CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-444

Clinical Pharmacology and Biopharmaceutics Review

MAR 4 2003

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Risperidone
PRODUCT (Brand Name):	RISPERDAL®
DOSAGE FORM:	Orally Disintegrating Tablets
DOSAGE STRENGTHS:	0.5, 1, 2 mg
NDA:	21-444
NDA TYPE:	S (Response to Approvable Letter)
INDICATION:	Treatment of Schizophrenia
SUBMISSION DATE:	10/11/02, 11/22/02, 01/31/03
SPONSOR:	Janssen Pharmaceuticals
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

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RECOMMENDATION

The amendments dated 10/11/02, 11/22/02 and 01/31/03 to the NDA 21-444 are acceptable. The reason's for the amendments along with its acceptability from the perspective of Office of Clinical Pharmacology and Biopharmaceutics are provided in the following sections on AMENDMENTS 1, 2 and 3.

The re-analysis of the bioequivalence Study RIS-USA-125 is acceptable and did not change the conclusions of the study.

The dissolution specifications and methodology accepted are given on page 6 and are in accordance with the Office of Clinical Pharmacology and Biopharmaceutics recommendation.

The labeling revisions recommended in the approvable letter for the 'Pharmacokinetics' and 'Drug Interaction' section of the label were accepted by the sponsor. The current version of these sections are provided on page 6 under the section RESPONSE TO APPROVABLE LETTER along with minor editorial changes made by this reviewer represented by strikeouts and underline. These additional changes should be conveyed to the sponsor to be incorporated in the labeling.

3/4/03

/S/

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. /S/ 03/04/03

REASON FOR AMENDMENT 1 (Dated 11/22/02)

The original document was amended because the analysis of adverse events (as performed by the CRO, i.e., the number of events per reported adverse event) was not according to the standard JRF procedures (i.e., the number of subjects per reported adverse event).

REASON FOR AMENDMENT 2 (Dated 11/22/02)

The original document was amended to comply with the requirement from Canadian authorities to provide them with additional information on the bioequivalence trial RIS-USA-125 in the Canadian [redacted] submission.
Additional information for Canadian submission include orgainization of the report material with specific tables added for clarity of the report. The specific requests were:

- Any abnormal results of tests used for health verification should be reported.
- If smoking was allowed in the study, the number of cigarettes smoked per day should be reported.
- An adverse event reaction table should be included in the report. The table should include at least the following information:
  subject number, treatment (test vs. reference), causality, treatments required for event
- An adverse event reaction table should be included in the report. The table should include at least the following information: subject number, treatment (test vs. reference), causality, treatments required for event
- Organize Pharmacokinetic data in a certain way. No new data was added.

Reviewer's Comment: These amendments 1 and 2 do not change conclusions of the study.

REASON FOR AMENDMENT 3 (Dated 10/11/02)

This amendment is in response to the FDA Inspector request during site inspection:

Response to DSI COMMENT 1

Comment: Verify BE results to include 37 eligible subjects in the analysis of the data instead of the original 43 subjects for Study RIS-USA-125

The original document was amended to clarify in the main body of the Clinical Research Report the number of subjects (N=37) included in the bioequivalence statistics (analysis of variance, 90%-confidence intervals for treatment ratio). This was done in response to DSI inspection that made the recommendation for RIS-USA-125 to use 37 eligible subjects instead of the original bioequivalence analysis in which 43 subjects were included. Subjects A3004, 11, 13, 19, 22, 24, 25, 26, 29, 32, 45, 47 and 139 were removed as requested by DSI from the list of 50 subjects, who received at least one dose of the study mediaction and the data was reanalyzed.

This amendment presents the number of subjects for whom bioanalytical data was available for pharmacokinetic data analysis and an explanation of subjects who were excluded from the bioequivalence assessment. This amendment also provides summary

statistics on plasma concentrations and pharmacokinetic parameters for the 37 subjects included in the bioequivalence assessment.

Study RIS-USA-125 was a bioequivalence trial comparing a single oral intake of 2 x 0.5 mg risperidone as [redacted] (risperidone) tablets with 2 x 0.5 mg conventional marketed Risperdal (risperidone) tablets in healthy volunteers.

The data was re-analyzed by the reviewer. The results obtained by taking 37 subjects were identical to that of the sponsor. The results for the active moiety, risperidone and 9-hydroxy risperidone are given below.

Pharmacokinetic parameters and 90% confidence limits for active moiety (risperidone+ 9-OH risperidone):

Table 4-1: Plasma pharmacokinetic parameters: active moiety (N=37)

Pharmacokinetic parameter	[redacted] Quicklet™ 2 x 0.5 mg		Risperdal® 2 x 0.5 mg	
	Mean ± SD	Median	Mean ± SD	Median
t_{max} (h)	1.79 ± 0.70	1.50	1.43 ± 0.52	1.50
C_{max} (ng/mL)	12.55 ± 4.05	11.90	13.73 ± 3.88	13.40
AUC_{last} (ng.h/mL)	204.55 ± 69.94	197.10	207.84 ± 72.58	198.22
AUC_{∞} (ng.h/mL)	215.27 ± 74.04	206.50	222.50 ± 90.28	204.98
$t_{1/2}$ (h)	22.20 ± 3.82	22.49	23.64 ± 5.42	23.15

Table 4-2: Bioequivalence results of the active moiety (log transformed data) (N=37)

Parameter	[redacted] M/Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max} (ng/mL)	11.882	13.191	90.08	84.05 - 96.54
AUC_{last} (ng.h/mL)	194.630	198.361	98.12	91.98 - 104.67
AUC_{∞} (ng.h/mL)	204.814	210.701	97.21	91.21 - 103.60

Source: Annex 1 to Amendment 3

Pharmacokinetic parameters and 90% confidence limits for risperidone:

Table 4-3: Plasma pharmacokinetic parameters: risperidone *(N=37)*

Pharmacokinetic parameter	[redacted] Quicklet™ 2 x 0.5 mg		Risperdal® 2 x 0.5 mg	
	Mean ± SD	Median	Mean ± SD	Median
t_{max} (h)	1.52 ± 0.63	1.50	1.22 ± 0.45	1.00
C_{max} (ng/mL)	8.83 ± 3.82	8.30	9.27 ± 3.85	8.85
AUC_{last} (ng.h/mL)	48.33 ± 35.72	36.08	45.01 ± 36.62	34.26
AUC_{∞} (ng.h/mL)	49.42 ± 35.94	37.31	46.21 ± 38.10	34.82
$t_{1/2}$ (h)	3.53 ± 2.21	2.93	3.58 ± 2.69	2.59

Table 4-4: Bioequivalence results of risperidone (log transformed data) (N=37)

Parameter	[redacted] M/Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max} (ng/mL)	8.063	8.542	94.39	85.91 - 103.70
AUC_{last} (ng.h/mL)	40.253	36.686	109.73	97.92 - 122.95
AUC_{∞} (ng.h/mL)	41.331	37.605	109.91	98.40 - 122.77

Pharmacokinetic parameters and 90% confidence limits for 9-hydroxy risperidone:

Table 4-5: Plasma pharmacokinetic parameters: 9-hydroxy-risperidone (N=37)

Pharmacokinetic parameter	[redacted]/Quicklet™ 2 x 0.5 mg		Risperdal® 2 x 0.5 mg	
	Mean ± SD	Median	Mean ± SD	Median
t_{max} (h)	6.40 ± 7.77	5.00	5.53 ± 6.71	4.00
C_{max} (ng/mL)	6.11 ± 2.36	6.34	6.84 ± 2.51	7.03
AUC_{last} (ng.h/mL)	156.10 ± 56.26	145.49	161.80 ± 51.82	157.83
AUC_{∞} (ng.h/mL)	166.97 ± 59.96	156.05	175.66 ± 60.38	165.83
$t_{1/2}$ (h)	22.70 ± 4.39	23.33	24.16 ± 6.23	23.98

Table 4-6: Relative bioavailability of 9-hydroxy-risperidone (log transformed data) (N=37)

Parameter	[redacted]/Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max} (ng/mL)	5.470	6.203	88.17	82.74 - 93.96
AUC_{last} (ng.h/mL)	145.108	152.871	94.92	89.12 - 101.10
AUC_{∞} (ng.h/mL)	156.052	166.159	93.92	88.28 - 99.92

Reviewer's Conclusions from the re-analysis:

The results of the study do not change as a result of the re-analysis. Risperidone 2 x 0.5 mg as [redacted] risperidone) tablets are bioequivalent to conventional 2 x 0.5 mg risperidone tablets.

Response to DSI COMMENT 2:

Comment: Evaluate the impact of Cmax (for the active moiety and RIS in the secondary analysis) failing to meet the BE criteria on the outcome of Study RIS-NED-25.

Reviewer's Comment: *This has been reviewed by Dr. Brian Booth in the review of the original NDA. He agrees that the outlier could be excluded from the analysis. Hence, the Cmax bioequivalence issue from secondary analysis (n=43) was not considered a problem.*

RESPONSE TO APPROVABLE LETTER (Dated 1/31/03)

1. The final dissolution specifications and methodology requested in the approvable letter was accepted by the sponsor and are as follows. This was also accepted in the 9/10/02 submission:

   Method: USP apparatus 2,
   Speed 50 rpm,
   Media: 500 mL of 0.1 N HCl
   Q = — % in 10 minutes

2. The sponsor has responded to the approvable letter for all the changes proposed in the "Pharmacokinetics" and "Drug Interaction" sections of the label. The following label has been proposed for these changes. The sponsor has incorporated all the comments provided by the Office of Clinical Pharmacology and Biopharmaceutics for these sections. Few additional editorial changes have been made by this reviewer in the sponsor's proposed label which are represented by strikeouts and underline.

These comments should be conveyed to the sponsor.

"Pharmacokinetics

Absorption

[redacted]

2 pages redacted from this section of the approval package consisted of draft labeling

Reviewer's Comment:

The sponsor has accepted all the recommendations made to the 'Pharmacokinetics' and 'Drug Interactions' section of the label. They have some changes in the numbers to reflect accuracy of the data:

1. *Fluoxetine: Correction to the increased plasma concentration of risperidone with concomitant fluoxetine administration, from [redacted] for the active moiety (risperidone plus 9-hydroxyrisperidone) to a 2.5-2.8 fold increase for risperidone.*
2. *Valproate: The number of subjects changed from [redacted] to 21.*

The changes reflect the true data and are acceptable.

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

/s/

Veneeta Tandon
3/4/03 06:56:12 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/4/03 10:33:06 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-444

Drug :	**RISPERDAL —— /QUICKLET**
Generic name:	Risperidone
Formulation:	0.5, 1.0 and 2.0 mg tablets
Indications:	treatment of schizophrenia
Applicant:	Janssen Pharmaceutica
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Neuropharmacological Drug Products (HFD-120)
Submission Dates:	11/16/01; 2/22/02; 4/22/02
Team Leader:	Patrick J. Marroum, Ph.D.
Type of Submission:	NDA-original

I. Executive Summary

The applicant submitted NDA 21-444 Risperdal Quicklet/ —— (Risperdal ——) for marketing approval as a treatment for schizophrenia. The proposed dosing regimen of Risperdal is 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective.

Resiperidal —— is a novel formulation that disintegrates in the patient's mouth, and the drug-coated beads are then easily swallowed. The purpose of the current NDA was to demonstrate bioequivalence between the 0.5 and 2 mg Risperdal —— formulations and the conventional Risperdal tablets of equal strength. The sponsor is granted a biowaiver for the 1.0 mg strength Risperdal —— formulation because of the proportional composition of the formulation and the similarity of the dissolution profiles in of the 0.5 1.0 and 2.0 mg strengths of Risperdal —— . Both the 0.5 mg and 2.0 mg Risperdal —— formulations were shown to be bioequivalent to the conventional tablet based on the comparison of C_{max} and AUC_{∞} for the parent, the metabolite and the sum of the parent and metabolite. However, it should be noted that the determination of bioequivalence is based on the successful fulfillment the acceptance criteria for the parent alone.

