# 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

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

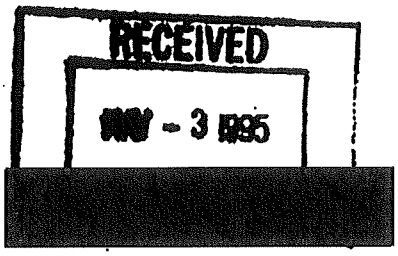
DEPARTMENT OF HEALTH & HUMAN SERVICES

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.

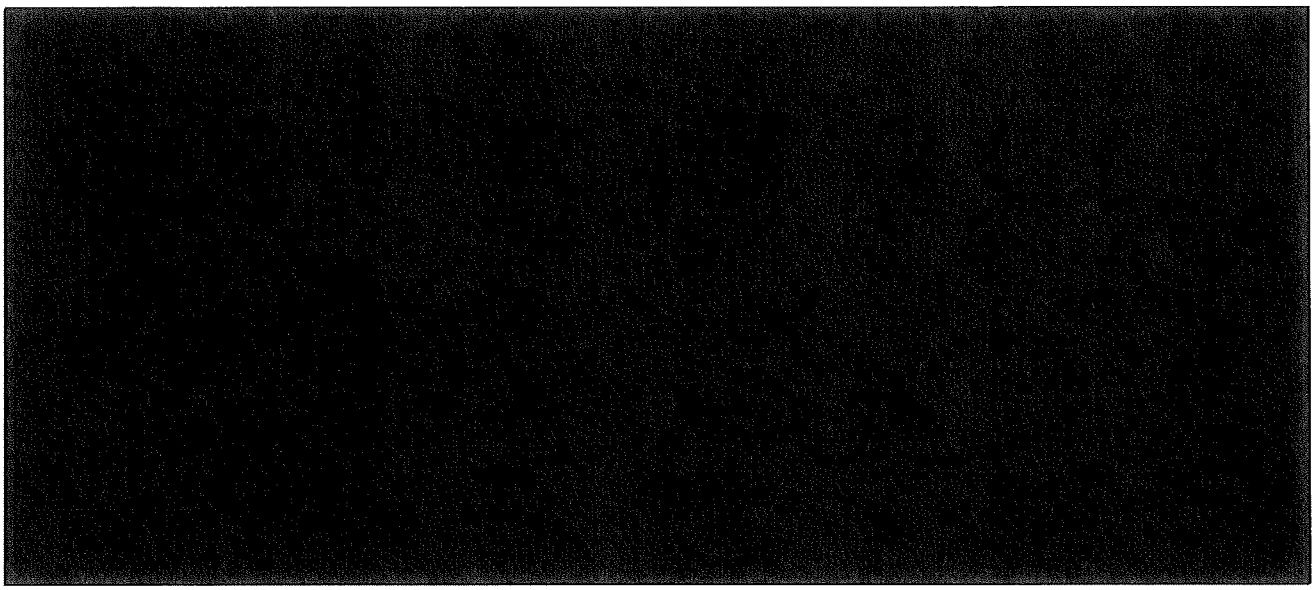
In conclusion, the trial you propose cannot provide results that would, on their own, serve as a basis for expansion of the claimed indications for the use of Risperdal, nor would they be sufficient to serve as a basis for any other substantive modification of current product labeling. However, the results 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,

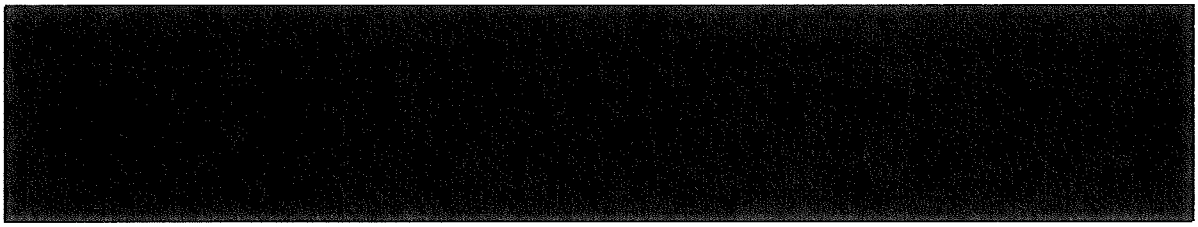
Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

# EXHIBIT 3



**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.



# EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

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]



Janssen
NDA 20-272 (MACMIS 6908)

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.

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, 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:**
**Cc:** [redacted]
**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.

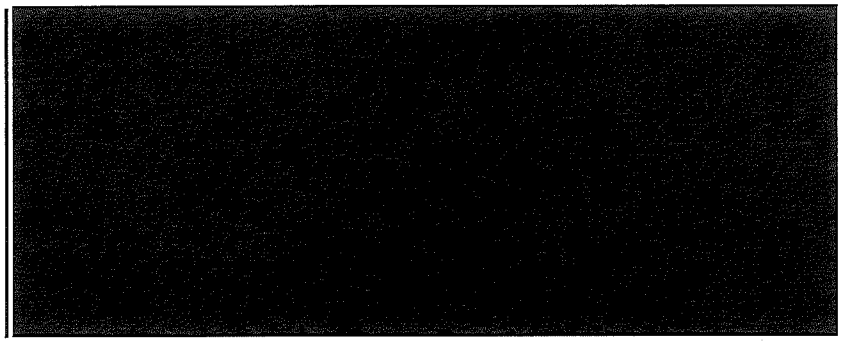
Ivo

[redacted]

# EXHIBIT 7

# Risperdal in BPSD

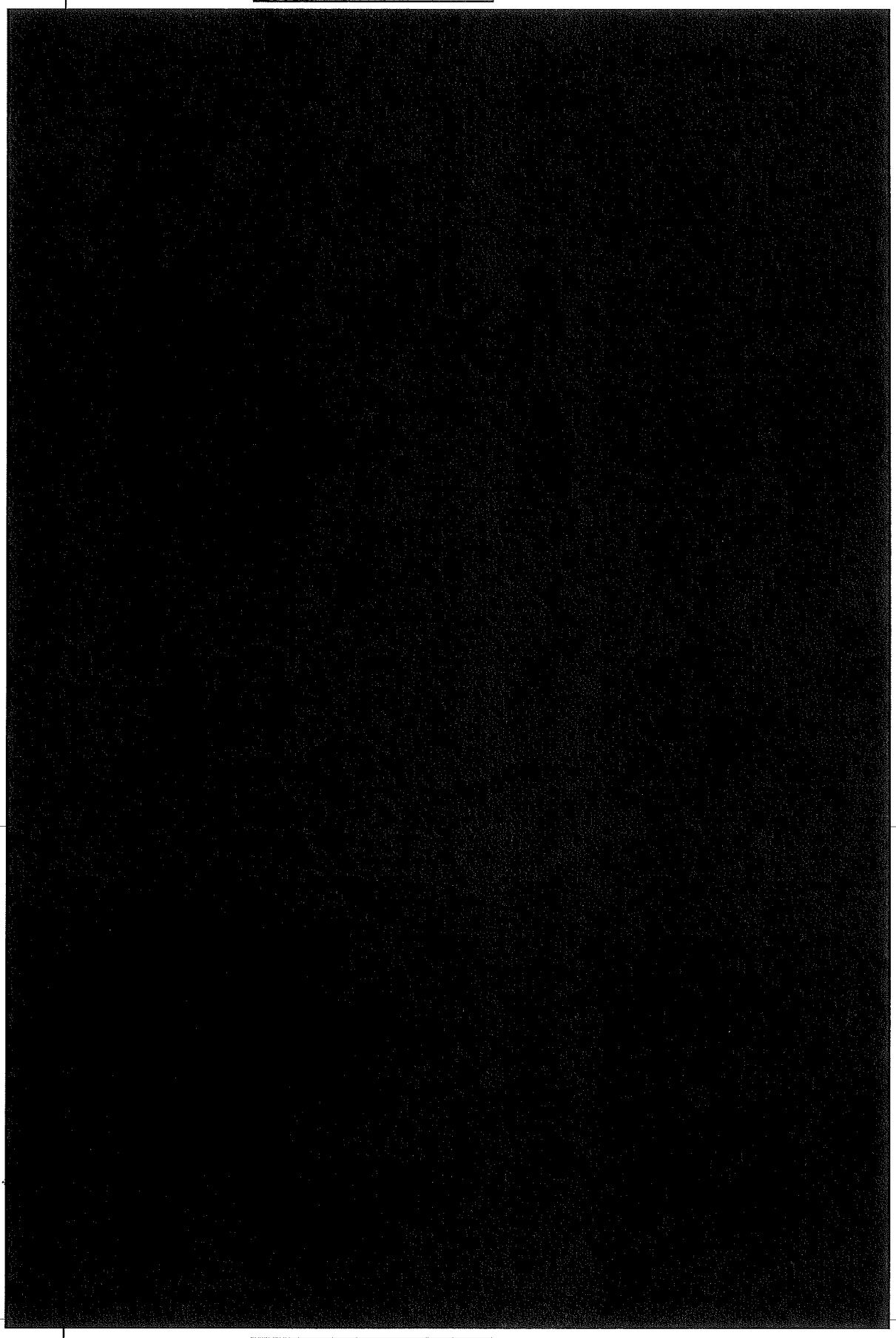
The BPSD project shall be terminated as ethically, legally and quickly as possible. The team should prepare a DCC presentation in the implications of exit.



