NDA Safety Review for NDA 20-272, Risperdal (risperidone) November 7, 1993

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-272
Sponsor: Janssen
Drug: Risperidone
Drug Category: Antipsychotic
Material Reviewed: NDA Safety Update
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I. Background

Janssen submitted NDA 20-272 for risperidone on April 15, 1992. The clinical review of this application was completed May 11, 1993. The present submission is a safety update report on risperidone, which includes routine clinical data collected from 5/31/91 (the cutoff date for the NDA safety database) to 4/15/93. Janssen has also included deaths of patients on risperidone reported through 9/30/93, and foreign postmarketing data on serious adverse events through 8/31/93.

II. Additional Exposure Data

During the period 5/31/91 to 4/15/93, an additional 285 patients received risperidone in Phase II-III clinical trials. Together with the 2322 patients reported in the database for the NDA, this yields a total of 2607 patients exposed to ripseridone in clinical trials. Added safety data on 278 patients who continued to receive risperidone in open label use since the time of the original NDA database has also been included. In addition, since the original NDA submission 56 additional patients have received risperidone in Phase I clinical pharmacology trials.

The following tables present (by treatment group) the updated exposure in Phase I studies and in studies contributing data to Janssen's integrated safety database (which excludes Phase I data). A total of 101 new risperidone patients were administered risperidone in controlled Phase II-III trials; the remaining 184 new risperidone patients received open label treatment.

Patients in Phase I Clinical Trials

Drug Treatment	Phase I through 5/31/91	Phase I 5/31/91-4/15/93	Total
Risperidone	175	56	231
Active Control	7	0	7
Placebo	6	0	6

Patients in Integrated Database Phase II-III Clinical Trials

Drug Treatment	Through 5/31/91	5/31/91-4/15/93	Total
Risperidone	2322	285	2607
Active Control	533	88	621
Placebo	176	19	195

Patient Exposure Years in Integrated Database Phase II-III Clinical Trials

Drug Treatment	Through 5/31/91	5/31/91-4/15/93	Total
Risperidone	508	350	858
Active Control	61	10	71
Placebo	13	2	15

The following table presents updated demographic information for patients in the integrated safety database of the sponsor. It should be noted that no patients under age 15 have been exposed to risperidone, either in the original NDA trials or the post-NDA studies. Within each category, percentages are based on the total number of patients with data.

Demographic Profile for Phase 2 and 3 Studies Through 4/15/93			
	Risperidone (N=2607)	Placebo (N=195)	Haloperidol (N=459)*
AGE (years)			
N	2486	161	429
Mean	39	43	38
Range			
≤44 Years	72%	67%	ns
45-64 Years	25%	20%	ns
≥65 Years	3%	13%	ns
SEX: Male	66%	74%	71%
Female	34%	26%	29%
RACE: White	78%	63%	75%
Non-white	22%	37%	25%

*The sponsor did not provide updated demographic data for other active controls.

The table below depicts the updated exposure to risperidone in the integrated safety database by dose and duration of treatment, for all patients having dosage information. In comparison to the original NDA database, there is now data on a larger number of patients receiving long term risperidone therapy. This is also reflected in the fact that from 5/31/91 to 4/15/93, patient-years of exposure to risperidone increased from 508 to 858 years, while only 285 additional patients received risperidone for the first time.

Number of Patients Receiving Risperidone According to Mean Daily Dose and Duration of Therapy in Phase 2 and 3 Studies Through 4/15/93 (N =2590)

Duration (Days)	≤2mg	2<mg≤6	6<mg≤10	>10mg	TOTAL	(%)
1-21 Days	67	110	78	70	325	(12)
22-49 Days	62	306	153	113	634	(25)
50-64 Days	160	225	194	288	867	(33)
65-274 Days	14	73	113	82	282	(11)
≥275 Days	29	128	158	167	482	(19)
TOTAL	332	842	696	720	2590	(100)
(%)	(13)	(32)	(27)	(28)	(100)	

In addition to the added exposure in clinical trials outlined above, the sponsor estimates that worldwide some 8000 patients have received risperidone either as marketed drug or on a compassionate use basis.

III. Safety Findings from Safety Update

A. Deaths in clinical trials

The table below presents a summary of deaths among risperidone treated patients in clinical trials subsequent to the original NDA submission. None of the deaths appears to be causally related to risperidone treatment. Two of the deaths were suicides, a topic discussed below.