A. Overall Recommendations

The clinical pharmacology and biopharmaceutics information submitted in the NDA for Zometa is acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics, pending the completion of the Division of Scientific Investigations inspections of the study sites. The applicant has demonstrated bioequivalence between the 0.5 and 2 mg strengths of Risperdal — and the comparable strengths of the conventional tablets. OCPB recommends the following dissolution method and specification:

- USP apparatus 2,
- 50 rpm,
- 500 ml of 0.1 N HCl
- Q = — % in 10 minutes.

The applicant should also incorporate the labeling changes suggested by FDA.

B. Labeling Recommendations

1. Replace the current bioequivalence description with the simpler description below:

CLINICAL PHARMACOLOGY, Pharmacokinetics
"Pharmacokinetic studies have demonstrated bioequivalence of the 0.5, 1.0 and 2.0 mg strengths of RISPERDAL tablets and RISPERIDAL — tablets."

2. Re-organize the clinical pharmacology information in the labeling under the headings of Absorption, Distribution, Metabolism and Excretion (ADME).

2. Update the AADMA and Drug Interactions section of labeling with the FDA-recommended sections regarding carbamazepine, lithium and valproate.

The Clinical Pharmacology and Biopharmaceuitcs briefing was held on July 23, 2002.

Attendees: Patrick Marroum, Ramana Uppoor, Thomas Laughren, Andrew Mosholder,

/S/ /S/

Reviewer: Brian Booth, Ph.D. Team Leader: Patrick Marroum, Ph.D.

CC: NDA 21-444
HFD-120/Division File
HFD-120/SHardeman, AMosholder, TLaughren
HFD-860/MehtaM, Marroum P, Ramana U, Booth B
CDR/Biopharm

II. Table of Contents

III. Clinical Pharmacology Summary

Risperdal is an orally administered drug used to treat schizophrenia. The applicant developed a new formulation that consists of risperidone bound to a resin. The new formulation Risperdal — quickly disintegrates in the saliva and is swallowed. It is believed that this new formulation will be of clinical use in schizophrenic patients who might be reluctant to take medication. The approvablity of this NDA is based on bioequivalence of Risperdal — with the conventional oral formulation of Risperdal. Two pivotal bioequivalence studies were conducted. The first is RIS-USA-125 which was a comparison of the 0.5 mg strength of Risperdal — to the convention 0.5 mg strength of Risperdal. The second study (RIS-NED-25) was a comparison of the 2.0 mg strength (the highest to-be-marketed strength) of Risperdal — to the 2.0 mg strength of the conventional tablet. FDA granted a waiver for the 1.0 mg strength of Risperdal — based on the proportional composition of the intermediate strength and the comparability of the dissolution profiles of all three strengths in three media.

Both pivotal BE studies demonstrated bioequivalence of Risperdal — to the conventional formulations of Risperdal, as defined by FDA. The RIS-NED-25 study contained one patient who caused a failure of bioequivalence based on C_{max} of the parent molecule. However, this patient appeared to satisfy the statistical criteria for an outlier, and exclusion of this data yielded bioequivalence of the formulations. FDA agrees with this treatment of the data, and the conclusion of bioequivalence with both formulations. These conclusions were supported by two pilot bioequivalence studies in healthy volunteers (RIS-BEL-40 and –47). Conversely, one pilot bioequivalence study of the 4 mg strength (RIS-BEL-48) in 6 schizophrenic patients appeared to fail bioequivalence. The applicant did not seek marketing approval the for 4 mg strength of Risperdal — in the current submission. The applicant also assessed the palatability of Risperdal — in several studies, but these were not extensively reviewed, nor were these studies pertinent to the assessment of bioequivalence.

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IV.Question Based Review

Background

Risperidone is benzisoxazole derivative which acts centrally to inhibit serotonin 5-HT_{2A} and dopamine-D_2 receptors.

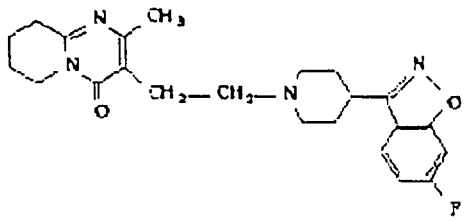

Figure 1. Risperidone, MW 410.9

Risperidone is rapidly absorbed orally (absolute bioavailability =70%). Metabolism is mediated by cytochrome P-450 2D6 (CYP 2D6), which generates an equi-active metabolite, namely 9-hydroxyrisperidone (9-OH-risperidone). The pharmacokinetics of risperidone and 9-OH-risperidone are dose-proportional from 1 to 16 mg, and are unaffected by food. The pharmacokinetics of risperidone for fast and slow CYP 2D6 metabolizers are compared in the table below.

Table 1. Pharmacokinetics of Risperidone

Parameter	Fast Metabolizers		Slow Metabolizers	
	Parent	Metabolite	Parent	Metabolite
T_{max} (hrs)	1	3	1	17
$t_{1/2}$ (hrs)	3	21	20	30

No significant differences in safety or efficacy of risperidone were observed between fast and slow metabolizers.

Risperdal — is a new formulation of risperidone that allows administration of risperidone without water. Resperiodone is coated on a resin at a concentration of 2mg /g. The formulation rapidly disintegrates in saliva, which is then swallowed. This formulation provides an additional therapeutic option for patients who may be reluctant to take medication.

Is Risperidone Quicklet — bioequivalent to the conventional Risperdal tablets?

Yes. The applicant conducted two pivotal bioequivalence studies to determine the bioequivalence of 0.5 mg and 2 mg of Risperdal — (the lowest and highest strength formulations) to 0.5 and 2 mg tablets of conventional Risperdal.

1. RIS-USA-125 was a bioequivalence study of the new and conventional 0.5 mg formulations. This study was conducted at a single center in the USA. The study was a randomized, two-way, two-period, two-sequence cross-over design with a washout period of 14 days. Patients were fasted overnight and for 2 hours post-dose. Thirty-nine patients were enrolled in the study, and data from 31 patients were analyzed. Data from 11 patients were withdrawn due to missing samples at critical times, and one patient voluntarily withdrew. With 31 patients, the power was 80% at an α of 0.05 to detect a 20% difference. Validated RIAs was used to assay the active moiety (parent and 9-OH-risperidone) and parent alone.

Results

Table 4-2: Relative bioavailability of the active moiety (log transformed data)

Parameter	Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max}	11.882	13.191	90.08	84.05 - 96.54
AUC_{last}	194.630	198.361	98.12	91.98 - 104.67
AUC_{∞}	204.814	210.701	97.21	91.21 - 103.60

Source: Display 19

Table 4-4: Relative bioavailability of risperidone (log transformed data)

Parameter	Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max}	8.063	8.542	94.39	85.91 - 103.70
AUC_{last}	40.253	36.686	109.73	97.92 - 122.95
AUC_{∞}	41.331	37.605	109.91	98.40 - 122.77

Source: Display 23

Table 4-6: Relative bioavailability of 9-hydroxy-risperidone (log transformed data)

Parameter	Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max}	5.470	6.203	88.17	82.74 - 93.96
AUC_{last}	145.108	152.871	94.92	89.12 - 101.10
AUC_{∞}	156.052	166.159	93.92	88.28 - 99.92

Source: Display 27

Conclusion

The applicant's analysis demonstrated that C_{max} and AUC_{∞} for the active moiety, risperidone and 9-OH-risperidone of 0.5 mg Risperdal Quicklet was bioequivalent to 0.5 mg of the conventional Risperdal tablet. Re-analysis by FDA confirmed this conclusion.

2. RIS-NED-25 was a bioequivalence study of the new and conventional 2.0 mg formulations. This study was conducted at a single center in the Netherlands. The study was a randomized, two-way, two-period, two-sequence cross-over design with a washout period of 10-21days. Patients were fasted overnight and for 2 hours post-dose. Forty patients were enrolled in the study, and data from 38 patients were

analyzed. One patient withdrew voluntarily, and data from one patient was withdrawn because the C_{max} and AUC following the second dose (Risperdal —) was uncharacteristically low compared to other patients. Although no explanation was found for these values, the patient was deemed a statistical outlier based on the Hotelling T^2 test, and was excluded from the "primary" analysis. A "secondary" analysis was also conducted with the inclusion of this patient. With 38 patients, the power was at least 80% at an α of 0.05 to detect a 20% difference. Validated — assay was used to assay the parent and 9-OH-risperidone simultaneously.

Results

Table 4-3: Bioequivalence statistics of the log transformed parameters C_{max}, AUC_{last} and AUC_{inf} (primary analysis, n=38)

Parameter	Active moiety *) Ratio (90% CI)	Risperidone *) Ratio (90% CI)	9-hydroxy-risperidone *) Ratio (90% CI)
C_{max}, ng/mL	92.1 (87.5 – 96.9)	88.4 (81.0 – 96.6)	96.9 (94.0 – 100.0)
AUC_{last}, ng.h/mL	98.1 (94.4 – 102.0)	99.3 (92.5 – 106.5)	97.6 (94.2 – 101.3)
AUC_{inf}, ng.h/mL	98.0 (94.2 – 101.9)	99.0 (92.3 – 106.2)	98.1 (94.3 – 102.0)

*) treatment ratio — versus RISPERDAL tablet (90% confidence interval)

Table 4-4: Bioequivalence statistics of the log transformed parameters C_{max}, AUC_{last} and AUC_{inf} (secondary analysis, n=39)

Parameter	Active moiety *) Ratio (90% CI)	Risperidone *) Ratio (90% CI)	9-hydroxy-risperidone *) Ratio (90% CI)
C_{max}, ng/mL	88.2 (80.6 – 96.5)	84.8 (75.7 – 94.9)	92.8 (85.6 – 100.7)
AUC_{last}, ng.h/mL	93.7 (85.8 – 102.3)	95.5 (86.8 – 105.1)	93.1 (85.0 – 101.9)
AUC_{inf}, ng.h/mL	93.7 (86.0 – 102.1)	95.4 (86.9 – 104.8)	93.4 (85.0 – 102.7)

*) treatment ratio — versus RISPERDAL tablet (90% confidence interval)

Conclusion

The applicant concluded that the 2 mg Risperdal — was bioequivalent to the conventional 2 mg tablet of Risperdal based on C_{max} and AUC_{∞} of the active moiety (parent and 9-OH-repseridone), the parent and the metabolite from the "primary" analysis (n=38). The secondary analysis demonstrated that bioequivalence failed due to C_{max} for the parent (risperidone) when all of the data was included.

FDA reanalysis essentially confirmed these results reported by the applicant, although the results were slightly different.

Table 1. "Primary" Analysis (n=38)

Parameter	Active moiety	Risperidone	9-OH Respseridone
Cmax	91.9 (87.4-96.7)	89.4 (82.1-98.3)	98.6 (94.3-103.1)
AUClast	98.1 (94.3-101.9)	94.1 (92.6-106.6)	97.7 (94.2-101.3)
AUCinf	98 (94.2-102)	94 (92.5-106.3)	98.1 (94.3-102.0)

Table 2. "Secondary" Analysis (n=39)

Parameter	Active moiety	Risperidone	9-OH Respseridone
Cmax	88.1 (80.7-96.2)	86.2 (77.0-96.6)	93.8 (85.3-103.2)
AUClast	93.7 (85.8-102.3)	95.6 (87.0-105.2)	93.1 (85.1-101.9)
AUCinf	93.8 (86.1-102.2)	95.7(87.2-104.9)	93.5 (85.1-102.7)

Examination of the data indicated that 9-OH-risperidone data was missing from several patients. This data may be important in assessing the bioequivalence of the metabolite, as well as the active moiety.

