



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

Janssen

NDA #s 20-272 and 20-588 (MACMIS #12195)

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

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studies, published case series, published clinical pharmacology studies, published preclinical studies, and unpublished studies for clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole.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

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

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

Omission of Material Information

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

Minimization of Risks/Misleading Comparative Claim

The DHCP letter states:

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

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

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

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.

Ajit Shetty, M.D.
Janssen
NDA #s 20-272 and 20-588 (MACMIS #12195)

Page 5

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/

Thomas Abrams

4/19/04 03:52:27 PM

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 research¹⁻⁸ 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.

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

Sincerely,

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

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

US.JANSSEN.COM

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.
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.