# 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

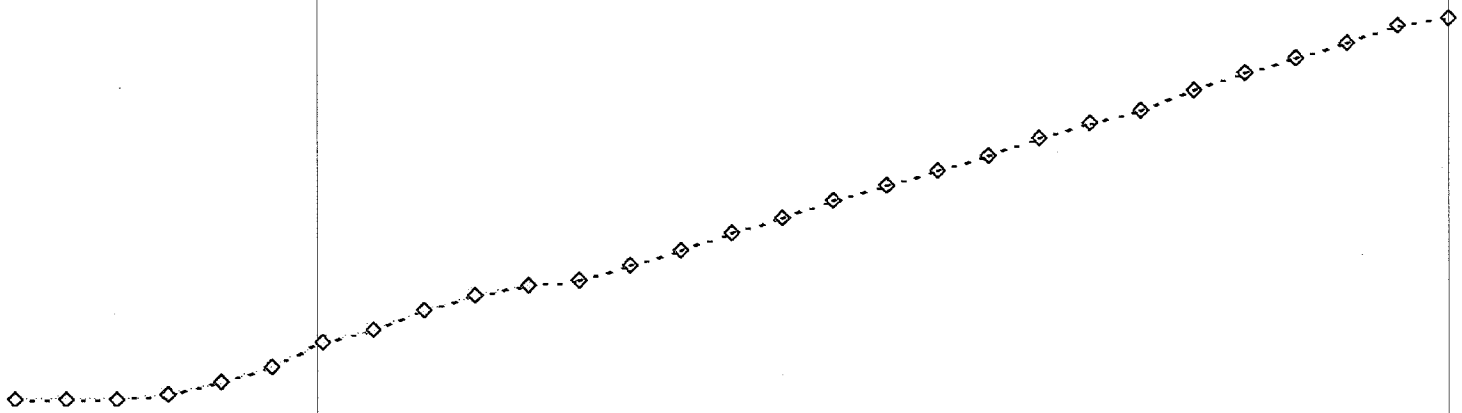
Aug 01: CVA document and proposed label change submitted to FDA

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
  - ➢ 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

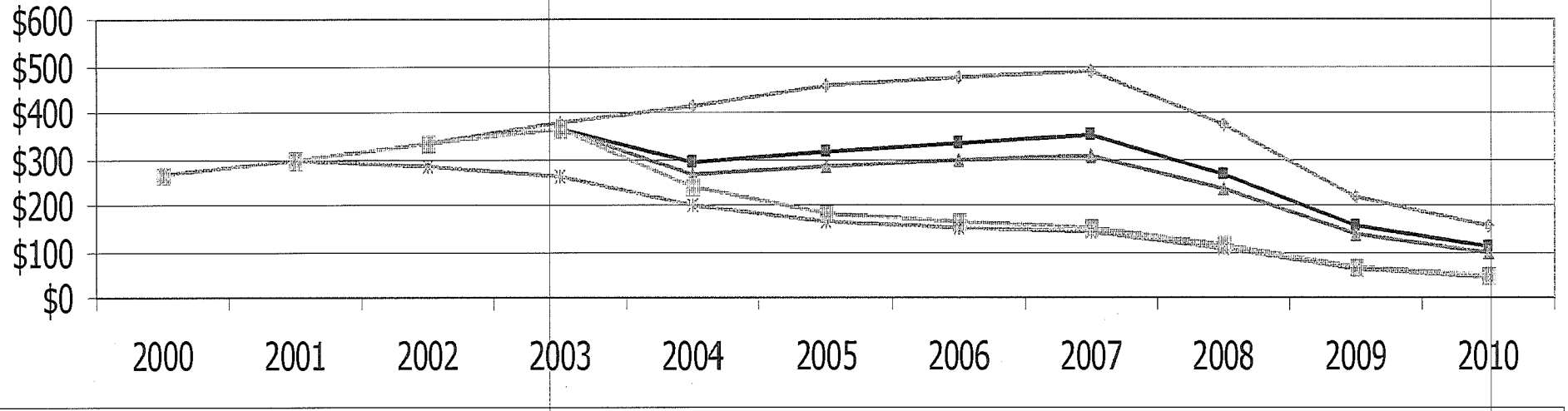
- **Credibility with FDA:** As the leader Janssen was 1st to file; prompted March Ad Board; led debate/discussion. Abrupt cancellation may be questioned.
- **Label at risk:** CVA observation remains unresolved with increased risk for unfavorable label that will impact entire brand.
- **FDAMA:** Must 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**

JANSSEN RESEARCH FOUNDATION

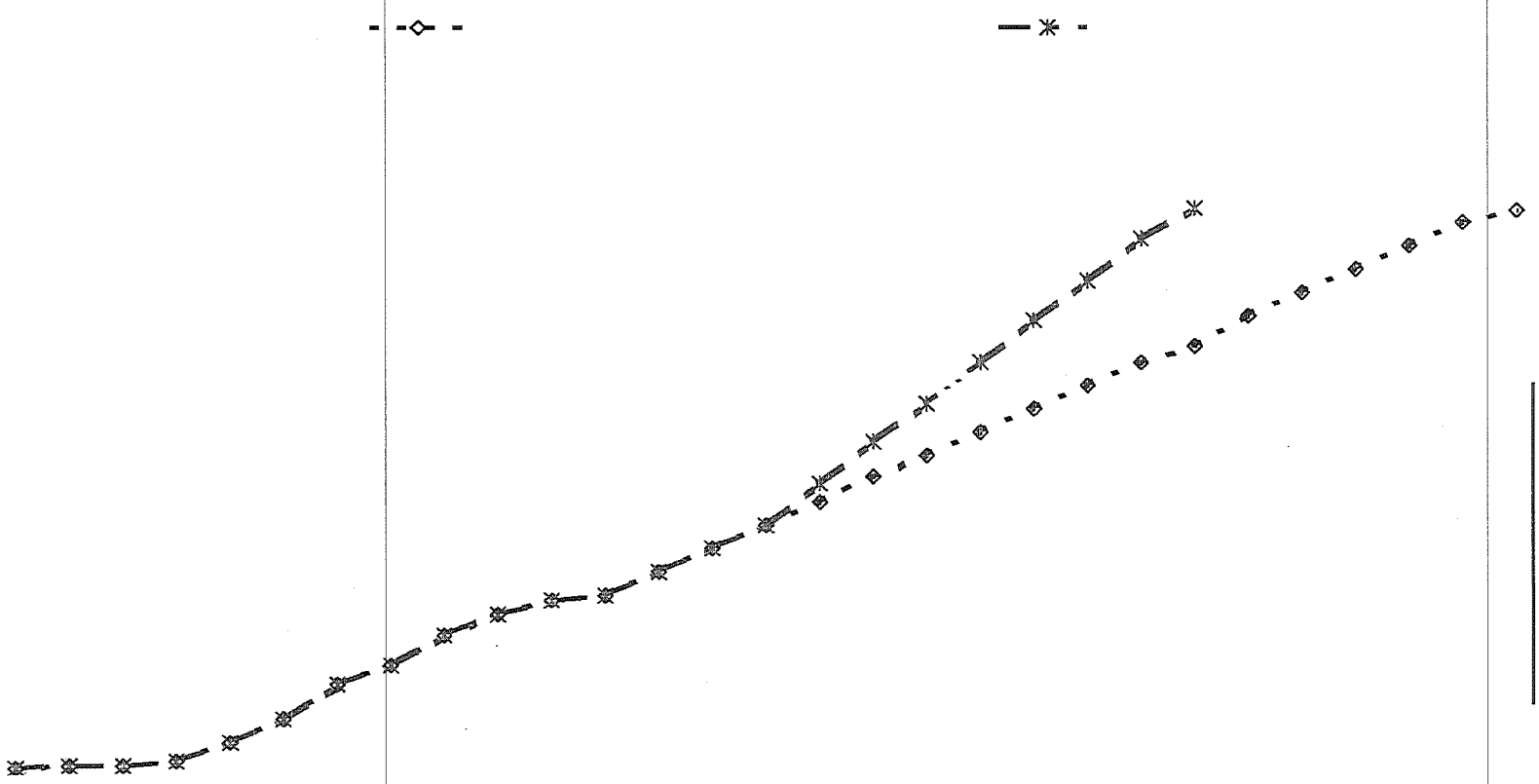
# Risperdal in BPSD - Alternative proposal

- 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...

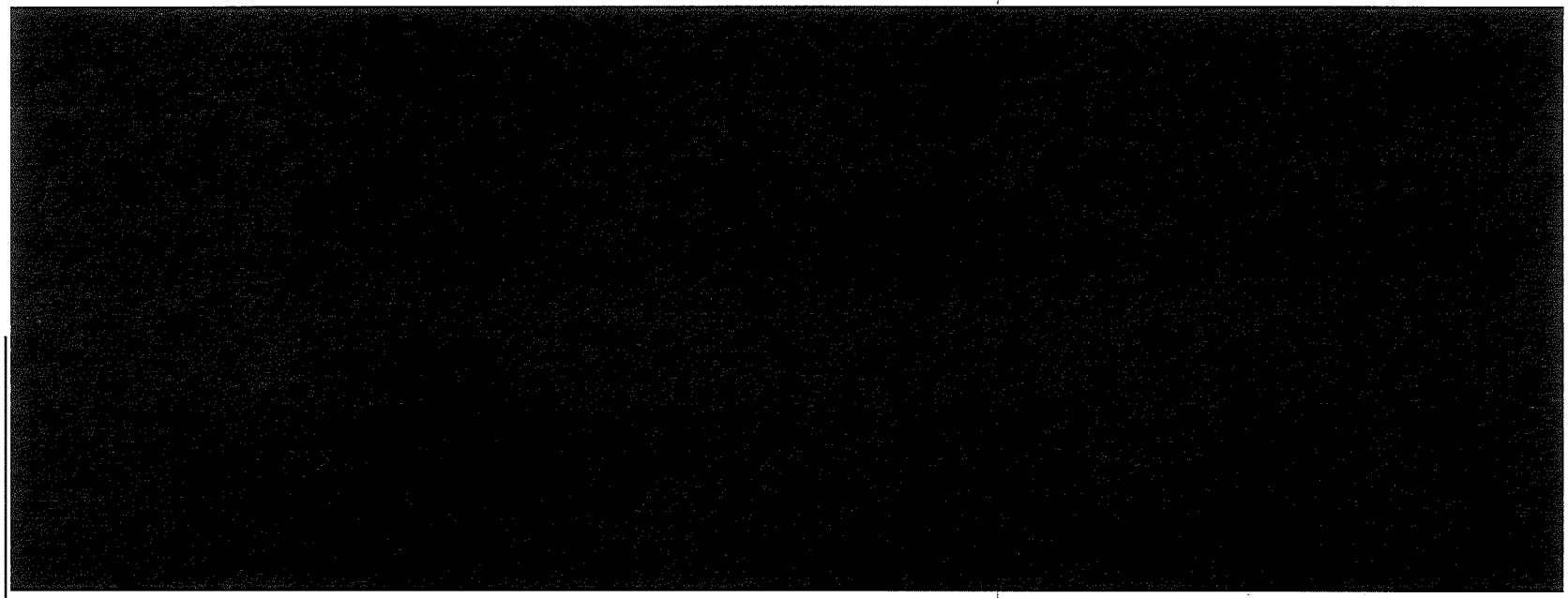
# Worst Case Label for CVA Data

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 must 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]