Table 3. Missing data

Patient	Analytes	Problem	Outcome
30016	metabolites	Missing AUC_{∞}	Not resolved
30019	metabolites	Missing AUC_{∞}	Not resolved
30025	Parent, met, both	Missing all data for B treatment	withdrawn
30036	metabolite	Missing AUC_{∞}	Not resolved
30037	Parent, met, both	Data low for B treatment	Outlier; excluded

The plasma concentration-time curves for 9-OH-risperidone from patients 30016, 30019 and 30036 are shown below.

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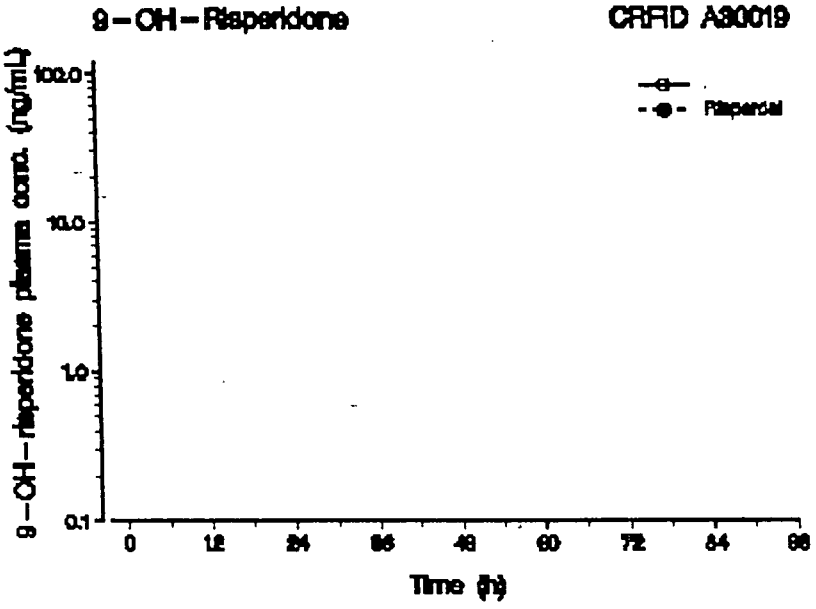

Figure 1. Plasma concentration vs. time curve for 9-OH-risperidone in patient 30016.

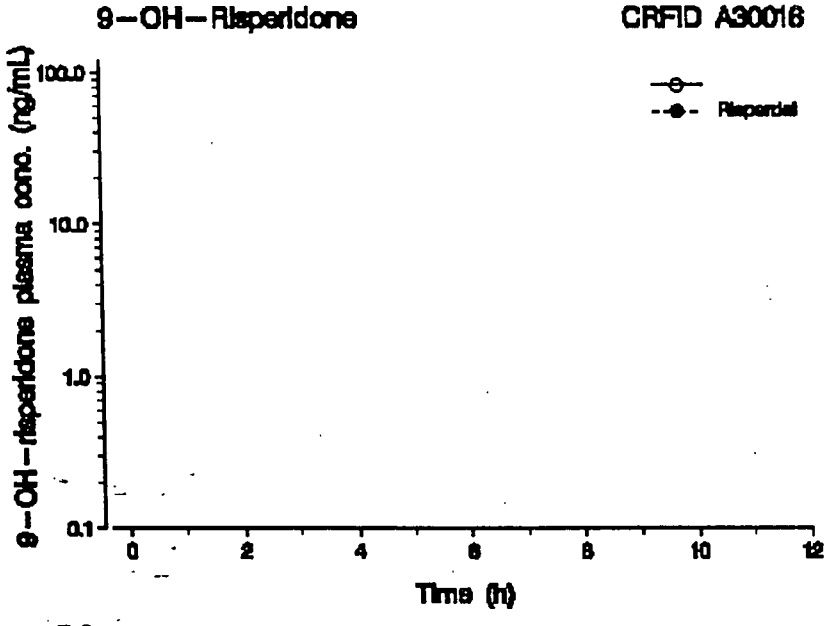

Figure 2. Plasma concentration vs. time curve for 9-OH-risperidone in patient 30019.

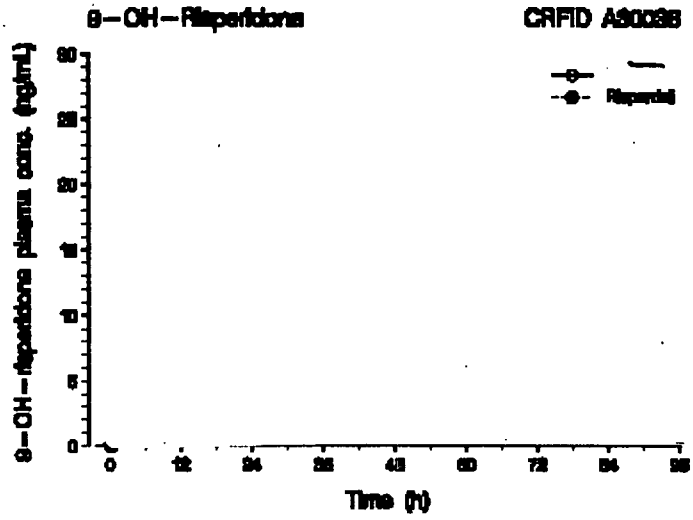

Figure 3. Plasma concentration vs. time curve for 9-OH-risperidone in patient 30036.

The plasma concentration-time curves suggest that the disposition of 9-OH-repseridone is essentially the same between the two formulations, and the reason for excluding the AUC_∞ data is unclear. In comparison to other patients, the terminal elimination of 9-OH-risperidone may be more prolonged, as indicated by the flatter terminal phases of the curves. However, FDA confirmed the applicant's determination of AUC and Cmax, and conclude that the two formulations pass the requisite bioequivalence criteria for C_{max} and AUC_∞.

3. Biowaiver for the 1.0 mg Risperdal — formulation. Bioequivalence was determined for the 0.5 and 2 mg strengths of Risperdal — Because 1.0 mg strength was intermediate between these two strengths, and because of the compositional proportionality of the of the formulations, and the comparability of the dissolution profiles in three media, a biowaiver from bioequivalence studies was granted for the 1.0 mg strength by FDA. The table below lists the components and amounts of each component in the 0.5, 1.0 and 2.0 mg Risperdal — formulations.

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Table 3.2.1-1: Risperidone Tablet Composition					
Component	Unit Quantity (mg per Tablet)			Function	Quality Standard
	0.5 mg	1 mg	2 mg		
Formulation Number	F554	F555	F556		
Risperidone	0.5	1.0	2.0	Drug Substance	DMF
Resin					DMF
Gelatin Type A					NF
Mannitol					USP
Glycine					USP
Simethicone					USP
Carbomer					NF
Sodium Hydroxide					NF
Aspartame					NF
Ferric Oxide					NF
Peppermint Oil					NF
Total Table Weight (mg)	*14.3*	*28.6*	*57.1*		

TM = Trademark of Janssen Pharmaceutica

4. Several preliminary comparative bioavailability studies were performed. RIS-BEL40 and RIS-BEL-47 were pilot bioequivalence studies that compared the 0.5 mg Risperdal — formulation to the conventional formulation. These studies were conducted in 6 and 8 healthy volunteers and suggested that bioequivalence between the formulations would be obtained. Additionally, RIS-BEL-48 and RIS-BEL-52 were pilot bioequivalence studies for the 4 mg strength of Risperdal — , which will not be marketed in the US at this time. The results of RIS-BEL-48 indicated that the C_{max} and AUC_{24} of the active moiety (96.6 ± 16.% and 105 ± 16.5 %, respectively) and AUC_{24} of risperidone (107 ± 12 %) would not have passed the FDA bioequivalence criteria, and the results of the RIS-BEL-52 study were not reported.

   Finally, the applicant conducted several taste studies to assess the palatability of the new Risperdal — formulation (RIS-BEL-39, RIS-BEL-48 AND RIS-BEL-51). Although unrelated to a bioequivalence assessment, the applicant reported that the new formulation was acceptably palatable.

2. Are the dissolution Method and Specification Appropriate for Risperdal —

No. The applicant submitted the following method and specification for 0.5, 1.0, and 2.0 mg Risperdal —

- USP Apparatus 2, paddle
- 50±2 rpm
- 37°C
- 500 mL 0.1 NHCl
- Q= —% in — minutes

However, the applicant only submitted data for a single method, and dissolution data for 0.5, 1.0 and 2 mg strengths in three media. The dissolution data for 4 mg strength (not to be marketed) was submitted in 5 media. The data for the dissolution of 0.5, 1.0 and 2.0

mg are shown in the 0.1 N HCl, purfied water and potassium buffer (pH 6.5) media in the figures below.

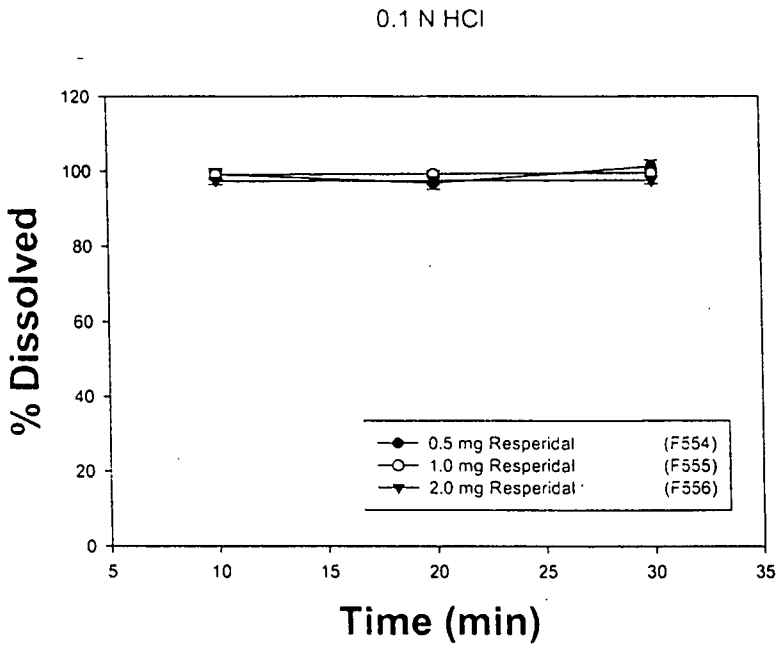


Figure 4. Dissolution profiles of Risperdal —— in 0.1 N HCl.

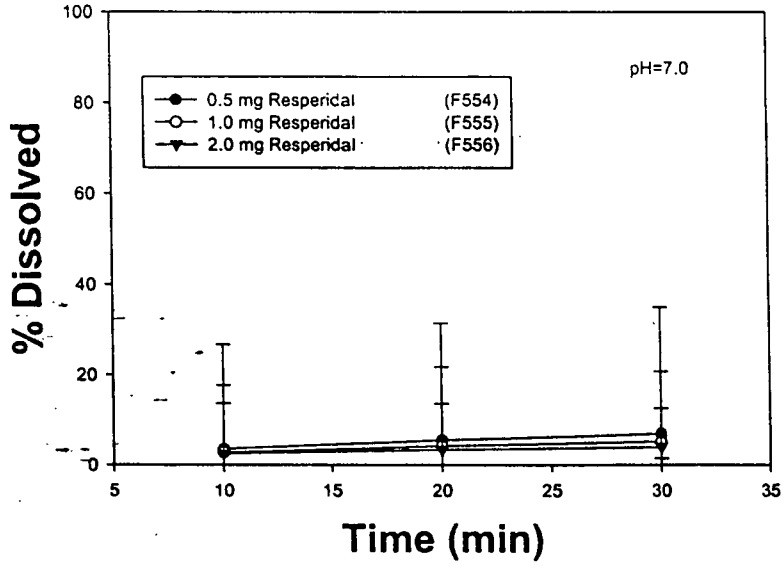


Figure 5. Dissolution profiles of Risperdal —— in purified water.