Summary of Deaths Occurring in Risperidone-treated Patients in Clinical Trials (post-NDA)

Study/Pt. No.	Age(yrs)	Sex	Dose (mg/d)	Duration (days)	Cause of Death and Comments
RIS-USA-08** #405	26	M	?	39	Suicide-self inflicted gun shot wound
RIS-FIN-9001 #117*	22	M	6	7	Acute viral myocarditis one month post treatment
RIS-USA-9005 #1001*	41	M	16	270	Suicide-desipramine intoxication
RIS-INT-2/INT-4 #2166/(52)*	53	M	2-6	78	Cancer of bronchus 3 months post treatment

*Patient included in post-NDA integrated safety database **Ongoing study, blind not yet broken

In addition, two deaths reported in the NDA but not included in the original integrated safety database have now been added to the updated safety database (patient 39 in study 029, and patient in study INT-4).

The mortality by treatment group in the integrated safety database, incorporating the post NDA data, is given in the following table.

Drug	Number of Patients	Patient years of exposure	Deaths	Crude mortality	Mortality/ 100 Patient Years
Risperidone	2607	858	15	0.0058	1.7
Active Controls	621	71	1	0.0016	1.4
Placebo	195	15	0	0	0

It will be seen that although the crude mortality was highest in the risperidone treatment group, when corrected for duration of exposure the mortality in the risperidone and the active control groups are similar. This is consistent with the findings in the original NDA database. Thus risperidone treatment does not appear to be associated with excess mortality in clinical trials.

B. Safety Update Data on Premature Discontinuations

Overall Pattern of Dropouts

The table below presents the updated listing of premature discontinuations from clinical trials by treatment group and reason.

Rates of Dropout by Treatment Group and Reason for Pooled Phase II-III Database
NDA and Post-NDA Data Combined

	Percent Dropping Out		
Reason for Dropout	Risperidone (N=2607)	Placebo (N=195)	Active Control (N=533)
Inadequate Response	15.3%	38.5%	12.6%
Adverse Experiences	9.4%	6.2%	11.4%
Asymptomatic/Sufficient Response	0.6%	0%	0.2%
Non-Treatment Related	12.6%	8.7%	10.2%
Total Dropouts	37.9%	53.4%	34.3%

Adverse experiences also includes intercurrent illnesses, abnormal lab results, and patient death. Non-treatment related includes patient moved, chose to discontinue, lost-to-follow-up, uncooperative, ineligible, and other reasons. Inadequate response also includes deterioration of symptoms. Chose to discontinue also includes patient moved.

As in the original NDA data, the placebo group had the highest rate of discontinuation for inadequate response, while the two drug groups had higher rates of discontinuation for adverse events.

Adverse Events Associated with Dropout: Updated data

The following table lists all those adverse experiences that were associated with ≥ 0.3% of risperidone patients discontinuing the drug, combining NDA and post-NDA data. Placebo rates for the same adverse experiences are shown for comparison. Some data is missing, since the sponsor did not designate the adverse event resulting in discontinuation for 0.8% of risperidone patients or 1.0% of placebo patients. For these cases, this reviewer assigned an adverse event leading to premature discontinuation wherever possible using information available from case report forms or narrative case summaries; 14 risperidone patients were assigned reasons for premature discontinuation by this method.

	Percentage of patients dropping out	
Reason	Placebo (n=195)	Risperidone (n=2607)
Extrapyramidal symptoms	0.0%	2.1%
Suicide attempt	0.5%	1.2%
Dizziness	0.0%	0.7%
Hyperkinesia	0.0%	0.6%
Agitation	0.0%	0.5%
Somnolence	0.0%	0.5%
Aggressive Reaction	0.0%	0.4%
Psychosis	0.0%	0.3%
Fatigue	0.0%	0.3%
Nausea	0.0%	0.3%
Insomnia	0.0%	0.3%
Anxiety	0.0%	0.3%

C. Search for Emergence of Suicidality

Two additional suicides of patients receiving risperidone in clinical trials (patient in study 207, and patient in study 202) have been reported in the safety update. One of these (patient in study 202) has been included in the post NDA integrated safety data base; in addition, another suicide reported in the original NDA as being too recent to be included in the integrated safety database has now been added (patient in INT-4). With these data it is possible to update the incidence of completed suicide among risperidone paitents in the integrated safety database, as shown below.