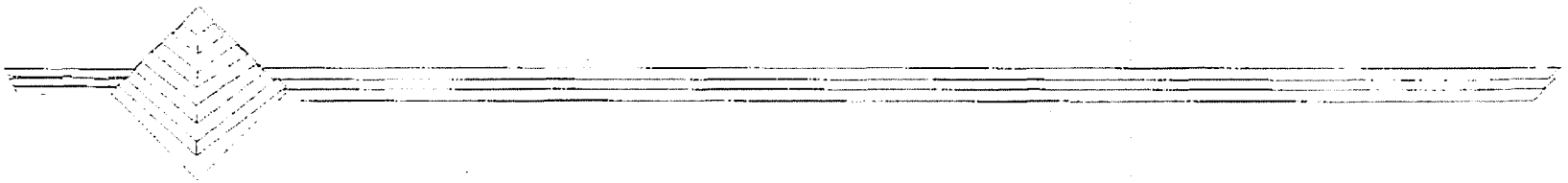
# EXHIBIT 10

# 1999

# RISPERDAL

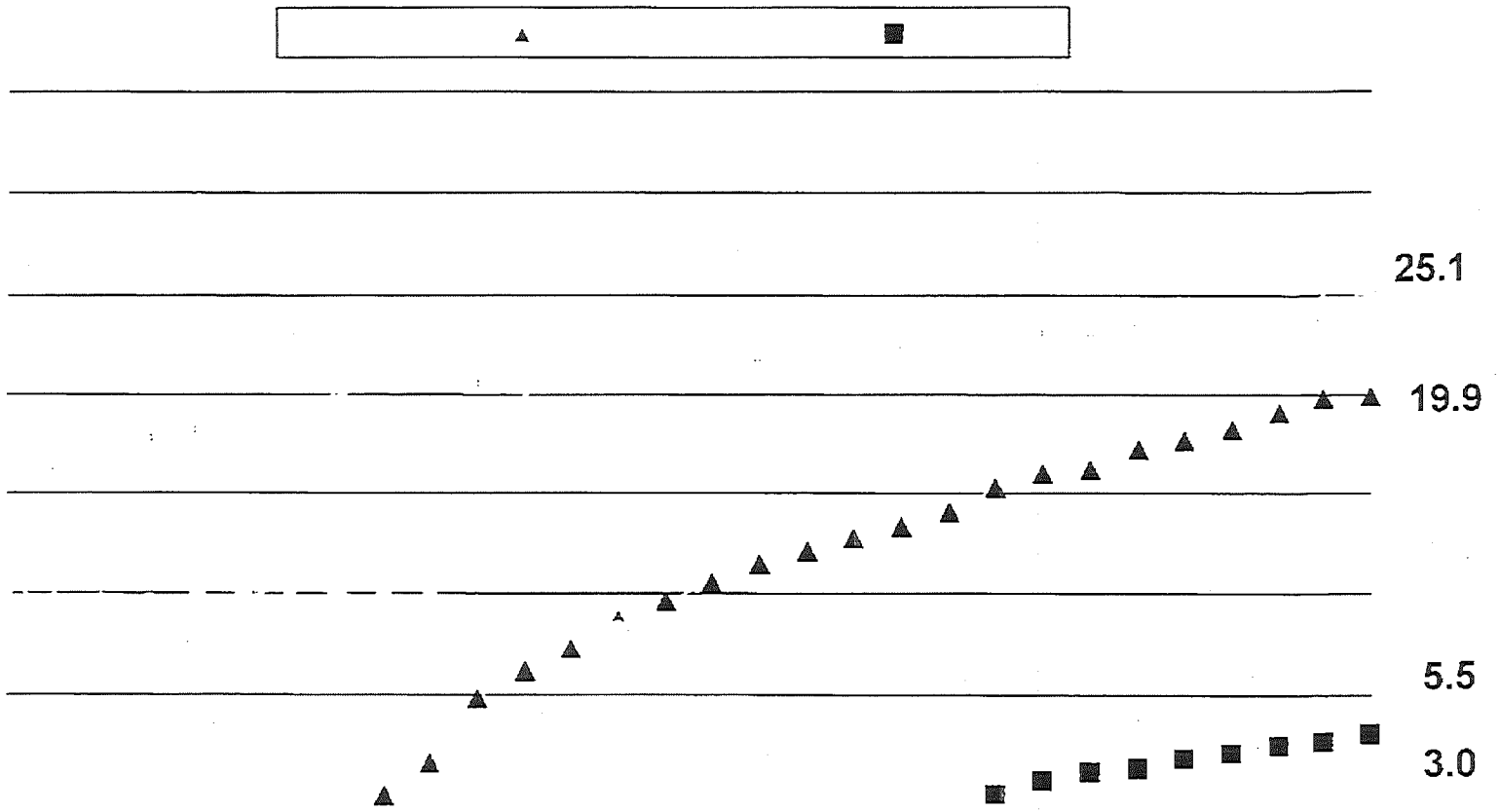
# Strategic Business Plan

# 1998 Critical Success Factors



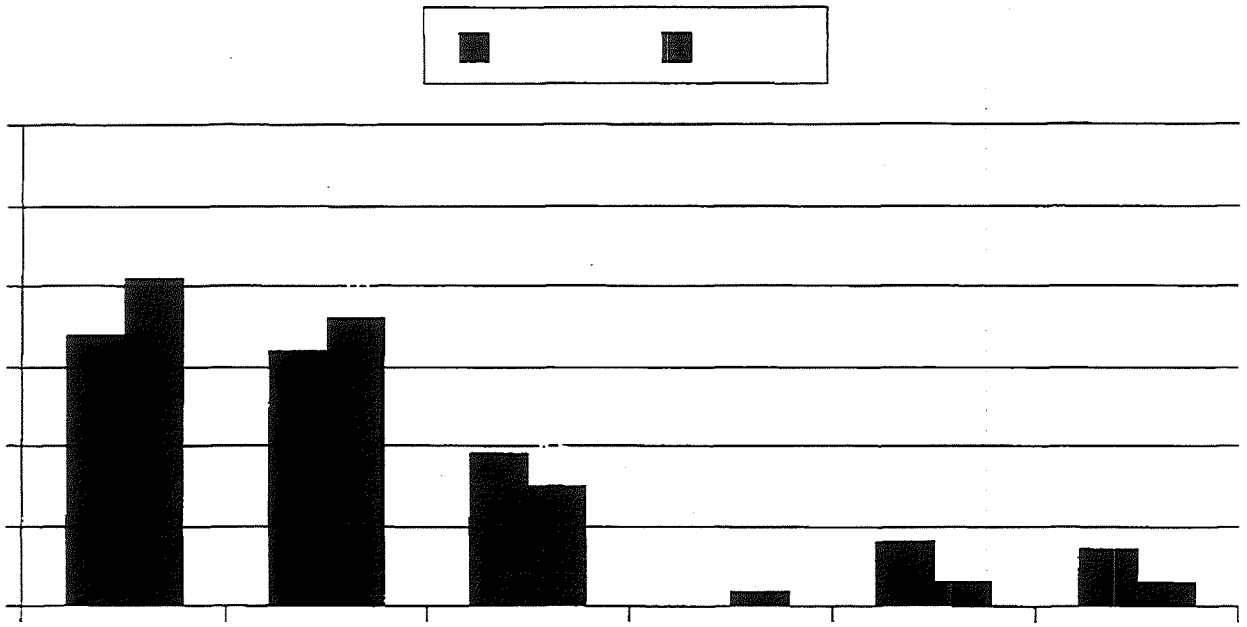
- Own Schizophrenia
- Stop the competition

# Antipsychotic NRx Share



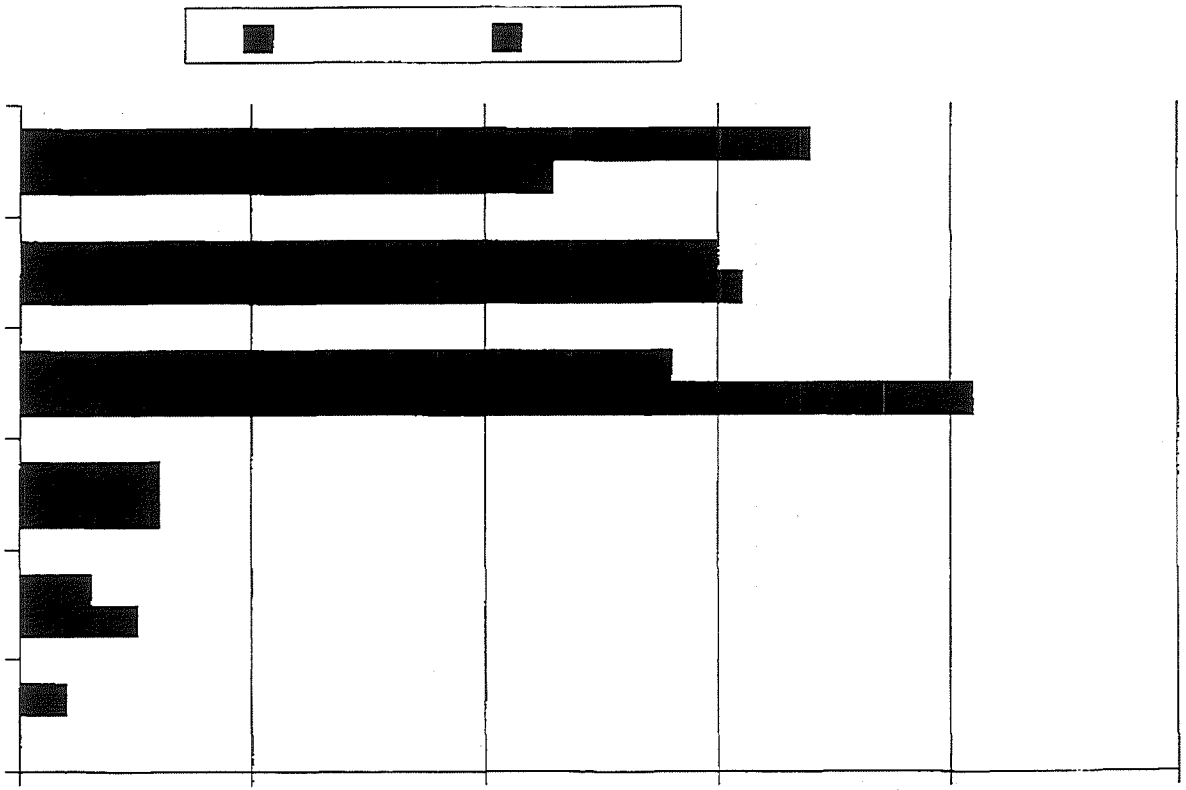

Source: NPA (IMS)