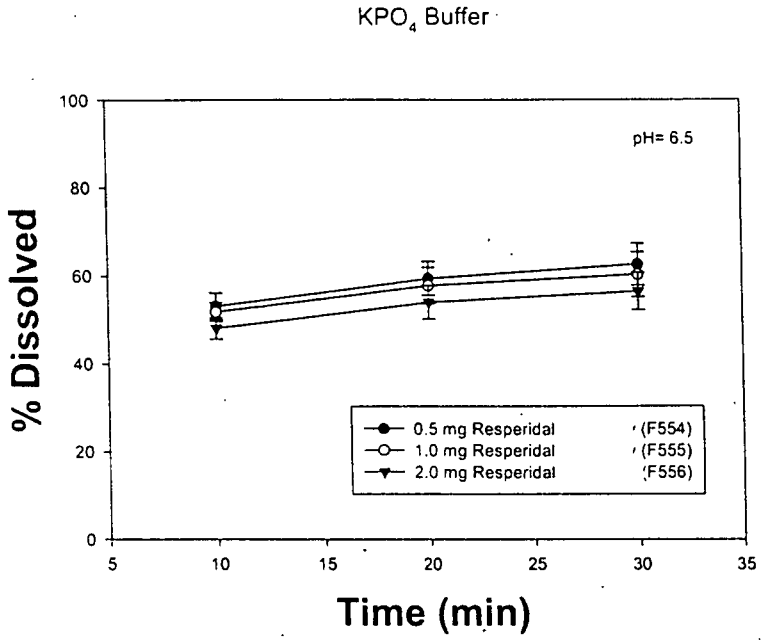


Figure 6. Dissolution profiles of Risperdal — in potassium phosphate buffer (pH 6.5)

Although there appears to be no difference between the three strengths of Risperdal —, in the 0.1 N HCl, all three are completely dissolved within 10 minutes. The specification of Q = — % in — minutes should be changed to Q = —% in 10 minutes.

5. Were the Analytical Assays Adequately Validated for the Bioequivalence Studies?

Yes. Two methods were used in the bioequivalence studies to measure plasma concentrations of risperidone and its active metabolite 9-OH-risperidone. In the RIS-NED-25 study, plasma concentrations of risperidone and its metabolite 9-OH-risperidone were simultaneously measured by a — method. The dynamic range of the assay was — ng/ml for both analytes. The LOQ was — ng/ml for both analytes. No significant discrepancies were noted with this assay.

In study RIS-USA-125, as well as the other pilot studies, plasma concentrations of reperidone and its metabolite 9-OH-risperidone were measured together (active moiety) with RIA-I, and risperidone alone was measured by RIA-II. The LOQ for RIA-I was — ng/ml and the dynamic range was — ng/ml. For RIA-II, the LOQ was — ng/ml, and the dynamic range for RIA-I was — ng/ml. Again, no significant discrepancies were noted, and these assays were deemed validated.

22 pages redacted from this section of the approval package consisted of draft labeling

VI. Study Synopses

1. RIS-NED-25 PIVOTAL BE

Open-label, randomized, two-treatment, two-period, two sequence cross-over study in 40 subjects.
2 mg risperidone RESPIRDAL —— vs.. 2 mg RESPIRDAL tablet

A. Assay validation

Risperidone and 9-hydroxyresperirdone

Range: —— ng/ml (11 points); linear
QC: 0.25, 10 and 200 ng/ml
Selectivity: No notable interference; some no more than 20% of LLOQ at in any case
Accuracy:

Table 3-2: Accuracy and precision of the —— method for the determination of risperidone - spiked quality control samples.

Analytical batch	Curve No.	Spiked ng/ml	Measured, ng/ml repl. 1	repl. 2	%CV	% Accuracy repl. 1	repl. 2
04-004							
04-005							
04-006							
04-007							
04-008							
04-009							
04-010							
04-011							
04-012							
04-013							
04-014							
04-015							
04-016							
04-019							
04-021							
04-022							
04-023							
04-024							
04-025							
04-026							
04-028							
04-029							
n							44
%Accuracy							104.0
%C.V.							7.7

[1] Accuracy out of limits (> 20%)

Table 3-2 (cont.) : Accuracy and precision of the ——— method for the determination of risperidone - spiked quality control samples.

Analytical batch	Curve No.	Spiked ng/ml	Measured, ng/ml repl. 1	repl. 2	%CV	% Accuracy repl. 1	repl. 2
04-004							
04-005							
04-006							
04-007							
04-008							
04-009							
04-010							
04-011							
04-012							
04-013							
04-014							
04-015							
04-016							
04-019							
04-021							
04-022							
04-023							
04-024							
04-025							
04-026							
04-028							
04-029							
n							44
%Accuracy							104.0
%C.V.							8.1

Accuracy out of limits (> 20%)

Table 3-2 (cont.) : Accuracy and precision of the ——— method for the determination of risperidone - spiked quality control samples.

Analytical batch	Curve No.	Spiked ng/ml	Measured, ng/ml repl. 1	repl. 2	%CV	% Accuracy repl. 1	repl. 2
04-004							
04-005							
04-006							
04-007							
04-008							
04-009							
04-010							
04-011							
04-012							
04-013							
04-014							
04-015							
04-016							
04-019							
04-021							
04-022							
04-023							
04-024							
04-025							
04-026							
04-028							
04-029							
n							44
%Accuracy							103.0
%C.V.							10.5

Accuracy out of limits (> 20%)

Table 3-3 (cont.): Accuracy and precision of the ___ method for the determination of 9-hydroxyrisperidone - spiked quality control samples.

Analytical batch	Curve No.	Spiked ng/ml	Measured, ng/ml repl. 1	repl. 2	%CV	% Accuracy repl. 1	repl. 2
04-004							
04-005							
04-006							
04-007							
04-008							
04-009							
04-010							
04-011							
04-012							
04-013							
04-014							
04-015							
04-016							
04-019							
04-021							
04-022							
04-023							
04-024							
04-025							
04-026							
04-028							
04-029							
n							44
%Accuracy							92.9
%C.V.							11.2

[1] Accuracy out of limits (> 20%)

Table 3-3: Accuracy and precision of the ___ method for the determination of 9-hydroxyrisperidone - spiked quality control samples.

Analytical batch	Curve No.	Spiked ng/ml	Measured, ng/ml repl. 1	repl. 2	%CV	% Accuracy repl. 1	repl. 2
04-004							
04-005							
04-006							
04-007							
04-008							
04-009							
04-010							
04-011							
04-012							
04-013							
04-014							
04-015							
04-016							
04-019							
04-021							
04-022							
04-023							
04-024							
04-025							
04-026							
04-028							
04-029							
n							44
%Accuracy							96.0
%C.V.							10.1

[1] Accuracy out of limits (> 20%)

Table 3-3 (cont.): Accuracy and precision of the , method for the determination of 9-hydroxyrisperidone - spiked quality control samples.

Analytical batch	Curve No.	Spiked ng/ml	Measured, ng/ml repl. 1	repl. 2	%CV	% Accuracy repl. 1	repl. 2
04-004							
04-005							
04-006							
04-007							
04-008							
04-009							
04-010							
04-011							
04-012							
04-013							
04-014							
04-015							
04-016							
04-019							
04-021							
04-022							
04-023							
04-024							
04-025							
04-026							
04-028							
04-029							
n							44
%Accuracy							93.0
%C.V.							8.1

[1] Accuracy out of limits (> 20%)

Table 3-7: Accuracy and precision of the method for the determination of 9-hydroxyrisperidone - back-calculated concentrations of calibration standards.

	Back-calculated concentrations, ng/ml										
Analytical batch	0.10	0.20	0.40	1.00	2.00	4.00	10.0	20.0	40.0	100	250
04-004											
04-005											
04-006											
04-007											
04-008											
04-009											
04-010											
04-011											
04-012											
04-013											
04-014											
04-015											
04-016											
04-019											
04-021											
04-022											
04-023											
04-024											
04-025											
04-026											
04-028											
04-029											
Mean	0.10	0.19	0.40	0.99	1.99	3.98	10.0	20.2	40.1	101	251
%C.V.	0.0	5.3	5.0	4.0	3.5	4.3	4.0	3.6	2.7	4.0	2.8
%Accuracy	100.0	95.0	100.0	99.0	99.5	99.5	100.0	101.0	100.3	101.0	100.4
n	22	22	20	22	21	22	22	22	21	21	22

[1] More than 15% deviation from nominal value; not used for calibration and for summary statistics
[2] Preparation error

Accuracy and precision for both is acceptable.

LLOQ: — ng/ml for both

Storage: -20°C

Stability:

- Benchtop: ——
- Freeze-Thaw: stable
- Long-term:

B. BE

Fasted overnight and for 2 hrs post dose; 10-21 day washout.
— administration. Tongue moistened, then — swallowed with saliva
Conventional Tablet administered 150 ml water.

Batch: TS55098 B; Formulation F556; batch size — tablets

Genetic testing done, but not described.
Blood sampling at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, and 96 hours.
Stored at –20°C

Stats: ANOVA, two-one side t-tests using GLM in SAS

BE, Cmax AUCinf etc 90%C.I. within 80-125%

Patient A30025, withdrawn after dose one due to AE.
Patient A30037 deemed outlier and excluded
Therefore, 39 patients enrolled; 38 analyzed in primary analysis
A30036 poor metabolizer 2D6:GE

Cmax; All data-sponsor.

