we discussed your CPA results as of August 3, and you explained that there was a discrepancy in the data and your actual call averages. Remain cognizant of logging in regularly, if not, the system won't be updated with accurate data. In terms of your call frequency across your top 25 doctors, you covered 17 of them 6x's or greater giving you a frequency of 68%. This is also strong performance; however, make it your goal to get to 80% coverage on these important physicians. From a DDD activity standpoint, you also performed as your DDD Scorecard total was 226 points among the highest in the district. With regard to resource utilization, you conducted 20 inservices in July (district goal is 10), 1 speaker program, and did not complete a teletopic for July (district goal is 2 / quarter).

VI - OBJECTIVES / ACTIONS PLANS

OBJECTIVE: Improve selling effectiveness with focus on closing and social style selling.

Action Plan 1: Closing: While I observe you to close with consistency, there are some things you can work on to have greater impact when closing. Focus on these 4 things that will increase your impact.

1) *Trial close along the way*. As you share data, ask for their opinion and how this compares to their experience. If you get positive buy in, your confidence toward closing will grow, along with their comfort level with your product.

2) Just prior to your close, *restate product points* that the physician has already agreed upon. Doing so will establish common ground, and cement for your customers, our products advantages.
3) When closing *set a specific goal or expectation*. You can do this with a number or a time frame. For example, for your next 5 bipolar patients, or for this week use Risperdal exclusively. Doing this will emphasize exactly what you expect and you'll be much more likely to increase business as a result.
4) *Follow up* during the next call after you've closed holding your physicians accountable for action. Once you've closed, and your physician has agreed, you must follow up during your next visit. If you don't, your physicians won't take you serious when you do close.

Action Plan 2: Social Style Selling: read and recap the 4 social styles (expressive, amiable, driver, analytical) and how to identify and sell to each. Plan to complete this by **September 26.**

OBJECTIVE: Increase Product Knowledge

Action Plan 1: Read and recap information on Bipolar Disorder, and Parkinson's Disease. Your information source can be a book, journal article, or DSM IV. Plan to complete this by **October 31.**

VII - GENERAL COMMENTS

1. You are doing an excellent job of marketing what you're selling by maximizing product giveaway items such as samples and M-Tab materials.
2. You should plan to order product nametags by our next work session, as this will further assist you in your marketing efforts.
3. You have a great idea for M-Tab starter kits by including lollipops or small toys to be included in the kit along with a coupon and 1 box of sample. These will be great to use on any child & adolescent psychiatrists that you have ([redacted] *Plan to have these made for our next work session.*

VIII – DEVELOPMENT COMMENTS (SOL COMPETENCIES)

[redacted], during our work session we discussed your development and time lines for obtaining Professional Rep. status. Together, we mapped out a comprehensive plan that will help you develop and get you to this level by September of 2004. You have already completed 4 credits under the Product Knowledge competency and you still need to log on to enter those under your profile. Beyond the action items listed above you should plan to accomplish the following:

1) Complete Outlook training **by October 31.** This will satisfy 1 hour of elective credit under the Territory Management competency.

Johnson & Johnson SAFE

VEHICLE MAINTENANCE

MANAGER	DRIVER	CAR #	MILEAGE	DATE
[redacted]	[redacted]	210168	56,787	8/19/03

GENERAL APPEARANCE	YES	NO
Was the car washed recently?	X	☐
Was the interior of the car clean?	X	☐
Was there any body damage? If yes:	☐	X
In your opinion, was it caused by an accident?	☐	X
Did you instruct the driver to make repairs?	☐	X
Was there any glass damage? If yes:	☐	X
Did you instruct the driver to make repairs?	☐	X
Have repairs noted at last inspection been made?	☐	☐

TIRES:	Good	Fair	Poor
Left Front	X	☐	☐
Right Front	X	☐	☐
Left Rear	X	☐	☐
Right Rear	X	☐	☐

Date of Last Oil Change:

8/17/03

Date of Last Tune-up:

8/17/03

BRAKES and MUFFLER	YES	NO
Have the brakes been inspected and serviced recently?	x	
Is the muffler quite?	X	☐
Is the car free of fumes?	X	☐

DOCUMENTS	YES	NO
Is the driver's license valid and current?	X	☐
Is a current registration in the car?	X	☐
If applicable, does the vehicle have a valid inspection sticker?	X	☐
Is a current insurance card in the car?	X	☐
Does the odometer reading approximate that reported on expense reports?	X	☐
Are there accident forms and a car guide in the car?	X	☐
Does the driver have a copy of *Handling Materials Safely*?	X	☐

COMMENTS *** REQUIRED ***

[redacted] is a safe driver and her car is kept clean and well organized.

EXHIBIT 16

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Re: NDA #s 20-272 and 20-588
Risperdal® (risperidone)
MACMIS # 12195

WARNING LETTER

Dear Dr. Shetty:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a "Dear Healthcare Provider" (DHCP) Letter for Risperdal® (risperidone) disseminated by Janssen Pharmaceutica, Inc. on November 10, 2003. DDMAC has concluded that the DHCP letter is false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(a) and 321(n)) because it fails to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the approved product labeling (PI), minimizes the risk of hyperglycemia-related adverse events, which in extreme cases is associated with serious adverse events including ketoacidosis, hyperosmolar coma, and death, fails to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible, and misleadingly claims that Risperdal is safer than other atypical antipsychotics. The healthcare community relies on DHCP letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers is a serious public health issue.