# Most Preferred Agent - Schizophrenia



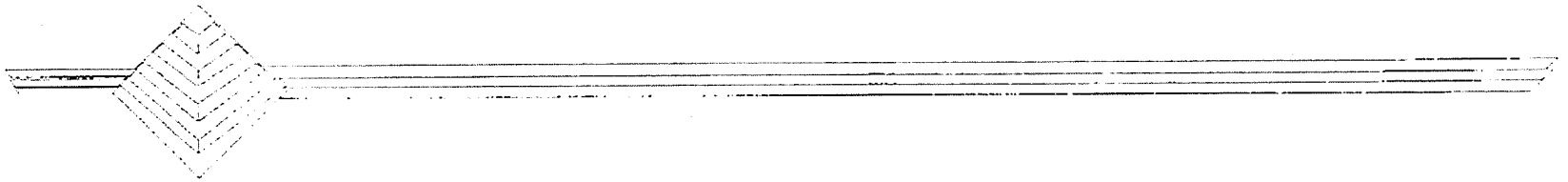
Source: 1998 Annual APA Survey, Hospital Research Associates

# Switching Preference from Conventionals



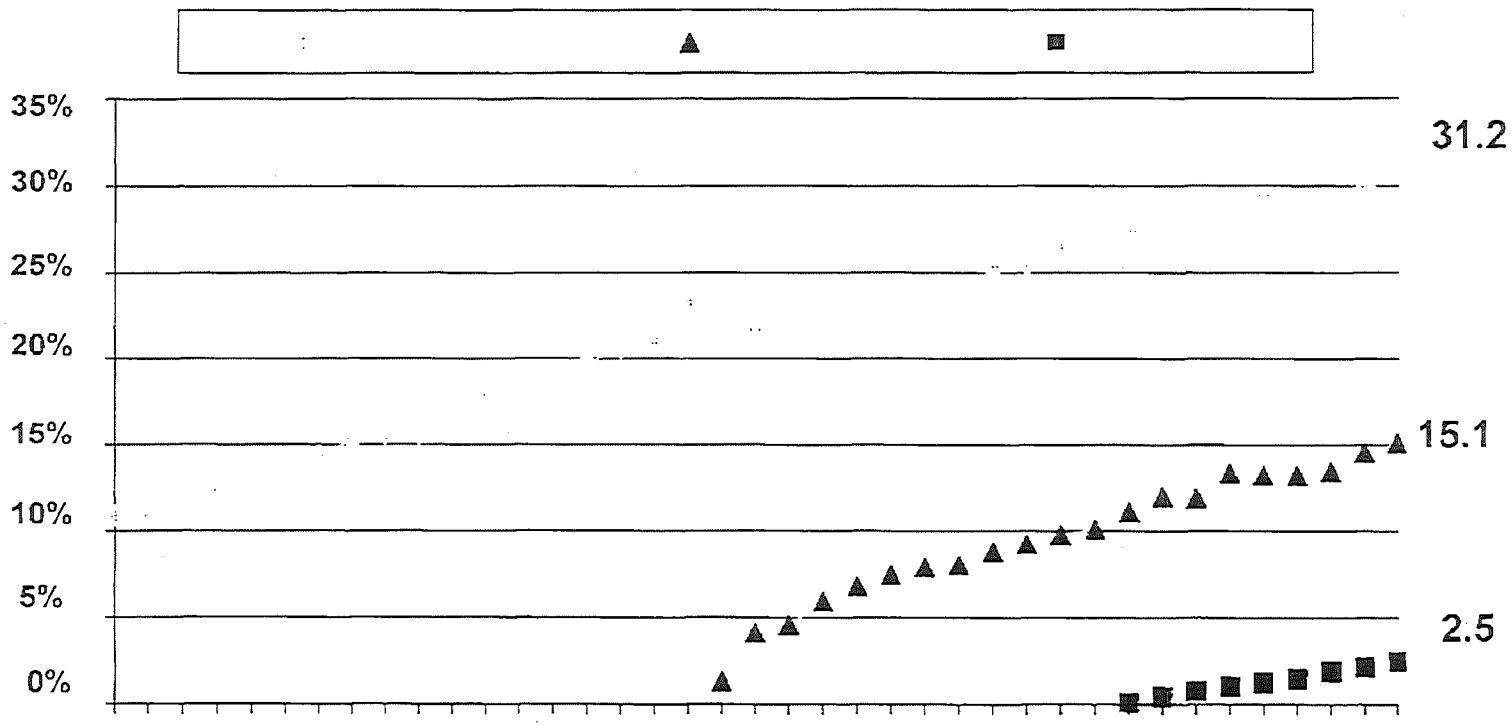
Source: 1998 Annual APA Survey, Hospital Research Associates

# 1998 Critical Success Factors



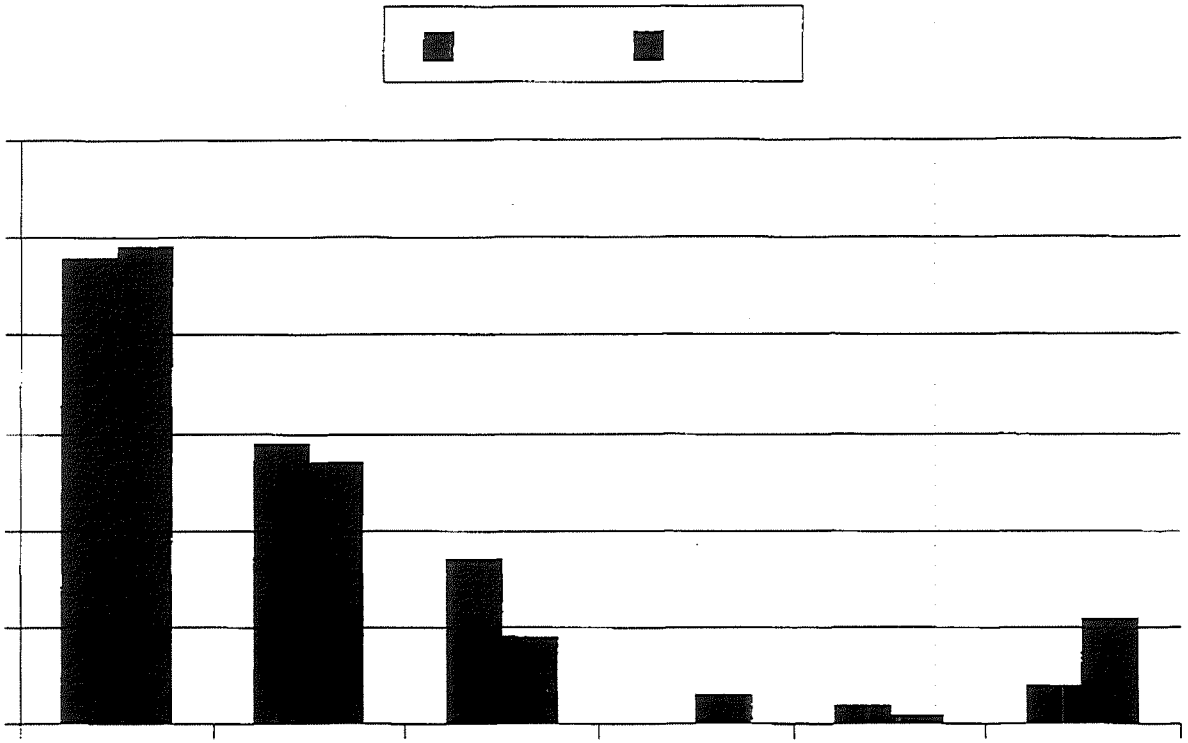
- Own Schizophrenia
- STOP the Competition
- Expand into New Markets

# Antipsychotic NRx Share LTC Market




Source: NPA Plus (IMS)

# Most Preferred Agent - Elderly



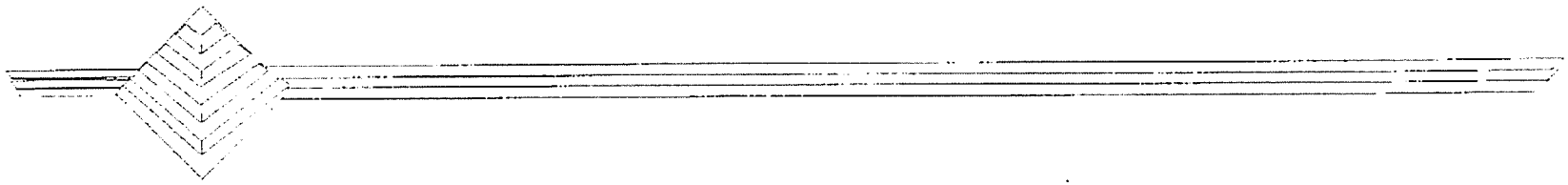
Source: 1998 Annual APA Survey, Hospital Research Associates

# 1998 Critical Success Factors

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

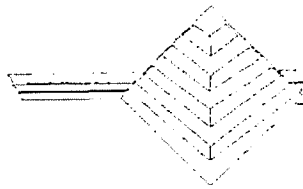
# Reimbursement Key Wins

# 1998 Critical Success Factors



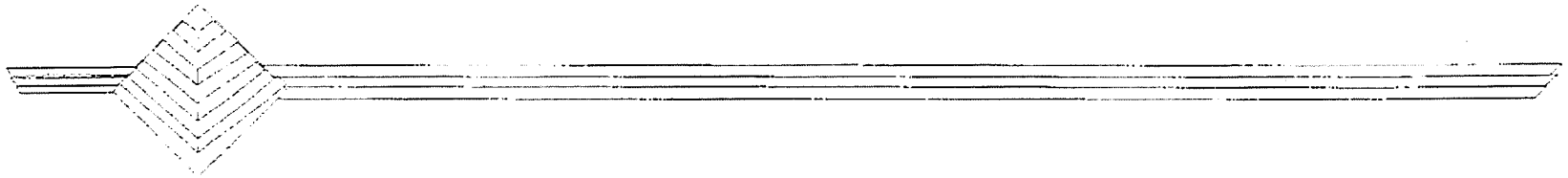
- Own Schizophrenia
- STOP the Competition
- Expand into New Markets
- Maximize Reimbursement Opportunities
- Optimize Teamwork

# 1998 Lessons Learned
# RISPERDAL - Base



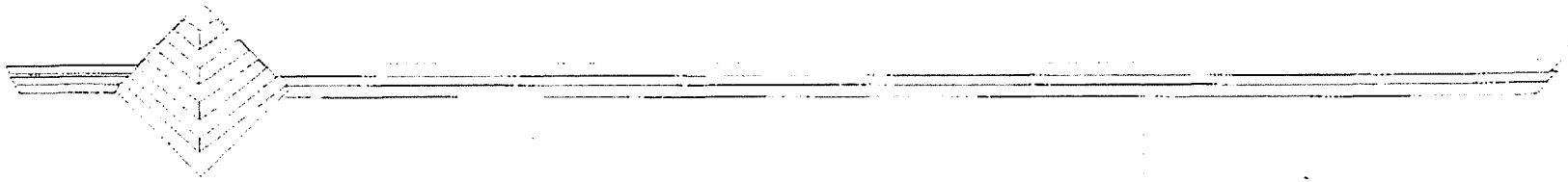
# __ JANSSEN CAN WIN!!!