Analyte	Concentration- ng/ml
—-parent	13.7 ± 6.06
Resperidine tablet-parent	15.8 ± 7.73
—-parent and metabolite	23.2 ± 6.50
Resperidine tablet-parent and metabolite	25.3 ± 7.84

Tmax was significantly longer for — than the tablet

Bioequivalence

BEST POSSIBLE COPY

Table 4-3: Bioequivalence statistics of the log transformed parameters C_{max}, AUC_{last}, and AUC_{inf} (primary analysis, n=38)

Parameter	Active moiety Ratio (90% CI)[a]	Risperidone Ratio (90% CI)[a]	9-hydroxy-risperidone Ratio (90% CI)[a]
C_{max} ng/mL	92.1 (87.5 - 96.9)	88.4 (81.0 - 96.6)	96.9 (94.0 - 100.0)
AUC_{last} ng.h/mL	98.1 (94.4 - 102.0)	99.3 (92.5 - 106.5)	97.6 (94.2 - 101.3)
AUC_{inf} ng.h/mL	98.0 (94.2 - 101.9)	99.0 (92.3 - 106.2)	98.1 (94.3 - 102.0)

[a] Treatment ratio: [illegible] versus RISPERIDAL tablet (90% confidence interval)

Table 4-4: Bioequivalence statistics of the log transformed parameters C_{max}, AUC_{last}, and AUC_{inf} (secondary analysis, n=39)

Parameter	Active moiety Ratio (90% CI)[a]	Risperidone Ratio (90% CI)[a]	9-hydroxy-risperidone Ratio (90% CI)[a]
C_{max} ng/mL	88.2 (80.6 - 96.5)	84.8 (75.7 - 94.9)	92.8 (85.6 - 100.7)
AUC_{last} ng.h/mL	93.7 (85.8 - 102.3)	95.5 (86.8 - 105.1)	93.1 (85.0 - 101.9)
AUC_{inf} ng.h/mL	93.7 (86.0 - 102.1)	95.4 (86.9 - 104.8)	93.4 (85.0 - 102.7)

[a] Treatment ratio: [illegible] versus RISPERIDAL tablet (90% confidence interval)

FDA Analysis: WinNonLin Pro 3.3 BE Wizard

Primary

Parameter	Active moiety	Risperidone	9-OH Respseridone
Cmax	91.9 (87.4-96.7)	89.4 (82.1-98.3)	98.6 (94.3-103.1)
AUClast	98.1 (94.3-101.9)	94.1 (92.6-106.6)	97.7 (94.2-101.3)
AUCinf	98 (94.2-102)	94 (92.5-106.3)	98.1 (94.3-102.0)

Secondary

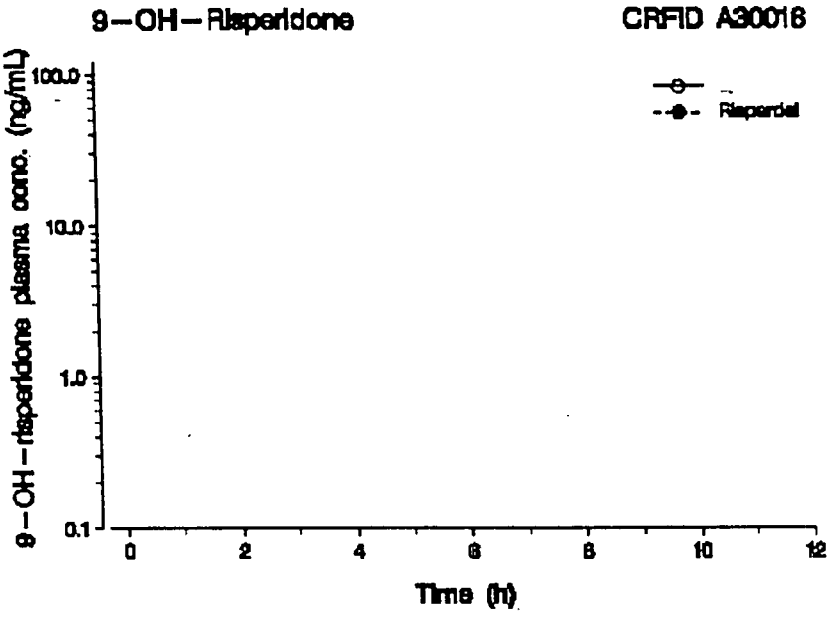
Parameter	Active moiety	Risperidone	9-OH Respseridone
Cmax	88.1 (80.7-96.2)	86.2 (77.0-96.6)	93.8 (85.3-103.2)
AUClast	93.7 (85.8-102.3)	95.6 (87.0-105.2)	93.1 (85.1-101.9)
AUCinf	93.8 (86.1-102.2)	95.7(87.2-104.9)	93.5 (85.1-102.7)

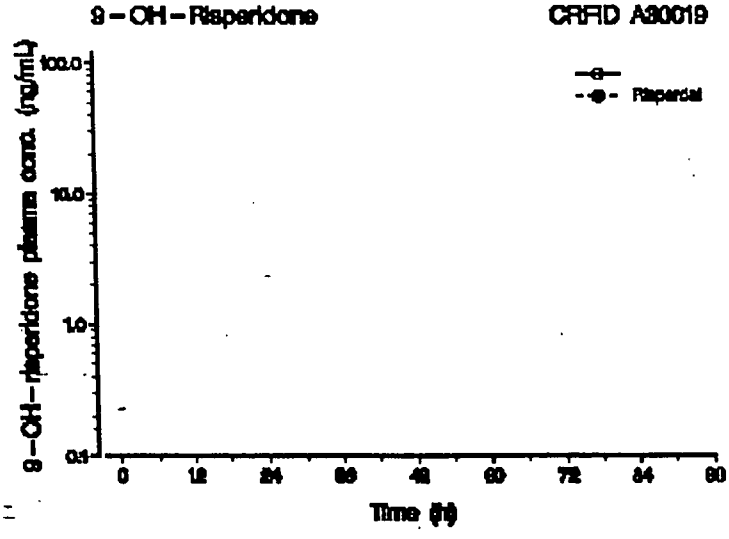
Problems

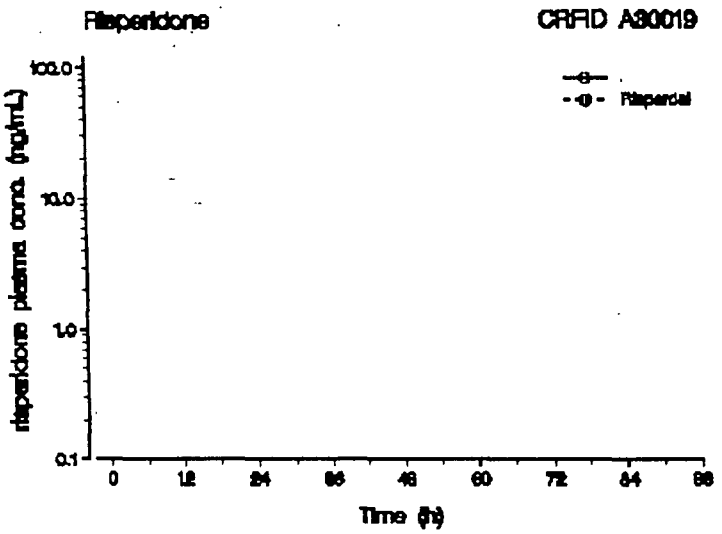
1. Some data missing:

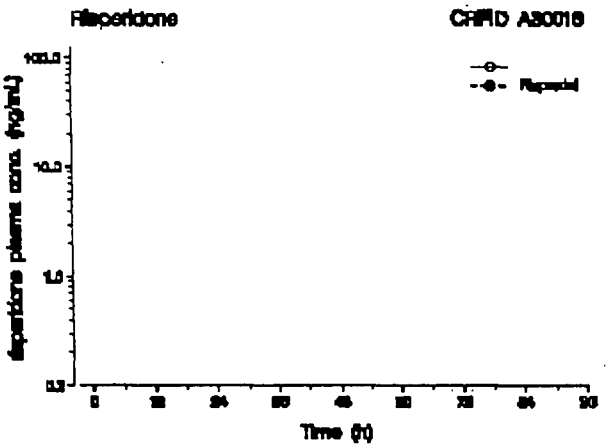
Patient	Analytes	Problem	Outcome
30016	metabolites	Missing AUCinf	Not resolved
30019	metabolites	Missing AUCinf	Not resolved
30025	Parent, met, both	Missing all data for B treatment	withdrawn
30036	metabolite	Missing AUCinf	Not resolved
30037	Parent, met, both	Data low for B	Outlier; excluded

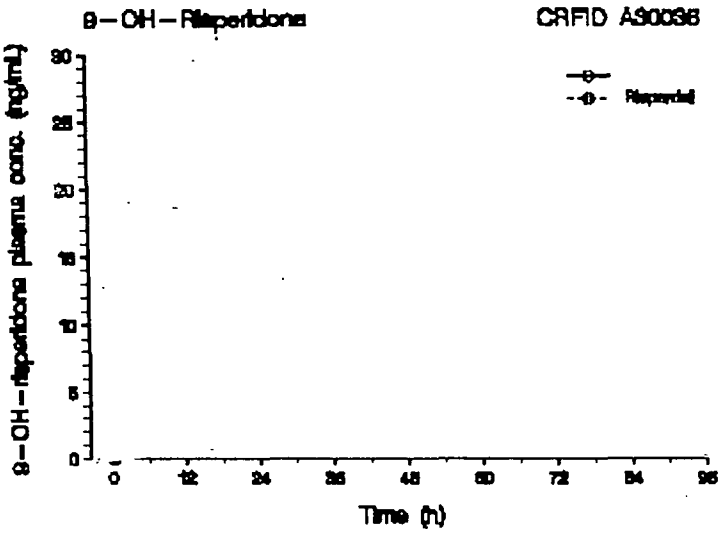
		treatment	


9-OH-Risperidone
CRFID A30016
9-OH-risperidone plasma conc. (ng/mL)
100.0
10.0
1.0
0.1
Risperdal
0
2
4
6
8
10
12
Time (h)


9-OH-Risperidone
CRFID A30019
9-OH-risperidone plasma conc. (ng/mL)
100.0
10.0
1.0
0.1
Risperdal
0
12
24
36
48
60
72
84
90
Time (h)


Risperidone
CRRD A30019
Risperdal
risperidone plasma conc. (ng/mL)
100.0
10.0
1.0
0.1
0
12
24
36
48
60
72
84
96
Time (h)


Risperidone
CRRD A30019
Risperdal
Time (h)



Conclusion: Plasma concentration profiles do not appear to be problematic. Formulation appears to meet BE criteria.

APPEARS THIS WAY
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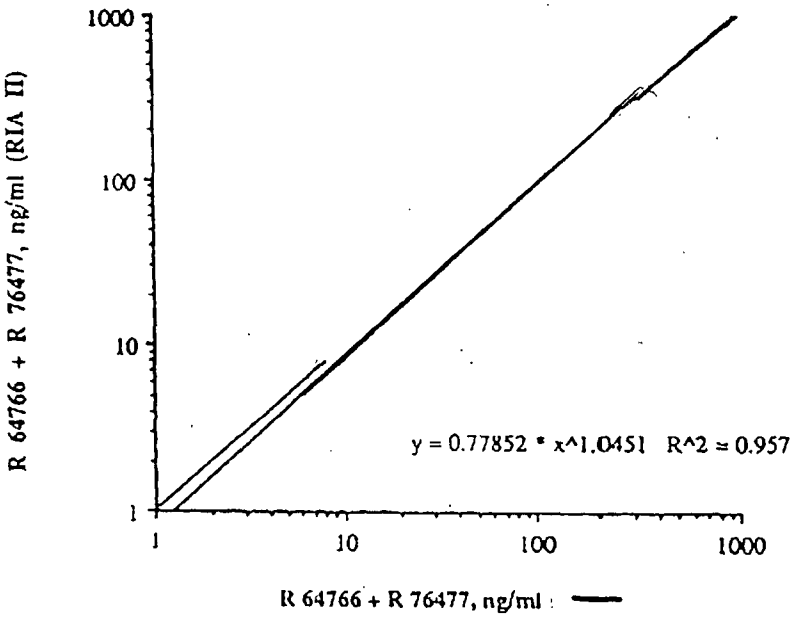
2. RIS-USA-125-PIVOTAL BE

A. Assay Validation

Assay: RIA for total (parent + metabolite; RIA-II) and parent (RIA-I) only

For total RIA-II. Calibration by respirdone (— ng/ml to — ng/ml)
IS antibody equally reactive to risperidone and 9-OH-risperidone?
Blanks; blank human plasma



LOQ: — ng/ml

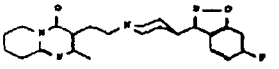
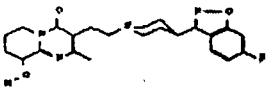
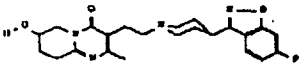
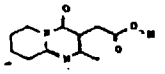
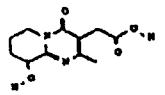
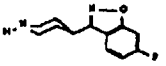
Accuracy

