

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-444**

**Medical Review(s)**

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-444

SPONSOR: JOHNSON AND JOHNSON

DRUG: RISPERIDONE ORALLY DISINTEGRATING TABLET

MATERIAL SUBMITTED: AMENDED REPORT OF PIVOTAL BIOEQUIVALENCE

STUDY RIS-USA-125

DATES SUBMITTED: 10-11-02 AND 11-22-02

These two submissions are amendments to the pivotal bioequivalence study report for protocol RIS-USA-125. The changes to the study report reflect corrections that followed the FDA site inspection in Belgium 9-30-02 to 10-2-02. The submission dated 10-11-02 is designated Amendment #3 to the study report; apparently, the study report had been amended twice before but these first two amendments were not submitted to the agency. For completeness, Johnson and Johnson submitted Amendments #1 and #2 on 11-22-02. (Both submissions are electronic, although the sponsor also provided a hard copy of the 10-11-02 submission.)

Amendment 1 (11-22-02) provides a re-analysis of the adverse events reported in the study. Amendment 2 (11-22-02) includes a variety of additional information requested by the Canadian regulatory authorities. Amendment 3 (10-11-02) includes new analyses of the pharmacokinetic data. The sponsor concluded that the new analyses support the bioequivalence of the marketed tablet and the orally disintegrating tablet.

Reviewer comment: There are no clinical data of concern in these amendments to the study report for protocol RIS-USA-125. The new information should be reviewed by OCPB, however.

Andrew D. Mosholder, M.D., M.P.H.  
Medical Officer, HFD-120

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

/s/

-----  
Andy Mosholder  
12/24/02 01:30:57 PM  
MEDICAL OFFICER

Thomas Laughren  
12/26/02 07:50:31 PM  
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-444

SPONSOR: JANSSEN

DRUG: RISPERIDONE ORALLY — TABLETS

MATERIAL SUBMITTED: ORIGINAL NEW DRUG APPLICATION

DATE SUBMITTED: 11-16-01

DATE RECEIVED: 11-19-01

PROPOSED DOSAGE STRENGTHS: 0.5 MG, 1 MG, 2 MG

This NDA provides for an orally — formulation of risperidone. The rationale is that it may be preferable for patients who resist medication or have difficulty swallowing tablets. There were no clinical efficacy trials in the development program for this product; rather, the sponsor has sought to show that the new formulation is bioequivalent to marketed Risperdal. Parenthetically, the sponsor estimates that worldwide cumulative exposure to marketed Risperdal tablets exceeds — patient years.

The table below, reproduced from the submission, provides an overview of the in vivo studies. An additional pilot study (RIS-USA-57) involved 6 subjects, but the study report for this trial was never completed. Although the 4 mg strength was used in four studies, the sponsor is not seeking approval for this strength. All studies were of a single dose crossover design except for study RIS-BEL-39 which was simply a single dose taste study; there were no multiple dose trials. Studies RIS-BEL-40 and RIS-BEL-47 in healthy volunteers, and studies RIS-BEL-39 and RIS-BEL-48 in patients, used an investigational formulation that will not be marketed.

In these clinical trials the subjects were administered the rapidly — tablet without water, after moistening the tongue with saliva.

Table 1: Number of subjects in the — Quicklet clinical program by clinical trial and risperidone dose

Trial	Objective(s)	No. of subjects				
		0.5 mg (N=26)	1 mg (N=62)	2 mg (N=65)	4 mg (N=61)	All doses (N=214)
<i>Healthy volunteers</i>						
RIS-BEL-40	Bioavailability and taste	8	0	0	0	8
RIS-BEL-47	Bioavailability and taste	6	0	0	0	6
RIS-USA-125	Bioequivalence <sup>a</sup>	0	50	0	0	50
RIS-NED-25	Bioequivalence	0	0	40	0	40
<i>Patients</i>						
RIS-BEL-39	Taste and tolerability	0	0	0	12	12
RIS-BEL-48	Bioavailability and taste	0	0	0	6	6
RIS-BEL-51	Taste <sup>b</sup>	12	12	25	11	60
RIS-BEL-52	Bioavailability & bioequivalence	0	0	0	32	32

<sup>a</sup> 2x0.5 mg

<sup>b</sup> with and without food/beverage.

The sponsor is claiming bioequivalence to marketed Risperdal tablets, based on the pharmacokinetic data from studies RIS-USA-125 and RIS-NED-25.

**Safety results:** A total of 214 subjects received the new formulation (104 healthy volunteers and 110 patients). Roughly 2/3 of the subjects were males, and the median age for subjects was approximately 38 years. The majority of subjects were either Caucasian or Hispanic.

There was one serious adverse event in these trials: Patient A30022 in study RIS-BEL-52 developed abdominal pain attributed to a pre-existing condition (peptic esophagitis); the time of onset did not indicate a clear relationship to risperidone administration. Two subjects discontinued from their studies because of adverse events (the events were dizziness and nausea in one patient, and dizziness in one healthy volunteer). Additionally, one patient had syncope after a 4 mg dose of the rapidly tablet (patient A30036 in study RIS-BEL-52). Somnolence, headache, dizziness, and fatigue were the most frequent non-serious adverse events, and the incidence of these events was similar for the new formulation and marketed drug. In trials that included post-dose vital signs, the data indicate decreases in mean systolic and diastolic blood pressure, but of course there is no placebo group for comparison. With respect to ECGs and clinical laboratories, the sponsor reports that these post-baseline assessments, if obtained at all, were usually performed 4 days after the final single dose of study medication; and so these data are of limited inferential value regarding the effects of risperidone.

Overall, there do not appear to be any safety findings that would preclude approval of the rapidly formulation.

**Labeling comments:** The proposed labeling includes the requested change in the indication from psychotic disorders to schizophrenia. The proposed labeling also includes a description of the drug-drug interaction with carbamazepine, and notes the absence of any interaction with lithium or valproate. The proposed labeling advises phenylketonuric individuals that this new formulation contains aspartame. Additionally, the labeling includes a new statement that risperidone and its major metabolite are excreted in human breast milk. The labeling incorporates the recent "changes being effected" supplement submitted 8-24-01 which added the term "cerebrovascular accident" to the Postintroduction Reports section. Finally, under Dosage and Administration, the sponsor has included instructions for patients that are specific for this formulation.

Overall, from a clinical standpoint the proposed labeling appears acceptable. The Chemistry and OCPB review teams should comment on the specific changes relevant to their disciplines.

Andrew D. Mosholder, M.D., M.P.H.  
Medical Officer, HFD-120

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

/s/

-----  
Andy Mosholder  
7/17/02 03:31:57 PM  
MEDICAL OFFICER

Thomas Laughren  
7/17/02 04:12:17 PM  
MEDICAL OFFICER