# Strategic Vision
# RISPERDAL - Base



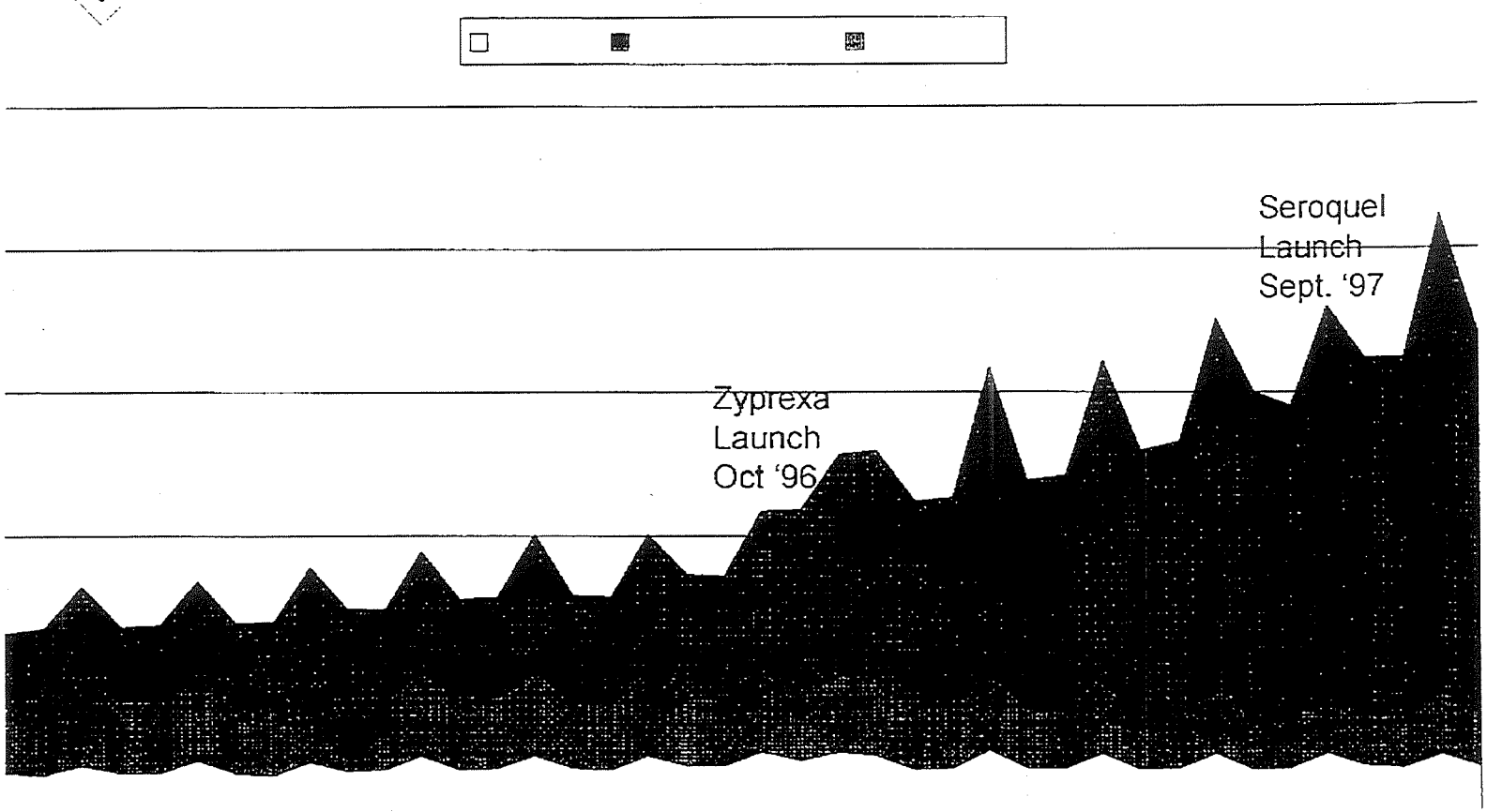
To be the first-line antipsychotic for the treatment of both psychotic and non-psychotic disorders

# Strategic Vision
# RISPERDAL - Geriatrics

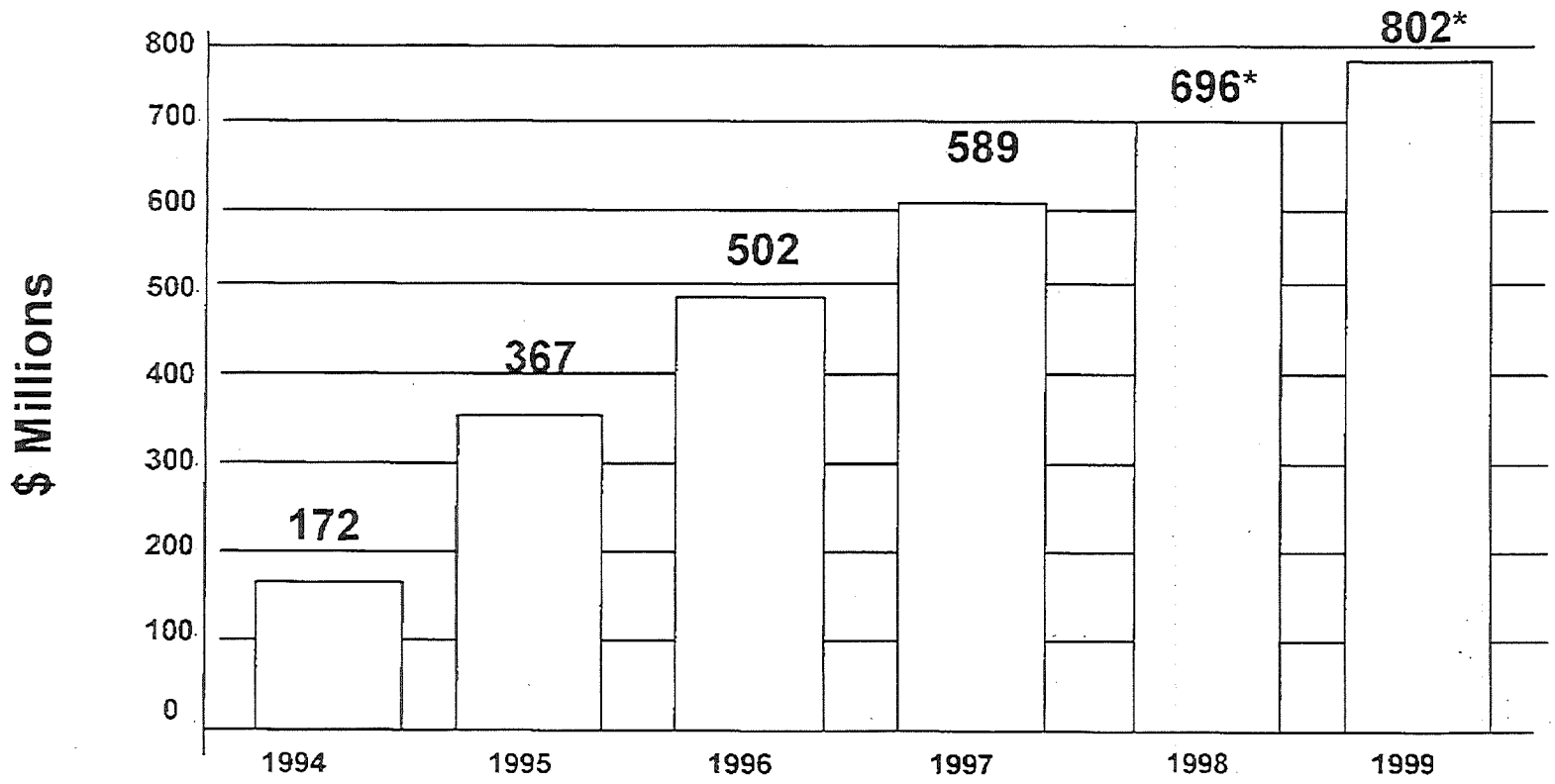


To be the product that healthcare professionals, families and caregivers rely on to treat late life mental disorders