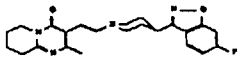
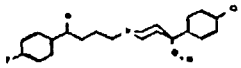
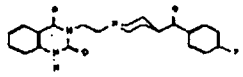
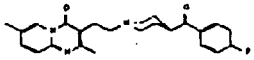
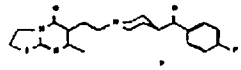
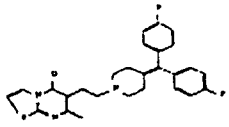
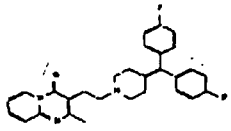
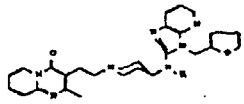
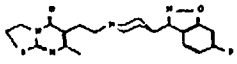
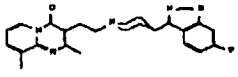
TABLE IV

ACCURACY AND PRECISION OF THE RIA METHOD FOR THE DETERMINATION OF RISPERIDONE IN PLASMA (RIA II)

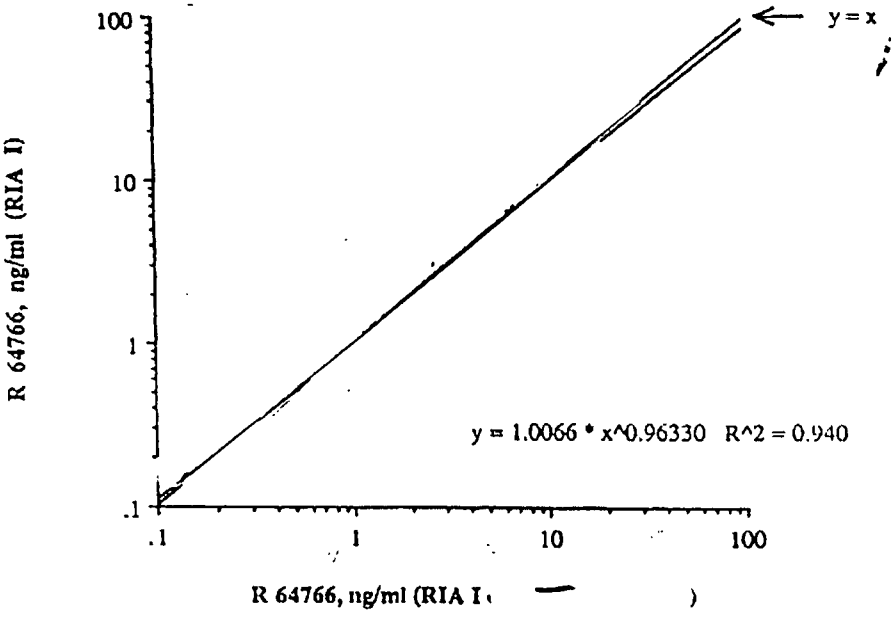
ng added	ng found (mean ± S.D.)	C.V.	Accuracy	n
0.020	0.018 ± 0.002	11.1%	90.0%	10
0.050	0.050 ± 0.003	6.0%	100.0%	12
0.100	0.102 ± 0.004	3.9%	102.0%	12
0.200	0.200 ± 0.003	1.5%	100.0%	13
0.500	0.490 ± 0.012	2.4%	98.0%	13
1.00	0.989 ± 0.045	4.6%	98.9%	13
2.00	2.13 ± 0.17	8.0%	106.5%	13
mean/range		5.4%	90.0% 106.5%	-

Specificity: tested against 9-OH-risperidone

COMPOUND	CHEMICAL STRUCTURE	ID_{50} (1)	(2)	(3)
R 64766 (risperidone)		1.0	1.0	1.0
R 76477 (9-hydroxyrisperidone)		12	150	0.9
R 79242 (7-hydroxyrisperidone)		8.5	560	1.3
R 78256 (metabolite)		> 5000	>5000	>5000
V 908-4 (metabolite)		>5000	>5000	>5000
R 56109 (metabolite)		>5000	>5000	>5000

COMPOUND	CHEMICAL STRUCTURE	LD_{50} (1)	(2)	(3)
R 64766 (risperidone)		1.0	1.0	1.0
R 1625 (haloperidol)		>5000	>5000	>5000
R 41468 (ketanserin)		>5000	>5000	850
R 50970 (mezenperone)		21	120	89
R 52245 (setoperone)		26	280	70
R 55667 (ritanserin)		>5000	>5000	>5000
R 56413 (seganserin)		700	>1000	>5000
R 57959 (ramastine)		18	500	>5000
R 63249		8.0	60	1.0
R 79598		150	350	2.9

RIA-I: calibration by risperidone (— to —ng/ml)



LOQ: — ng/ml

Accuracy:

TABLE III

ACCURACY AND PRECISION OF THE RIA METHOD FOR THE DETERMINATION OF UNCHANGED RISPERIDONE IN PLASMA (RIA I)

ng added	ng found (mean ± S.D.)	C.V.	Accuracy	n
0.025	0.026 ± 0.003	11.5%	104.0%	20
0.050	0.051 ± 0.003	5.9%	102.0%	21
0.100	0.100 ± 0.006	6.0%	100.0%	20
0.250	0.247 ± 0.009	3.6%	98.8%	21
0.500	0.497 ± 0.018	3.6%	99.4%	20
1.00	0.993 ± 0.067	6.7%	99.3%	21
2.50	2.68 ± 0.26	9.7%	107.2%	21
mean/range		6.7%	98.8% 107.2%	-

		Intra-assay variability		Inter-assay variability		
Method	Risperidone, ng/ml	C.V.	n	C.V.	R.E.	n
I	0.205	11.8%	11	14.9%	+ 9.1%	23
	2.56	9.0%	16	12.3%	- 2.4%	32
II	2.26	9.2%	10	15.9%	- 1.4%	20
	7.69	6.8%	10	12.5%	- 2.9%	20

Stability

Time (months)	Mean analytical recovery (%)
1	100.5
2	96.1
3	105.2
4	96.8
5	116.7
6	123.1
8	100.9

Conclusion: Both RIAs appear acceptable for the BE studies.

b. BE

Study Design: Single-center, randomized, two-way crossover comparing single doses of — 'Quicklet 2 x 0.5 mg (F554) to 2 x 0.5 mg tablets of Risperdal (F0) in healthy volunteers. Washout period was 14 days Reference was Treatment B (0.5 mg Risperdal tablets). Thirty-eight subjects (38) enrolled to ensure 34 for analysis. Patients should be equal numbers of males and females.

Batch: TS55298 B; Formulation F562; batch size — tablets

BE: ANOVA GLM/SAS

Blood sampling: 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96 hrs on both days.

Samples stored at or below –20 °C

Subjects: twelve withdrawn. 1 withdrew voluntarily, 11 withdrew due to missed samples.

36/50 were males, 39 of 50 were Hispanic

Table 4-1: Plasma pharmacokinetic parameters: active moiety

Pharmacokinetic parameter	[redacted]™/Quicklet™ 2 x 0.5 mg (N=43)		Risperdal® 2 x 0.5 mg (N=43)	
	Mean ± SD	Median	Mean ± SD	Median
t_{max} (h)	1.75 ± 0.67	1.52	1.49 ± 0.55	1.50
C_{max} (ng/mL)	12.28 ± 3.96	11.60	13.23 ± 3.86	13.10
AUC_{tau} (ng.h/mL)	200.81 ± 66.72	192.40	199.56 ± 73.62	194.22
AUC_{∞} (ng.h/mL)	211.24 ± 70.54	202.81	217.43[a] ± 87.03	202.60
$t_{1/2}$ (h)	22.14 ± 3.62	22.47	23.72[a] ± 5.22	23.26

a) N=42
Source: Display 16, Display 17

Table 4-2: Relative bioavailability of the active moiety (log transformed data)

Parameter	[redacted]™/Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max}	11.882	13.191	90.08	84.05 - 96.54
AUC_{tau}	194.630	198.361	98.12	91.98 - 104.67
AUC_{∞}	204.814	210.701	97.21	91.21 - 103.60

Source: Display 19

Table 4-3: Plasma pharmacokinetic parameters: risperidone

Pharmacokinetic parameter	[redacted]™/Quicklet™ 2 x 0.5 mg (N=43)		Risperdal® 2 x 0.5 mg (N=43)	
	Mean ± SD	Median	Mean ± SD	Median
t_{max} (h)	1.49 ± 0.62	1.50	1.25 ± 0.46	1.00
C_{max} (ng/mL)	8.43 ± 3.85	8.08	8.70 ± 3.87	8.42
AUC_{tau} (ng.h/mL)	46.47 ± 35.65	36.07	42.42 ± 35.08	32.07
AUC_{∞} (ng.h/mL)	47.56 ± 35.99	36.73	43.66 ± 36.39	33.15
$t_{1/2}$ (h)	3.66 ± 2.31	2.93	3.50 ± 2.52	2.69

Source: Display 20, Display 21

Table 4-4: Relative bioavailability of risperidone (log transformed data)

Parameter	[redacted]™ Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max}	8.063	8.542	94.39	85.91 - 103.70
AUC_{tau}	40.253	36.686	109.73	97.92 - 122.95
AUC_{∞}	41.331	37.605	109.91	98.40 - 122.77

Source: Display 23

Table 4-5: Plasma pharmacokinetic parameters: 9-hydroxy-risperidone

Pharmacokinetic parameter	— Quicklet™ 2 x 0.5 mg (N=43)		Risperdal® 2 x 0.5 mg (N=43)	
	Mean ± SD	Median	Mean ± SD	Median
t_{max} (h)	6.29 ± 7.42	5.00	5.05 ± 6.33	3.00
C_{max} (ng/mL)	6.13 ± 2.48	6.34	6.71 ± 2.44	6.71
AUC_{last} (ng.h/mL)	154.18 ± 55.92	145.49	156.18 ± 53.17	155.89
AUC_{∞} (ng.h/mL)	165.05 ± 58.51	156.05	172.83[a)] ± 57.83	165.81
$t_{1/2}$ (h)	22.98 ± 5.93	23.28	24.15[a)] ± 6.04	23.80

a) N=42
Source: Display 24, Display 25

Table 4-6: Relative bioavailability of 9-hydroxy-risperidone (log transformed data)

Parameter	— Quicklet™ 2 x 0.5 mg (A)	Risperdal® 2 x 0.5 mg (B)	% Ratio A:B	90% CI for ratio
C_{max}	5.470	6.203	88.17	82.74 - 93.96
AUC_{last}	145.108	152.871	94.92	89.12 - 101.10
AUC_{∞}	156.052	166.159	93.92	88.28 - 99.92

Source: Display 27

FDA re-analysis (n=31, power — %), all results virtually identical to sponsor.

Conclusion:

Acceptable.

3. RIS-BEL-40-BE Pilot-0.5 mg

Open-label, randomized 2-way cross-over study of 0.5 mg Risperdal — with conventional Risperdal tablets.

Subjects: 8 healthy subjects (4 males), 23 to 46 yrs.
Washout: 1 week.
Assay: RIA-I and II-validated.
Treatment A: 0.5 mg Risperdal — (F86)
Treatment B: 0.5 mg Risperdal tablet (F9)
Fasted overnight, no food until 2 hr post-dose
Sampling: 20, 40, 60, 90 min and 2, 3, 5, 8 hrs.
Tmax 0.5 hr later than conventional.