Drug	Number of patients	Patient years of exposure	Suicides	Crude Rate	Suicides per 100 Patient Years
Risperidone	2607	858	9	0.0035	1.0
Active Controls	621	71	1	0.0019	1.7
Placebo	195	15	0	0	0

Here again, the crude incidence is highest for risperidone patients, but when duration of exposure is accounted for the risperidone rate is comparable to the active control group.

Similarly, the sponsor has provided updated reports of suicide attempts in risperidone clinical trials. Here, suicides and all other kinds of self destructive behaviors are combined in a single category denoted as suicide attempts. Combined post-NDA and original NDA data is shown in the following table. (I have included an additional case from the original NDA, patient 53 in BEL-11, since a review of the newly translated case report form submitted by Janssen indicates that the patient was mutilating himself.)

Drug	Number of patients	Patient years of exposure	Suicide attempts	Crude Incidence	Suicide attempts per 100 Patient Years
Risperidone	2607	858	43	0.016	5.0
Active Controls	621	71	5	0.008	7.0
Placebo	195	15	0	0	0

Again, the crude incidence is highest in the risperidone patient group but when adjusted for length of exposure the rates are similar between risperidone and active controls. The placebo group had a much shorter duration of exposure, and the absence of suicide attempts is therefore not inconsistent. On balance, risperidone treatment dose not appear to be associated with increased self destructive behavior in clinical trials.

Regarding depression, which often occurs in association with self destructive behavior, in the post NDA period an additional four patients discontinued treatment with risperidone due to depression. This yields a total of 7 patients out of 2607 (0.27%) who discontinued risperidone due to depression; for active control patients the corresponding figure is 1/621 (0.16%). If corrected for duration of exposure, the incidence of discontinuation for depression is 0.8% per year for risperidone and 1.4% per year for active controls.

D. Premature discontinuations and serious adverse events

The sponsor provided premature discontinuation summaries and case report forms for patients who withdrew from integrated database clinical trials after the cutoff for the original NDA. Janssen also provided narrative case summaries for patients suffering serious adverse events who either did not discontinue treatment or were never in a clinical trial; however, no case report forms were available for these patients. (No narrative case summaries were provided for four patients who discontinued prematurely and were not in the integrated database; the reasons listed in the sponsor's table of premature discontinuations were exacerbation of psychosis, increased insomnia, and insufficient response (2 patients)).

The above information regarding serious adverse events and adverse events leading to premature discontinuations was reviewed with special attention to (1) adverse events not previously reported in the original NDA, and (2) further data on adverse events listed as important and possibly drug related in the original NDA review.

Premature Discontinuations

In their summary accompanying the safety update, Janssen reported that the only reasons for patients discontinuing risperidone in the post-NDA integrated safety data base that were not previously observed were the folowing: antidiuretic hormone disorder and aspiration (INT-4 patient), GI hemorrhage (INT-4 patient), and thrombocytopenia (INT-4 patient). These cases were reviewed. The patient with GI hemorrhage experienced esophagitis following an overdose of acetylsalicylic acid, and in my view is more properly regarded as a dropout for a suicide attempt. The patient listed with thrombocytopenia was actually described on the case report form as discontinuing due to headace and siallorhea; the patient did have a decreased platelet count of 78 giga/L at the time of discontinuation, but the significance of this is questionable since his baseline platelet count was also low (84 giga/L). The case of antidiuretic hormone disorder and aspiration involved a schizophrenic patient who appears to have become hyponatremic and went into a coma; from the information available it is not clear that psychogenic polydipsia was ruled out, although it is known to be common among schizophrenic patients. This patient recovered.

In addition to these three cases, my review disclosed a patient listed as discontinuing with hearing loss, a previously unreported reason for discontinuation (patient in study 033); this was a subjective complaint noted only at the final study visit, however, and was never documented objectively. Manic reaction was also newly reported as a reason for discontinuation from risperidone; the case was not included in the integrated safety database because the study is still in progress (paitent in study 208). As this is the only known case of mania associated with risperidone, a more likely explanation than drug-induced mania is that the patient's original diagnosis of schizophrenia was in error.