# APS Market Total Sales Volume



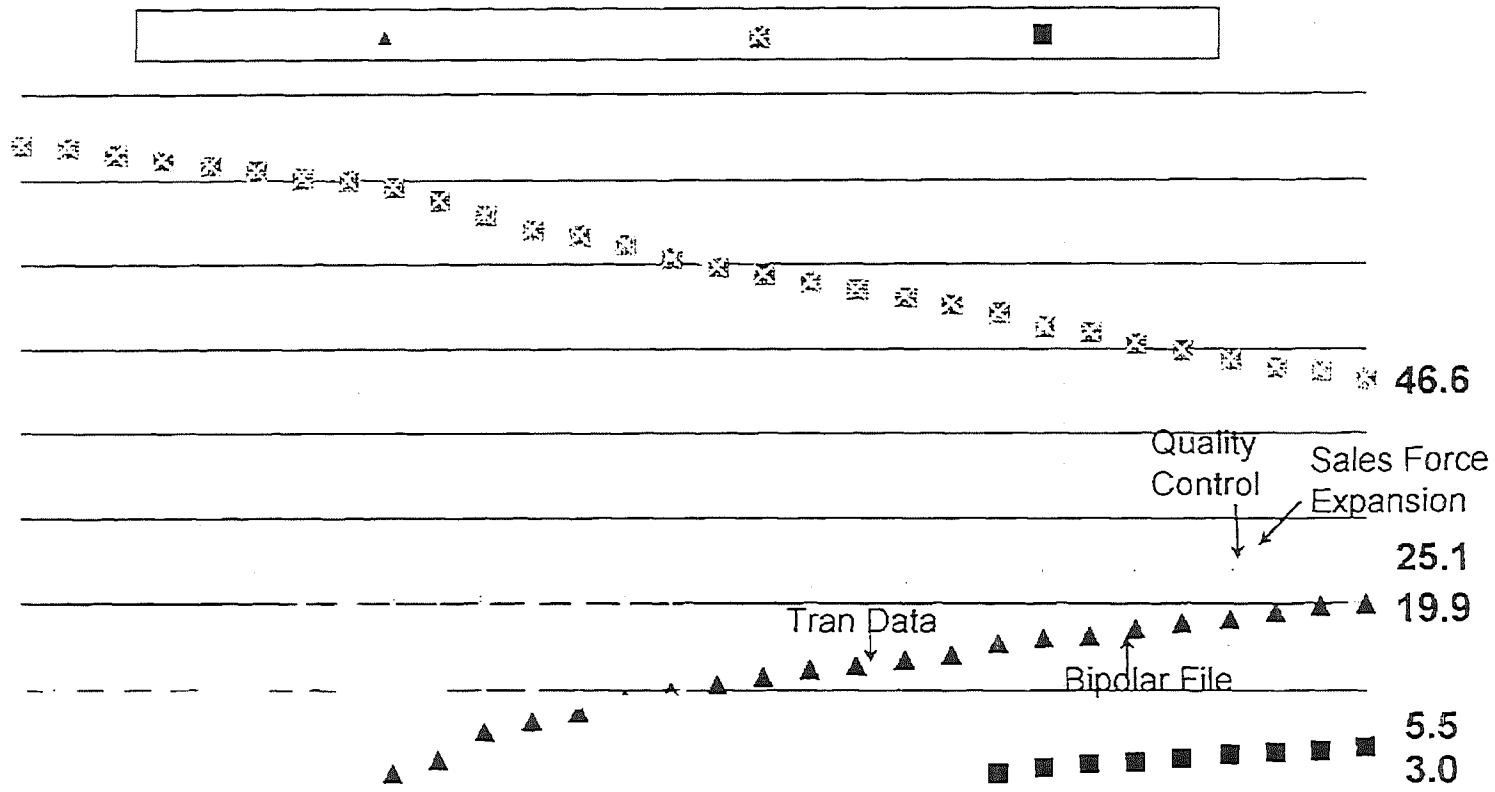
# RISPERDAL Annual Sales




* Projected

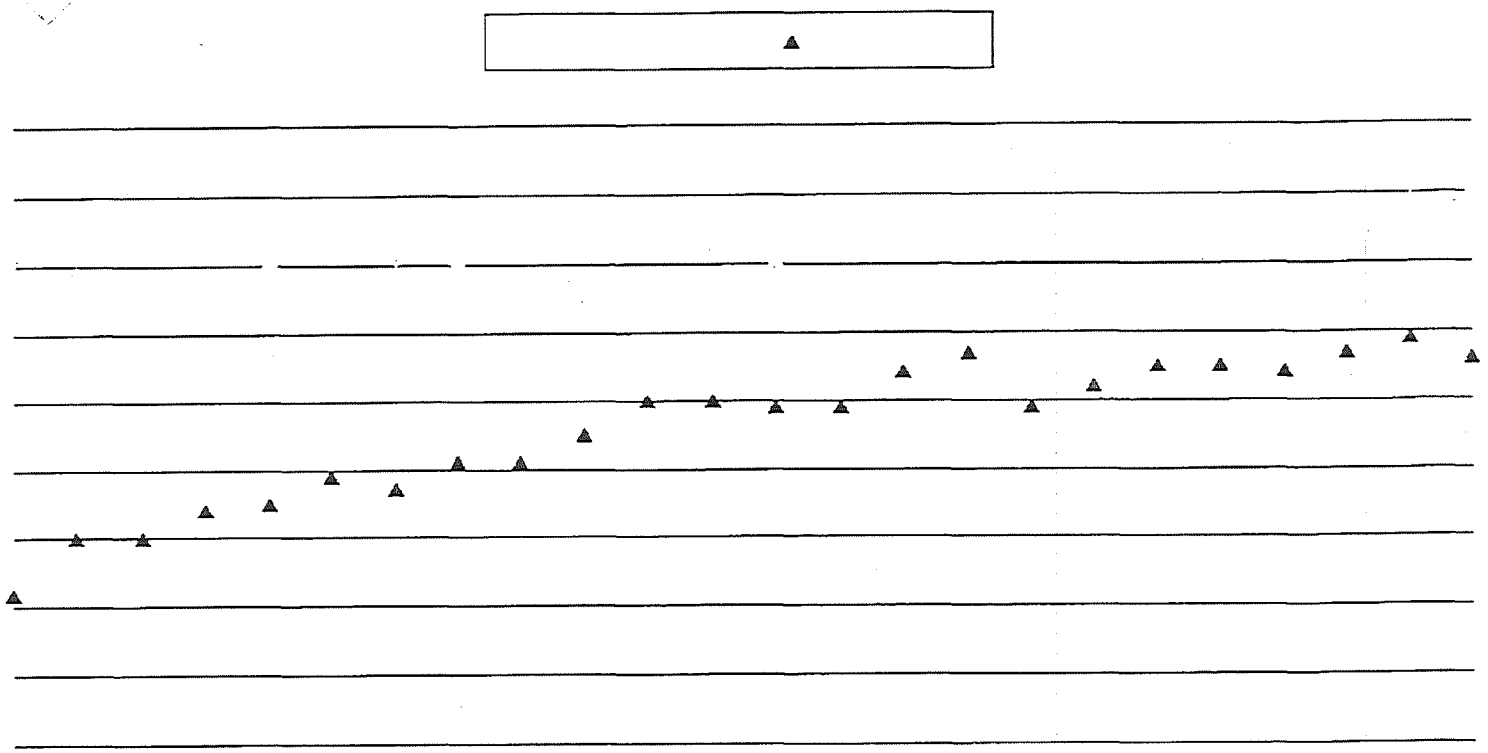
Source: Audit Sales

# Antipsychotic NRx Share



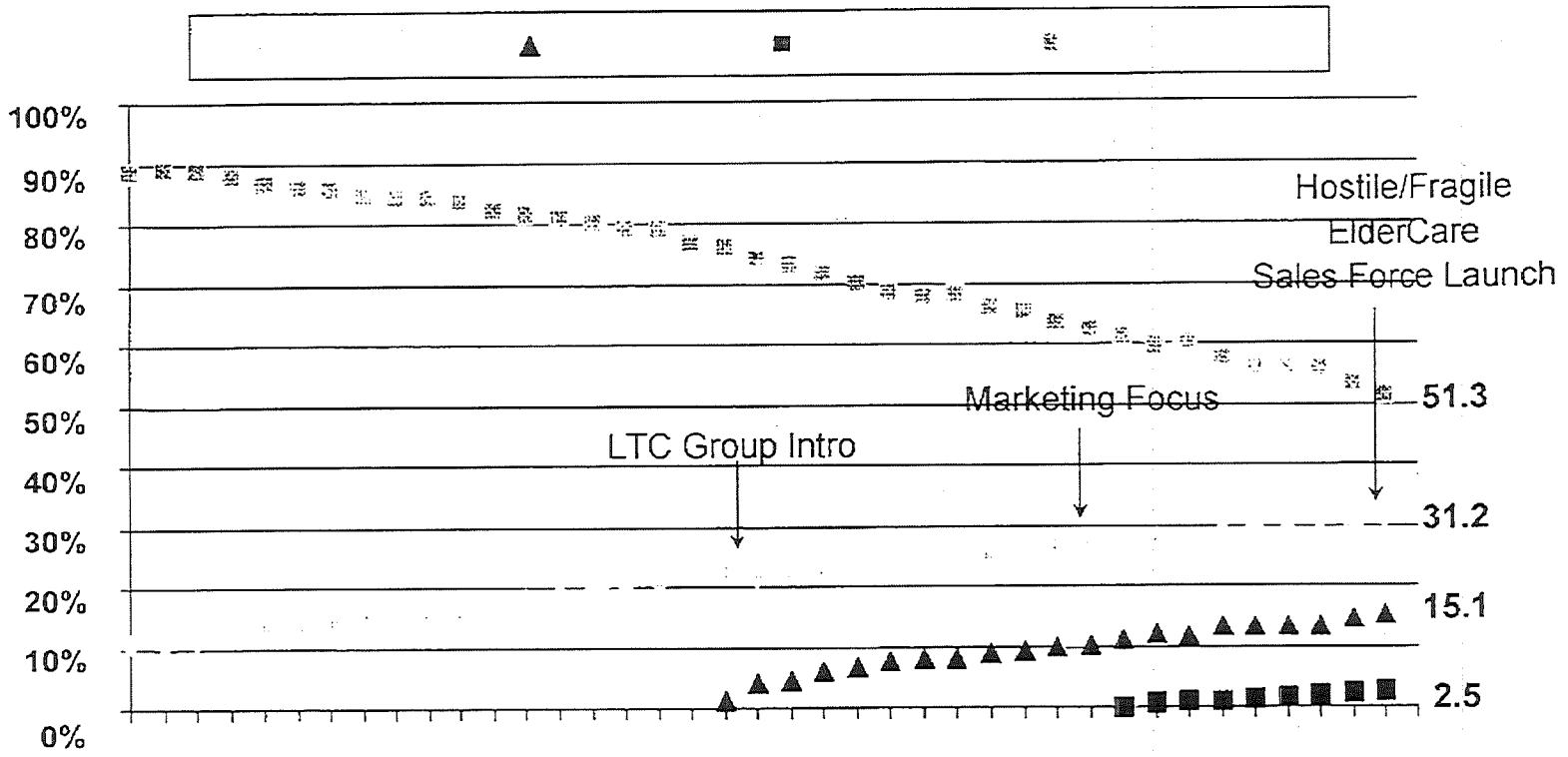

Source: NPA (IMS)