Results

Active Moiety (total)

Parameter	Risperdal —	Risperdal tablet
Cmax ng/ml	5.24	4.86
AUC24 ng•h/ml	27.6	28.3

Risperdal

Parameter	Risperdal —	Risperdal tablet
Cmax ng/ml	2.07	2.48
AUC8 ng•h/ml	8.57	8.81

Conclusion: Both are similar

4. RIS-BEL-47-BE Pilot 0.5 mg

Open-label, single-dose, randomized cross-over trial to assess relative BA and taste of 0.5 mg Risperdal — compared to conventional 0.5 mg Risperdal tablet.
Subjects: 6 healthy subjects.
Treatment A: 0.5 mg Risperdal —
Treatment B: 0.5 mg Risperdal tablet (reference)
Fasted overnight. No food until 2 hr post-dose.
Sampling: 0, 20, 40, 60, 90 minutes, and 2, 3, 5, 8,and 24 hours.
Assays: RIAs I and II
Results
Active Moiety (total)

Parameter	Risperdal —	Risperdal tablet	Ratio — /tablet
Cmax ng/ml	5.72 ± 1.84	6.04 ± 1.87	94.8 ± 7.7%
AUC24 ng•h/ml	65.8 ± 21.0	67.6 ± 24.6	98.7 ± 10%

Risperdal

Parameter	Risperdal —	Risperdal tablet	Ratio — /tablet
Cmax ng/ml	3.78 ± 1.5	3.84 ± 1.63	99.1 ± 15%
AUC24 ng•h/ml	23.9± 11.0	23.5 ± 12.0	105 ± 16%

Pilot study that investigated BE and taste.

5. RIS-BEL-48-BE 4 mg
Purpose: BE and taste of 4 mg Risperdal —
Randomized 2-way cross-over of 4 mg Risperdal — vs. 4 mg Risperdal tablet.
Subjects: 6 schizophrenic patients (5 males/1 female)
Washout: 10 days minimum
Sampling: 0, 20, 40, 60 and 90 min, 2, 3, 5, 8, and 24 hrs.
Assay: RIA-I and RIA-II-

Active Moiety (total)

Parameter	Risperdal —	Risperdal tablet	Ratio — /tablet
Cmax ng/ml	43.0 ± 8.3	44.0 ± 8.2	98.6 ± 16.5%
AUC24 ng•h/ml	566 ± 129	540 ± 110	105 ± 16%

Risperdal

Parameter	Risperdal —	Risperdal tablet	Ratio — /tablet

Cmax ng/ml	35.2 ± 9.0	46.3 ± 23.4	84.4 ± 21.2%
AUC24 ng•h/ml	402± 218	381 ± 198	107 ± 12%

Conclusion: probably would fail BE.

6. RIS-BEL-52-4mg

Purpose was to compare the pharmacokinetics of the new 4 mg formulation with the conventional Risperdal tablet. Schizophrenic patients were
30 patients were enrolled to ensure that 24 were available for analysis.
Study design: Randomized two-treatment, two-period cross-over design.
Treatment A: 4 mg Risperdal — (F562) and
Treatment B: 4 mg Risperdal tablet (F31), reference.
Patients were fasted over night and for four hours post-dose
Patient Demographics: 32 enrolled, 28 patients completed the trial; 56.3% male; median age was 38 (23 to 54 years).
1 patient withdrew.
Sampling: 0.5, 1, 2, 3, 4, 5, 8, 10, 24, 32,48, 56, 72, 96 and 104 hrs.
Bioanalysis was conducted using the validated RIAs for total and parent
No data currently available.

7. RIS-BEL-39-Taste

Purpose: Assess taste and texture of 4 mg Risperdal —
Subjects: 12 subjects
Study Design: Single dose of 4 mg risperdal
No BE data.

8. RIS-BEL-51-Taste-0.1, 1, 2 and 4 mg

Conclusion: — preferred to Risperdal tablets
Subjects: 60 schizophrenic and affective disorder patients.
Study design: Randomized cross-over
Food: with and without food/beverage

APPEARS THIS WAY
ON ORIGINAL

C. Chemistry/Dissolution

Table 3-1: Risperidone — Formulations To Be Marketed		
Strength	**Formula**	**Description**
0.5 mg	F554	Round, light coral, biconvex, etched "R0.5"
1 mg	F555	Square, light coral, biconvex, etched "R1"
2 mg	F556	Round, light coral, biconvex, etched "R2"

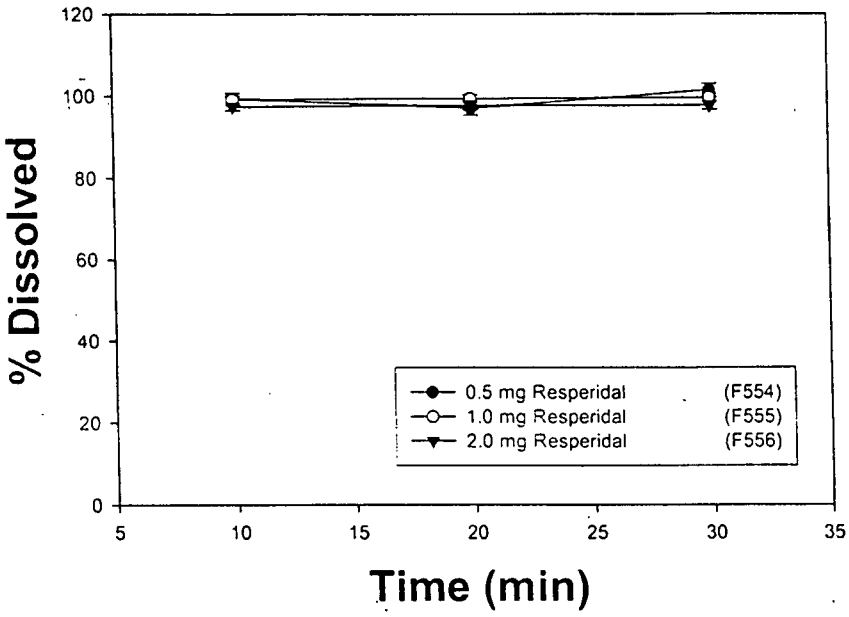
Table 3.2.1-1: Risperidone — Tablet Composition					
Component	**Unit Quantity (mg per Tablet)**			**Function**	**Quality Standard**
	0.5 mg	**1 mg**	**2 mg**		
Formulation Number	**F554**	**F555**	**F556**		
Risperidone	0.5	1.0	2.0		
Resin					DMF
Gelatin Type A					NF
Mannitol					USP
Glycine					USP
Simethicone					USP
Carbomer					NF
Sodium Hydroxide					NF
Aspartame					NF
Ferric Oxide					NF
Peppermint Oil					NF
Total Table Weight (mg)	*14.3*	*28.6*	*57.1*		

TM = Trademark of Janssen Pharmaceutica

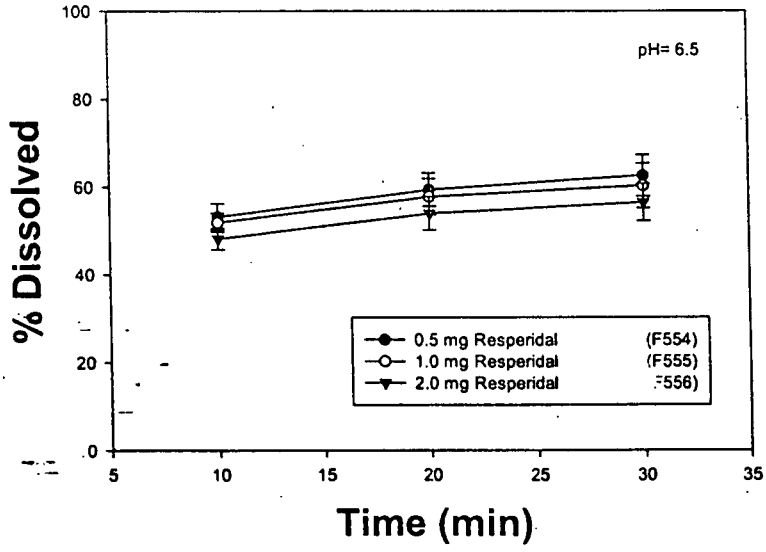
Dissolution specification/method

USP Apparatus 2, paddle
50 rpm
500 mL 0.1 N HCl
37°C
Q — % in — min, Single point (— min); 10, 20 30 for profile