The sponsor also compiled summary tables of adverse events and premature discontinuations from pharmacokinetics trials and from trials reported in the literature that were not part of the integrated safety data base. Although narrative case summaries were not provided for these patients, no previously unknown adverse events appeared in these listings.

The remaining narrative case summaries for premature discontinuations disclosed no significant new safety information. On balance, the adverse events described in the safety update as leading to premature discontinuation from risperidone do not materially affect the original NDA safety assessment.

Serious Adverse Experiences

Janssen supplied case summaries for patients experiencing serious adverse events in association with risperidone treatment. These cases were drawn from clinical trials, compassionate use, and foreign postmarketing reports. For the purpose of this review I will discuss all of these reports here in this section.

There was one report of hypoglycemia resulting in a one day hospitalization (patient in study 205). The patient was not diabetic. Hypoglycemia had not been previously reported with risperidone treatment.

While on compassionate use risperidone, a 28 year old female Canadian patient (IND safety report 9/21/93) developed jaundice, fever, bruising and thrombocytopenia. She was diagnosed with thrombotic thrombocytopenic purpura (TTP), and despite a stormy course eventually recovered after receiving plasmapheresis. To give a sense of the number of patients out of which this arose, this event ocurred in March 1993; as of 4/8/93 Janssen reported that there were a total of 587 compassionate use risperidone patients in Canada. The sponsor believes this may be a drug related adverse experience, as the patient did not have a recent viral illness, lupus, or exposure to other drugs except benztropine. TTP has not been reported with risperidone previously but has been associated with exposure to other drugs (for example, see the package insert for ticlopidine).

A middle cerebral artery infarct was reported in a 44 year old male receiving compassionate use risperidone (IND safety report 9/29/93); no cerebral vascular accidents were reported in the original NDA.

Other events in the sponsor's compilation of serious adverse experiences since the NDA were the following: seizures (7 patients); suicide attempt, increased CPK with dizziness, endometrial carcinoma, cholelithiasis, syncope and postural hypotension in a patient with preexisting cardiac disease, and myocardial infarction (1 patient each).

Overdose

An additional case of overdose on risperidone is described in the safety update. The report comes from Canada, where the patient was receiving marketed drug. The patient, a 38 year old female, took an overdose of 36 mg risperidone and 375 mg chlordiazepoxide and developed seizures. The patient's heart rate elevated to 160 beats per minute during the seizures, although her EKG reportedly remained normal. Follow up information on the patient's outcome is not yet available.

Another postmarketing report of overdose was received from Great Britain; the amount ingested was merely 20 mg of risperidone as a result of a prescribing error. The patient experienced tachycardia and pruritus.

Pregnancy

A congenital defect has been reported in a infant exposed to risperidone prenatally (IND safety report 10/25/93). The infant was born without a corpus callosum; the mother had taken risperidone for six days during her fourth month of pregnancy. Numerous other medications were also administered to the mother during the pregnancy. While the fourth month is roughly the time that the corpus callosum develops in the human fetus, this congenital defect is generally not attributed to prenatal toxin exposure; possible etiologies include maternal rubella, chromosomal abnormalities, and familial predisposition. In rodents the lesion has been produced by trypan blue injections during gestation, irradiation, and maternal riboflavin deficiency (Warkany, Congenital Malformations).

In my view, of the serious adverse experiences described in the safety update, most are either unlikely to be drug related or represent adverse drug reactions already documented in the original NDA. An exception is the case of TTP, which may possibly be drug related. Additionally, seizures following overdose on risperidone have not been described previously.

E. Adverse Drug Reaction Incidence

The post-NDA data base contains data from placebo controlled trials on 101 risperidone patients and 19 placebo patients. In my opinion, consideration of this data would not add any useful information on common adverse events, since the number of patients involved is small compared to the studies already reviewed in the original NDA submission.

F. Laboratory Findings

Additional cases of premature discontinuations or serious adverse events involving clinical laboratory findings reported in the safety updat have been described above. Janssen calculated revised incidences of laboratory abnormalities from the post NDA data; however, the utility of these revised figures is doubtful since they include very little additional placebo controlled data. Laboratory abnormalites of possible clinical significance, ocurring at an incidence of greater than 4% in the post-NDA patients, included low hematocrit, elevated eosinophils, hypokalemia, and elevated CPK. Regarding the latter, elevations of CPK have been associated with acute psychosis (Meltzer, J Psychiat Res 10:43-57, 1973). Lack of a meaningful comparison group makes interpretation of these findings difficult. Please refer to the original NDA review for an examination of clinical laboratory findings from placebo controlled trials, which are more readily interpretable.