# NRx Share - Weekly



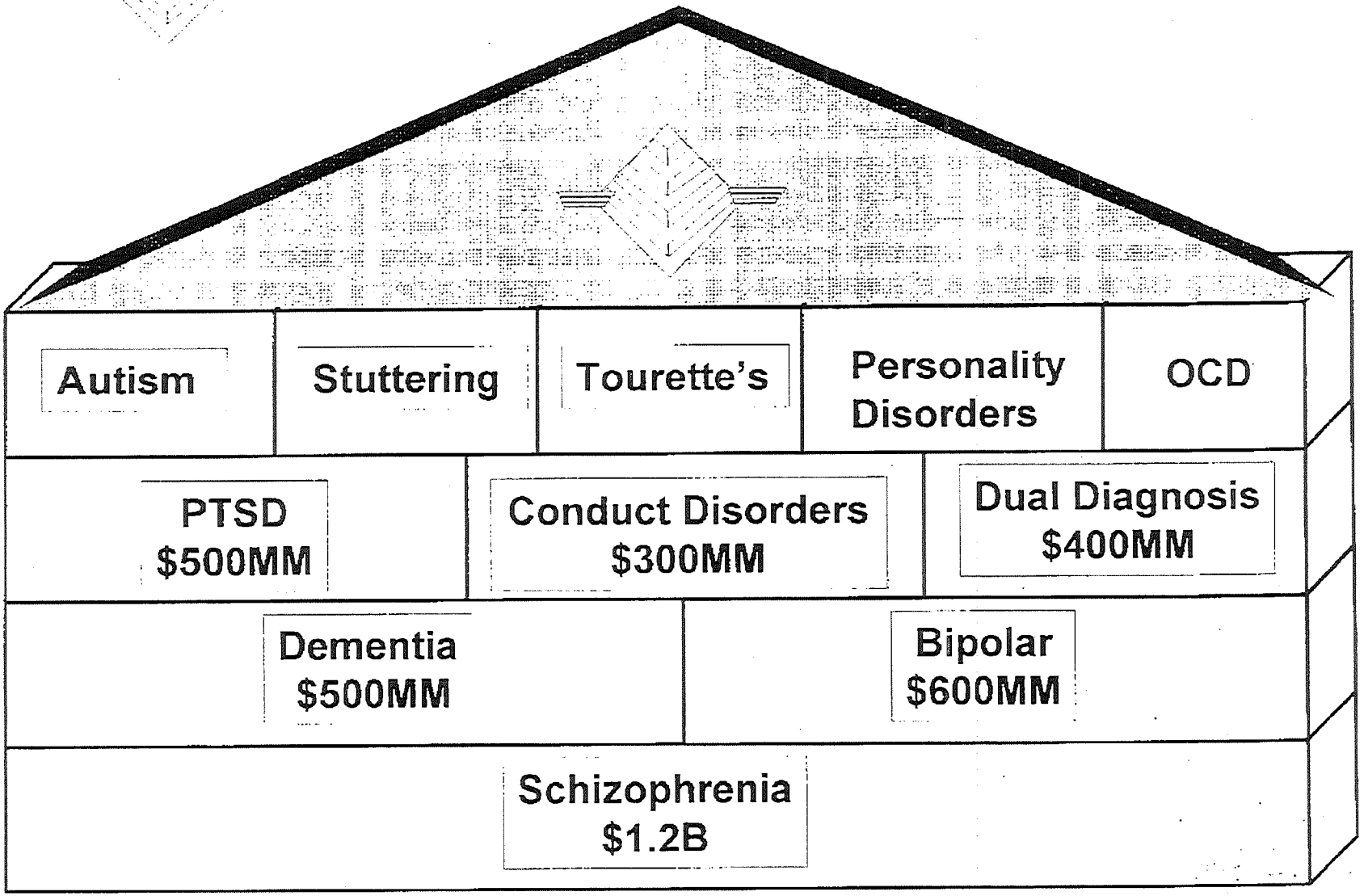
Source:: IMS Weekly (National) Market defined as USC5=64110 & 64190

# Antipsychotic NRx Share LTC Market

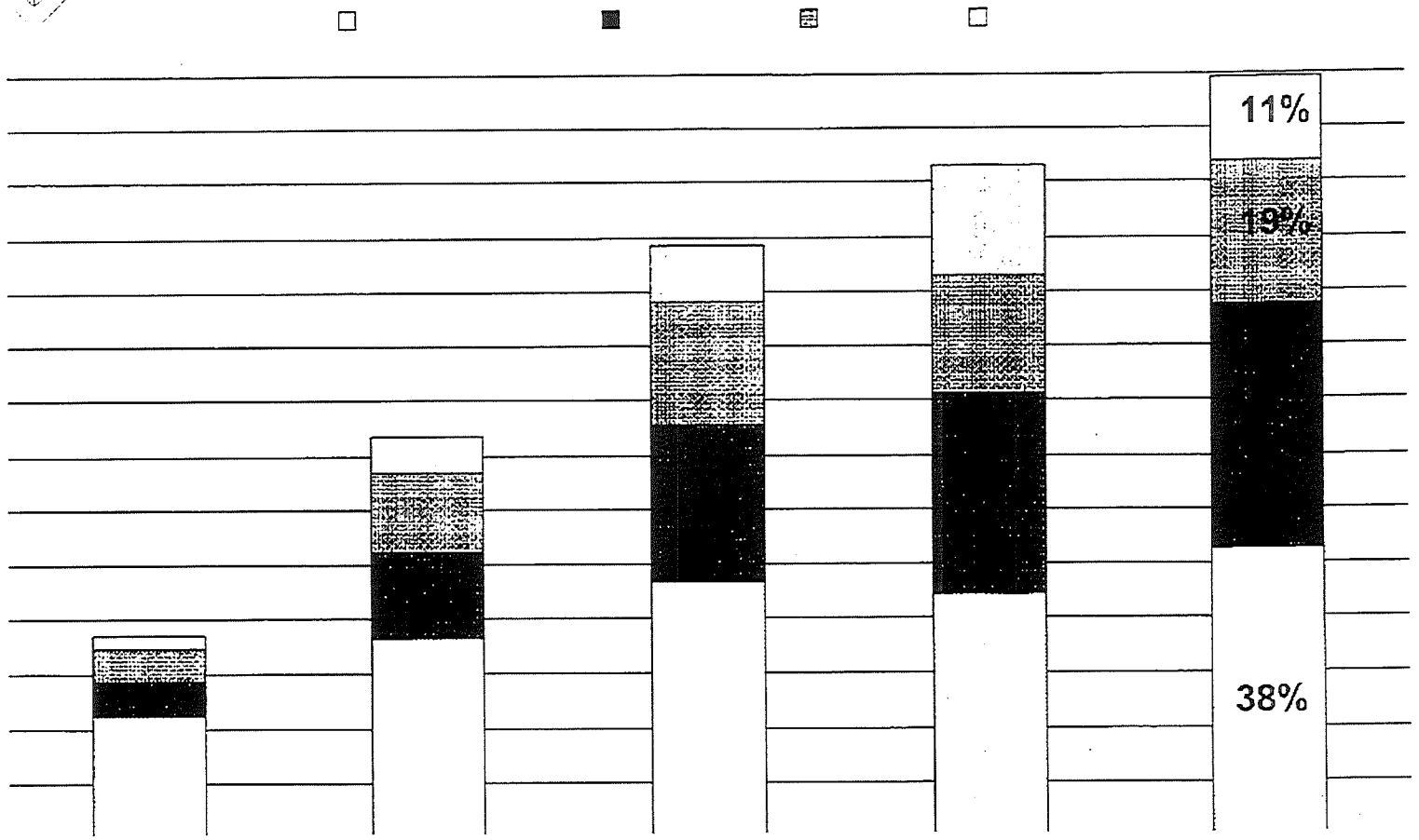



Source: NPA Plus (IMS)