Background

According to the approved product labeling (PI), Risperdal is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. Risperdal is indicated for the treatment of schizophrenia and for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Risperdal is also indicated in combination with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

Previously, information concerning the risks of hyperglycemia and diabetes appeared in the Adverse Reactions section of the PI under the subheading "Other Events Observed During the Premarketing Evaluation of RISPERDAL®." This section identified diabetes mellitus as an infrequent event (occurring in 1/100 to 1/1000 patients) and polyuria/polydipsia as a frequent event (occurring in at least 1/100 patients). In addition, the Adverse Reactions section of the PI

had a subheading titled "Postintroduction reports" and described hyperglycemia and diabetes mellitus aggravated, including diabetic ketoacidosis, as temporally (but not necessarily causally) related to Risperdal.

In response to post-marketing reports of diabetes mellitus, including some cases that resulted in hospitalization and/or death, FDA evaluated the risk of the development of diabetes mellitus in patients treated with atypical antipsychotics. This evaluation included a thorough review from a number of sources, including clinical trial data, spontaneous post-marketing reports, epidemiological studies, published case series, published clinical pharmacology studies, published preclinical studies, and unpublished studies for clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Based on this review, and given the severity of the events reported and the potential to identify those events at an earlier stage with additional monitoring, FDA determined to require the addition of language to the Warnings section of the PI for all atypical antipsychotics regarding the risk of hyperglycemia and diabetes. By letter dated September 11, 2003, FDA notified Janssen (through Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) of the new warning requirement. On November 6, 2003, Janssen submitted supplemental NDAs covering addition of the following information to the Warnings section of the PI for Risperdal:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiologic studies suggest an increased risk of treatment emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.
>
> Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

FDA subsequently approved these supplements, and requested that Janssen issue a DHCP letter communicating the important new risk information. FDA also asked Janssen to submit a copy of the letter to the NDA and to the MedWatch program, and reminded Janssen of its reporting requirements under 21 CFR 314.80 and 314.81.

Omission of Material Information

The DHCP letter fails to communicate the fact that information regarding the potential consequences of hyperglycemia and the recommendation of regular glucose control monitoring was added to the PI for Risperdal. Instead, as discussed below, the letter minimizes risks associated with Risperdal and claims that Risperdal is safer than other atypical antipsychotics, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Minimization of Risks/Misleading Comparative Claim

The DHCP letter states:

> Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1,2,3,4,5,6,7,8] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

This statement suggests that Risperdal does not increase the risk of diabetes, contradicting the Warning in the revised PI and minimizing the risks associated with the drug including hyperglycemia-related adverse events such as ketoacidosis, hyperosmolar coma, and death, and minimizing the importance of blood glucose control monitoring.

The references cited in the letter do not represent the weight of the pertinent scientific evidence. That evidence, as explained above, indicates an increased risk of hyperglycemia-related adverse events and diabetes with Risperdal. In addition, this statement does not accurately describe the results of the cited studies. Two of the studies[1,8] actually show an **increased** risk of diabetes and hyperglycemia with Risperdal. In the first study, investigators found that the risk for diabetes in the risperidone cohort was higher than in the haloperidol cohort (HR 1.23, 95% 1.01 - 1.5). In

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[1] Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.

[2] Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.

[3] Fuller MA, Shermock KM, Secic M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043.

[4] Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335.

[5] Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171.

[6] Gianfrancesco FD, Grogg AL, Mahmoud RA et al. Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930.

[7] Koro CE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-245.

[8] Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

the second study, for patients less than forty years old, olanzapine, clozapine, quetiapine and risperidone were all associated with a statistically significant increase in risk for diabetes. Thus, the cited studies as well as the complete "body of evidence" supporting the labeling change are misrepresented in the DHCP letter.

FDA is not aware of substantial evidence or substantial clinical experience to support Janssen's claim that "Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics." If you have data to support this claim, please submit them to FDA for review. FDA is unable to conclude, based on unpublished and published studies, whether the differences in results represent true differences in risk for diabetes mellitus among drugs or are due to limitations in the study designs or in some cases, the limited sample sizes examined. FDA's conclusion regarding the lack of evidence to support a ranking of risk among the atypical antipsychotics is reflected in the following statement from the Warnings section of the PI for Risperdal: "Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available."

Failure to Submit Post-Marketing Reports

The DHCP letter was not submitted to FDA on Form FDA 2253 at the time of initial dissemination, as required by the post-marketing reporting requirements (21 CFR 314.81 (b)(3)(i)).

Conclusions and Requested Actions

The DHCP letter misleadingly omits material information about Risperdal, minimizes potentially fatal risks associated with the drug, and claims superior safety to other drugs in its class without adequate substantiation, in violation of Sections 502(a) and 201(n) of the Act (21 U.S.C. §§ 352(a) and 321(n)).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Risperdal that contain claims the same as or similar to those described above and provide a plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials. Please submit a written response to this letter on or before May 3, 2004, describing your intent to comply with this request, listing all promotional materials for Risperdal that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12195 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Risperdal, and may determine that additional measures will be necessary to fully correct the false or misleading messages resulting from your violative conduct. It is your responsibility to ensure that your promotional materials for Risperdal comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications

Cc: William C. Weldon
CEO
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.

JANSSEN PHARMACEUTICA INC.

November 10, 2003

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-3] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Ramy Mahmoud, MD
Vice President CNS Medical Affairs
Janssen Pharmaceutica, Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
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References:

1. Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.

2. Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.

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