G. Vital Signs and Weight

Of the integrated safety database patients who discontinued treatment after the original NDA, only one discontinued for a change in vital signs: patient in study 9001 discontinued with postural hypotension. Janssen provided revised incidences for vital sign abnormalities in clinical trials, but in my opinion this data is not as meaningful as the data from placebo

controlled trials reviewed with the original NDA. The most common findings were changes consistent with postural hypotension, reduction in supine blood pressures, and weight increase.

F. Electrocardiograms

In the post-NDA period, no integrated safety data base patients discontinued risperidone due to an abnormal EKG. Abnormally increased QTc was reported in 22/267 (8.2%) of post-NDA patients, and decreased PQ interval was reported in 31/220 (14.1%) of post NDA patients. Of these, the finding with more potential clinical importance is the increase in QTc, which will be considered further here.

If one pools all double blind treated patients in the integrated database, 35/1271 (2.8%) of risperidone patients developed increased QTc, compared to 0/132 placebo patients. For comparison, the incidence of among haloperidol treated patients in double blind trials was 9/343 (2.6%); the current Haldol labeling does describe QT prolongation under adverse events. It should be recalled that these data come from a pooling of studies and that conditions across treatment groups are not necessarily comparable. The data from individual studies is not consistent regarding this possible EKG effect, as was discussed in the original NDA safety review. Thus, although some of the data suggests that risperidone may prolong the QTc, in my view this cannot be a definitive conclusion.

G. Additional information on important drug related adverse events

The original NDA review discussed several important adverse events that were considered possibly or probably drug related. The safety update was reviewed for additional pertinent information on these adverse events, which will be presented here.

Neuroleptic Malignant Syndrome

No new cases were reported.

Tardive Dyskinesia

No additional relevant information was reported. It is apparently still true that risperidone has never been implicated as the sole cause of any patient's tardive dyskinesia.

Postural Hypotension and Syncope

There were 2 additional premature discontinuations for dizziness (study 9001, patient study BEL-19, patient and one for postural hypotension (study 9001, patient . No additional cases of syncope were reported.

Seizures

In the post NDA integrated safety data, there were 2 additional cases of seizure reported (study 204, patients . With the 5 cases from the original NDA, this gives an incidence of 7/2607 (0.26%). Corrected for

duration of exposure, the incidence is 7/858 patient-years, or 0.82% per year.

Rash

No additional patients had to discontinue risperidone due to rash.

Edema

No additional patients discontinued risperidone due to edema.

Prolactin Elevation

There was no additional information on this finding.

Priapism

No additional cases were reported.

Extrapyramidal Symptoms

An additional 17 risperidone patients were listed by the sponsor as discontinuing for extrapyramidal symptoms. Comparative data to placebo has been discussed in the original NDA review.

Sedation

Two additional patients were listed as dropping out for somnolence.

Tachycardia

There were no additional dropouts for this adverse event.

EKG changes

Please refer to the discussion above.

Liver enzyme elevation

There were no additional reports of premature discontinuations or serious adverse events involving elevated transaminases.

H. World Literature

The sponsor submitted a worldwide clinical bibliography lising all publications on risperidone that were not included in the original NDA. Janssen has been asked to supply copies of these references for review. Dr. David Jackson from Janssen reports that there are no findings in the literature that would adversely affect conclusions regarding the safety of risperidone.

IV. Conclusions and Recommedations

Review of the data in the safety update indicates that risperidone is reasonably safe when used as an antispychotic. Adverse events not previously reported in the NDA include the following: manic reaction, hearing loss, hypoglycemia, thrombotic thrombocytopenic purpura (TTP), cerebral vascular accident, and congenital absence of the corpus callosum. Seizure following risperidone overdose was also reported for the first time. Of these adverse events, in my opinion the one of most significance in terms of both severity and possible relationship to risperidone use is the case of TTP. The apparent high incidence of prolonged QTc in the post NDA patients is of potential concern, although this finding is not borne out consistently by data from the controlled trials.

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