# Antipsychotic Potential

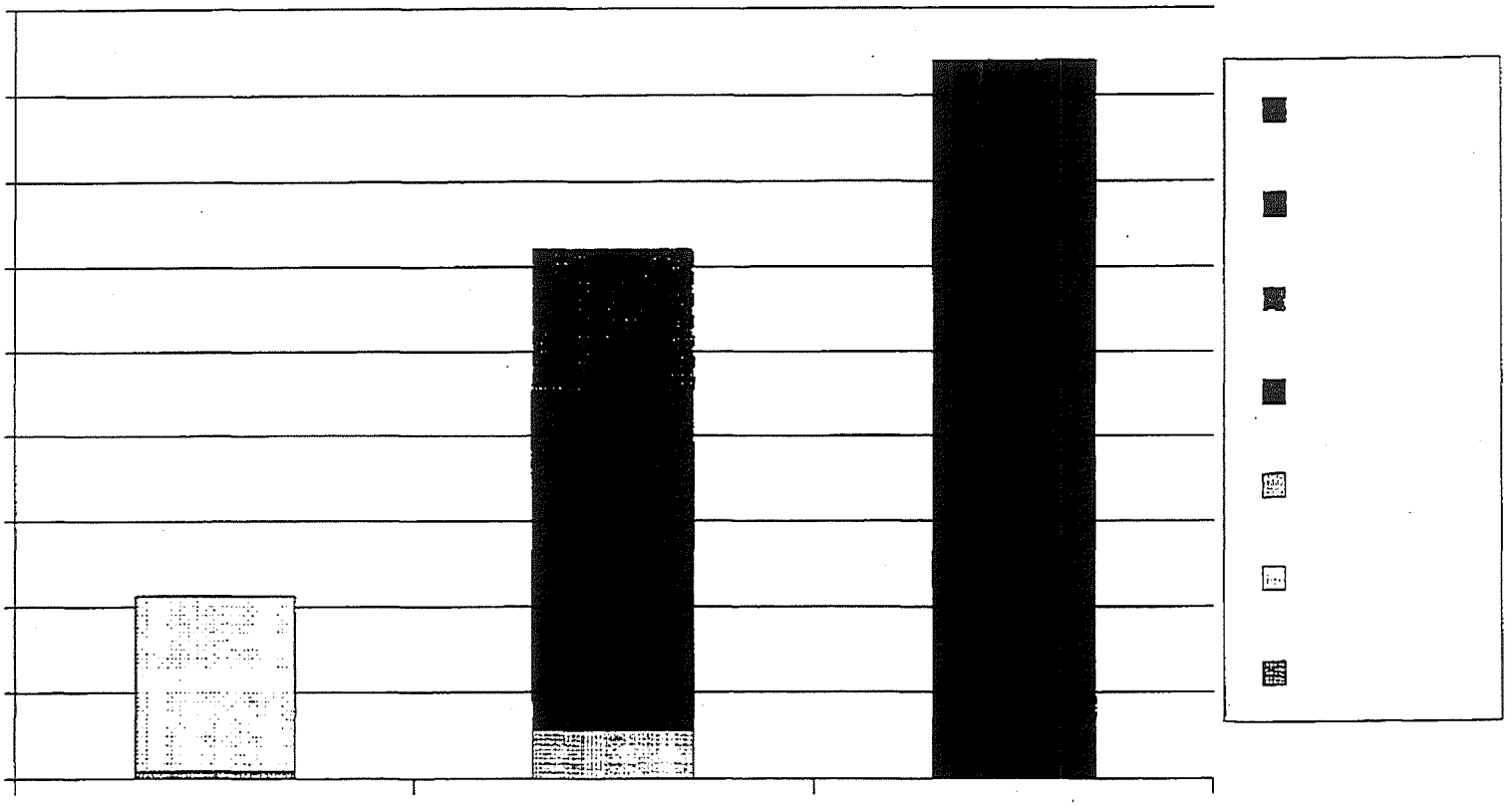


# RISPERDAL Dollar Volume by Diagnosis




Source: IMS NDTI and NPA Plus Audits * YTD Sales

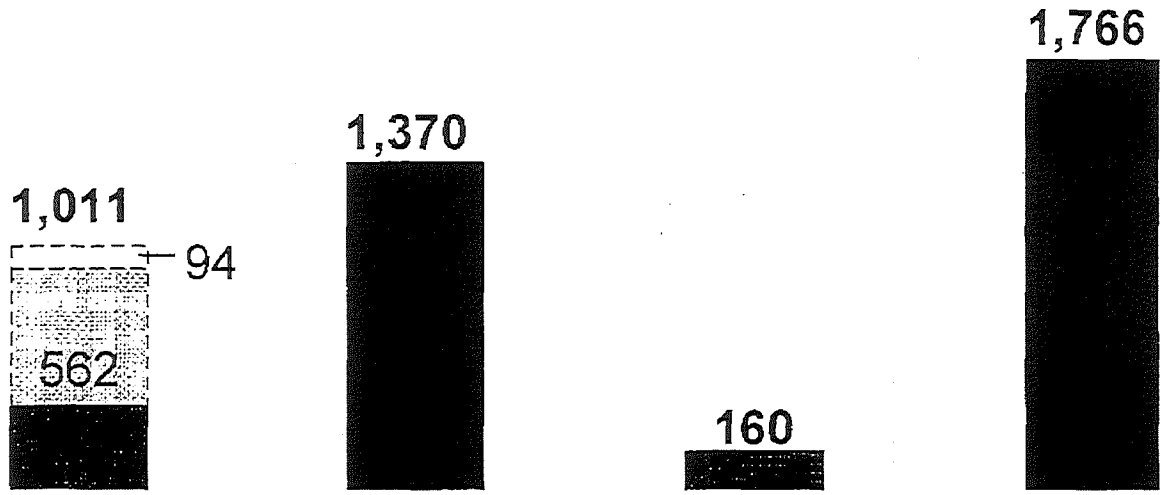
# CNS Portfolios



*Estimated Sales - first 12 months

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

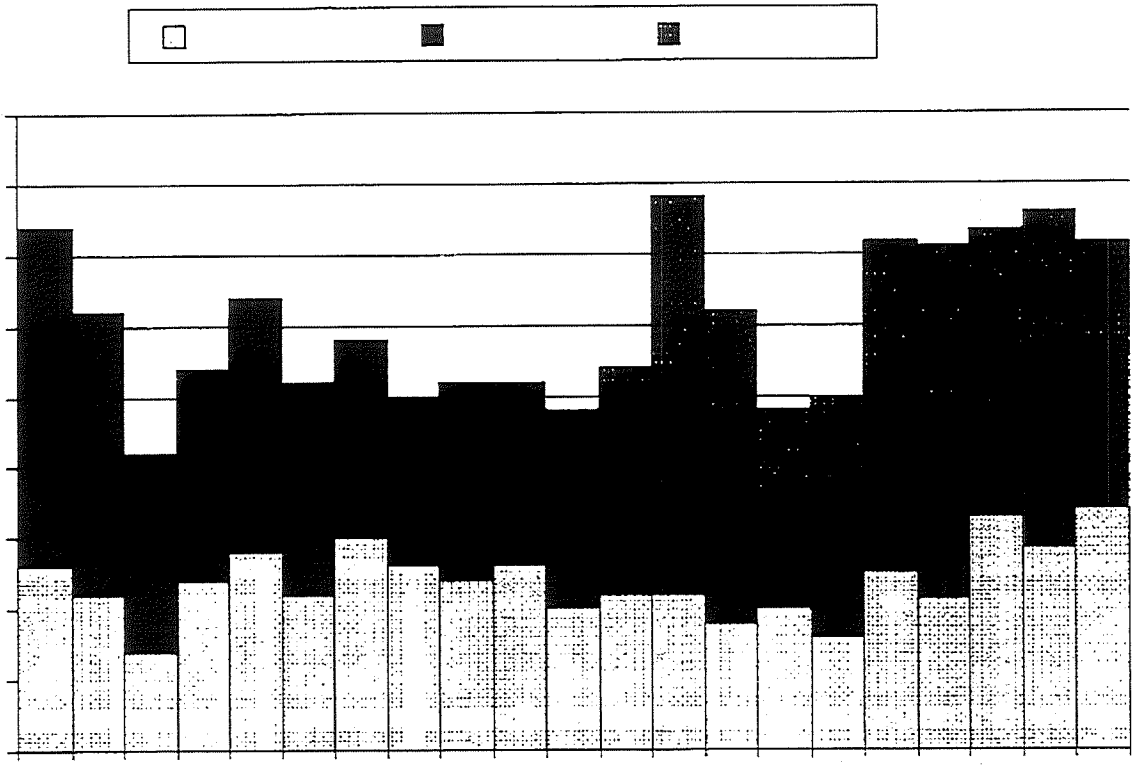
# CNS Sales Force Capacities




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 | 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

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)

**RISPERDAL**
**2000 BUSINESS PLAN**

## 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<br><br>POC Approval | Depot (2-wk formulation) | Bipolar Monotherapy | Depot (4-wk formulation) |
| Label Changes<br>New Indications<br><br>New Data | Dementia Labeling<br><br>Stuttering Data<br>Dual Diagnosis Data<br>Glucose Metabolism Data<br>Long-term<br>Conduct Disorder | Acute Mania<br>Bipolar (adjunctive therapy Labeling)<br>Maintenance Label | Conduct Disorders | | Palmitate |

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

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## 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 ndt 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<br>Relapse prevention data (RIS-79)<br>New data Vs Zyprexa (RIS-112)<br>Rapid onset of action<br>Low weight gain<br>QD dosing<br>Low TD<br>Low anticholinergic effects<br>Low sedation | Publication Volume<br>Dose-Dependent EPS<br>Perceived TD liability (EPS)<br>Prolactin elevation<br>Perception of more complex dosing<br>Breadth/number of speakers |
| **Opportunities** | **Threats** |
| Acute care setting<br>Psychiatric Residents<br>Low cost/changing reimbursement environment<br>Opinion leaders | WLF ruling<br>Zeldox (ziprasidone launch) tablets and IM formulations<br>Zyprexa "Zydis" (quick-solv) and IM formulations<br>Growth trend of Seroquel<br>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)<br>Market leadership<br>Performance based contracts<br>J&J LTCM/ElderCare team<br>Availability of dosing options | EPS at ≥ 2mg/day<br>Physician/customer targeting due to data<br>Delay in label change for RISPERDAL<br>No switching or 'head-to-head' data<br>Dosing confusion<br>OBRA<br>Orthostatic hypotension |
| **Opportunities** | **Threats** |
| RIS-OLZ Dementia Trial<br>Additional 'pull-through' programs<br>REMINYL synergy<br>OL/association relationships<br>WLF<br>AUS-5 Study | Dementia label for Zyprexa<br>Dementia label denied for RISPERDAL<br>Competitive sales force expansions<br>Zeldox/Aricept/Zoloft synergy<br>Seroquel geriatric focus<br>AChE, AC & ADP use<br>PPS<br>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<br>Low weight gain<br>Cost advantage vs. Zyprexa<br>Faster onset of action vs. mood stabilizers<br>"Improves quality of life"<br>RIS-USA-112 Data (Anxiety/Depression) | Dose-dependent EPS risk<br>Conventional agents perceived as faster acting in mania<br>Perceived mania induction |
| **Opportunities** | **Threats** |
| RIS-USA-102 Unsatisfied Market & RIS-INT-46 Data<br>Leverage Topiramate interest into RISPERDAL support<br>BD depression & maintenance<br>Improve compliance | Zyprexa BD mono-therapy label change: Acute indication (4Q'99), Depression (4Q'01), Maintenance (4Q'02), Zyprexa vs Depakote data<br>Zeldox launch<br>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

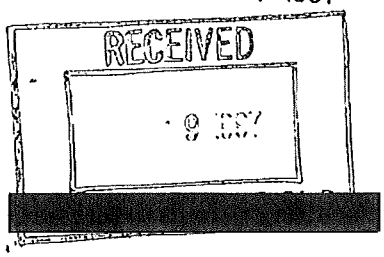
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

SEP 17 1997




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.

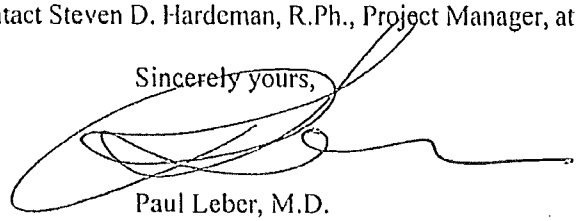
You have provided very little information to support these proposed labeling changes. You acknowledge that the supplements provide no i nterpretable efficacy data. The safety data submitted were also very limited, including data for n=14 pediatric patients exposed to Risperdal in Janssen-sponsored studies, 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:<br>IND NUMBER: 31,931 | INITIATED BY: JANSSEN X<br>FDA | BY TELEPHONE<br>IN PERSON X |
| FDA PERSONNEL: See below | DIVISION: Neuropharmacological Drug Products<br>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.

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# 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 |

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

### 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<br><br>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

**Comments**

| *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 |

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

**Comments**

| ***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 |

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.

[Page]

# 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.
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> 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.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Thomas Abrams
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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[1-6] 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.

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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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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.

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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.