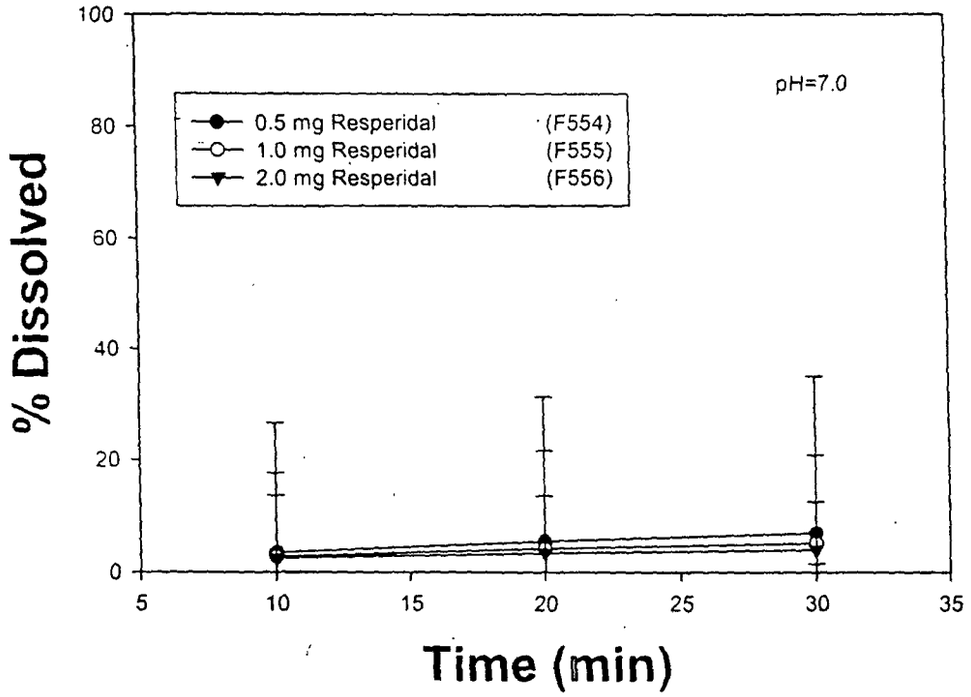
0.1 N HCl



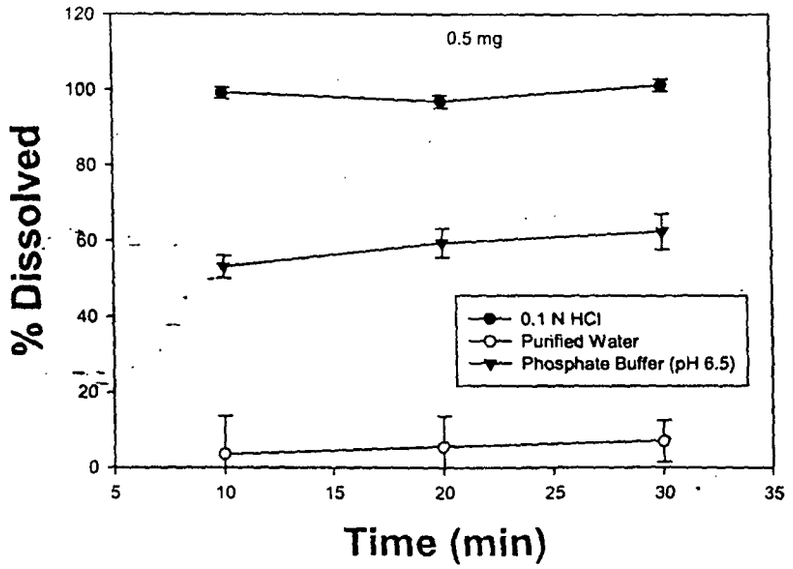
KPO_4 Buffer

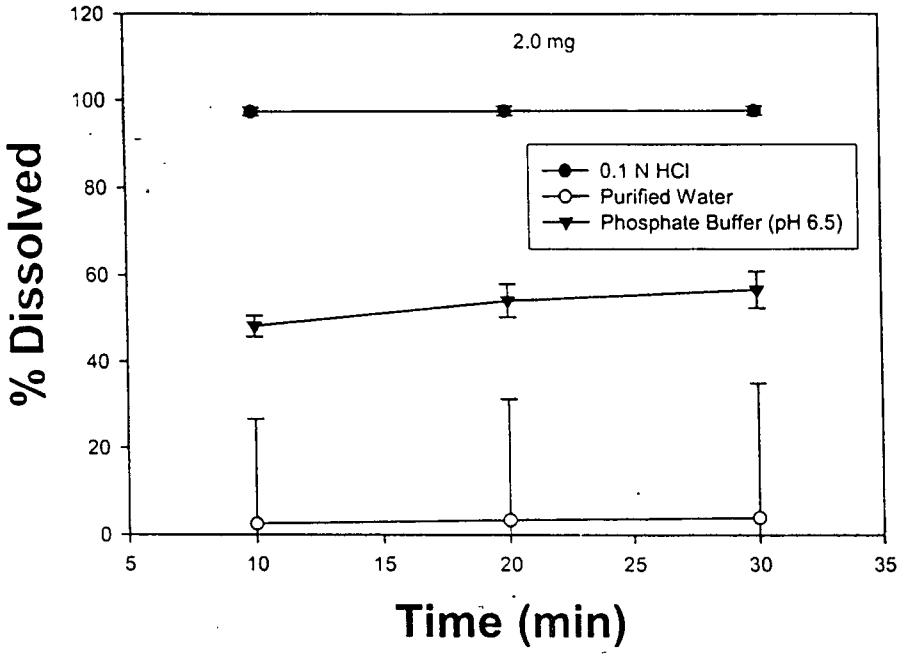


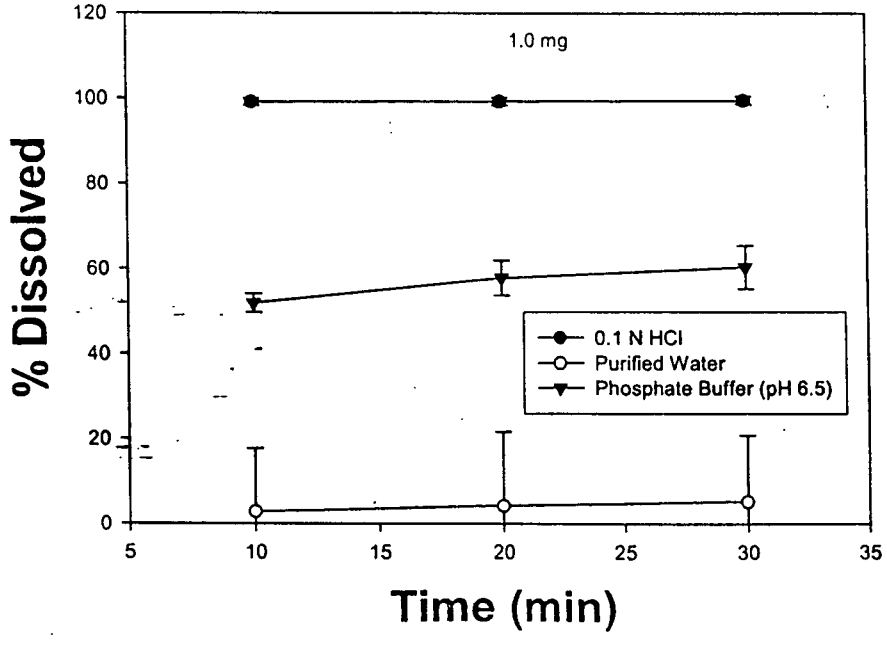
Purified Water

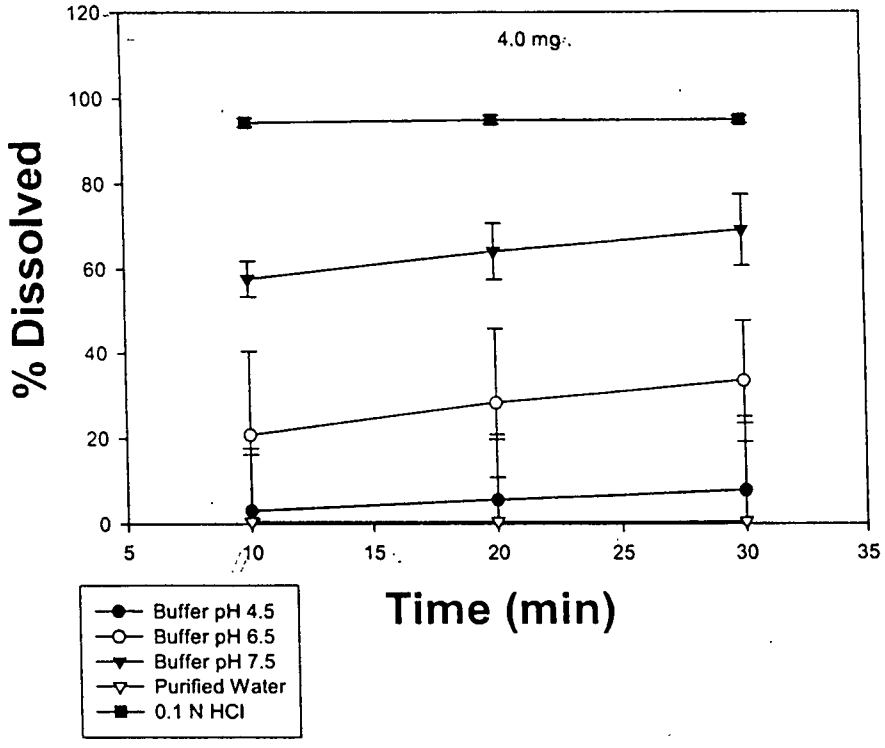


Dissolution method: See JRTC Report 98-02-01
Lots 0.5 mg TS16701, 1.0 mg TS17001, 2 mg TS17301.




2.0 mg
% Dissolved
Time (min)
0.1 N HCl
Purified Water
Phosphate Buffer (pH 6.5)
120
100
80
60
40
20
0
5
10
15
20
25
30
35


1.0 mg
% Dissolved
Time (min)
0.1 N HCl
Purified Water
Phosphate Buffer (pH 6.5)
120
100
80
60
40
20
0
5
10
15
20
25
30
35



All data used 12 units.

Specification and method 0.5, 1.0, 2.0 mg Risperdal —

USP Apparatus 2, paddle 50 rpm
Media: 500 ml, 0.1 N HCl , 37°C
Sample times 10, 20, 30 min.
Q= —% in — minutes .

FDA recommendation: Q = —% in 10 min

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	NDA 21-444	Brand Name	Risperdal® [redacted]
OCPB Division 1	HFD-860	Generic Name	risperidone
Medical Division	HFD-120	Drug Class	Benzisoxazole derivatives
OCPB Reviewer	Maria Sunzel, Ph.D.	Indication(s)	Treatment of schizophrenia
OCPB Team Leader	Ramana Uppoor, Ph.D.	Dosage Form	Orally disintegrating tablets 0.5 mg, 1mg, & 2 mg strengths
Date of Submission	November 16, 2001	Dosing Regimen	BID or QD Initial titration to effect (4-8 mg/day gives max. effect)
Estimated Due Date of OCPB Review	ASAP (late June, 2002)	Route of Administration	Oral
PDUFA Due Date	September 19, 2002	Sponsor	Janssen Research Foundation
Division Due Date	End-June, 2002 (at the latest)	Priority Classification	3S (new formulation)

BACKGROUND:
The Agency has approved two oral formulations (0.25, 0.5, 1, 2, 3, 4 mg IR tablets & 1 mg/mL solution) of risperidone.

This new NDA concerns orally disintegrating risperidone tablets (0.5 mg, 1 mg, and 2 mg strengths) intended for adult schizophrenic patients who have difficulty swallowing tablets, or are uncooperative or wary of taking medication. Risperdal [redacted] tablets can be taken without water. The tablet rapidly disintegrates in the mouth, releasing risperidone bound to a resin into the saliva prior to swallowing.

The sponsor has performed 8 Phase I studies in a total of 214 subjects (104 healthy volunteers & 110 schizophrenic patients), see attachment for study descriptions. PK data is available in 96 healthy volunteers. All studies were single dose bioequivalence and safety studies, no clinical efficacy studies were performed. Risperidone [redacted] tablets were studied in the dose range 0.5 - 4 mg.

PK information from the submitted trials covers the following items:
- Bioequivalence ([redacted] *vs.* approved IR Risperdal tablets after single doses; 0.5 & 2 mg tablets) – No data on 1 mg [redacted] tabl, but data can be bracketed - tabl strengths are compositionally proportional (see Attachment)
- Relative bioavailability (pilot formulations)
- Investigations of taste and texture, with and without food (no PK sampling)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	No. studies submitted	No. studies reviewed	Comments
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Electronic submission
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	Incomplete			Need to contact sponsor for documentation (Addenda missing for study RIS-NED-25)
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I):				
Healthy Volunteers-				
single dose:	X	4		2 studies w/pilot formulations, 2 w/TBM formulations RIS-NED-25; RIS-USA-125)

multiple dose:	-			
Patients-				
single dose:	X	4		3 studies w/pilot formulations, 1 w/TBM formulation (but higher, 4 mg, strength than TBM)
multiple dose:	-			
Dose proportionality -				
fasting / non-fasting single dose:	-			
fasting / non-fasting multiple dose:	-			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			
pediatrics:	-			Waiver request
geriatrics:	-			
renal impairment:	-			
hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
Population Analyses -				
Data rich:	-			
Data sparse:	-			
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			Commercial IR tablet as ref.
Bioequivalence studies -				
traditional design; single dose:	X			0.5 & 2mg TBM formulations
replicate design; single / multi dose:	-			
Food-drug interaction studies:	-			
Dissolution:	X			In CMC section, 5 pH media
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			Deferral, proposal sent to FDA May 2000
Literature References	X			Available electronically
Total Number of Studies	8			5 studies contain PK info (1 study PK not yet available, 2 studies no PK) See attachment

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	• The sponsor is asked to provide Addenda no. 1, 3, 4, 5, & 8 to the Assay Validation Report for Study RIS-NED-25 • Please provide data sets (as SAS transport files) for the pharmacokinetic parameters (individual values) from studies RIS-NED-25 and RIS-USA-125. • Is the sponsor planning to submit the pharmacokinetic evaluation for Study RIS-BEL-52 to this NDA? If yes, when will the data be submitted? • The sponsor is requested to submit the individual values for the *in vitro* dissolution data in 5 pH media (presented in CMC Report 98-02.01), and also clarify which tablet strength is presented in the report (as a figure) for the validation of the media & selection of the proposed *in vitro* dissolution method. • The sponsor is requested to submit comparative dissolution data for the 1 mg strength in at least 3 pH media, compared to either the 0.5 mg or the 2 mg (biobatch) strength
QBR questions (key issues to be considered)	• Is the cross-validation between the RIA and the [redacted] method acceptable? • Has bioequivalence been established between the [redacted] and commercially available IR Risperdal tablets? • Can a waiver be granted for the 1 mg [redacted] tablet strength? • Can it be assumed that the reported decrease in salivation after repeated risperidone doses (2 [redacted]tiple tablets) does not adversely affect the bioavailability of the [redacted] tablets at steady state compared to single doses? Should specific instructions (add a sip of water if dry mouth) be included in the label? • Is the proposed *in vitro* dissolution method acceptable? • Does the submitted data support the proposed label text?	
Other comments or information not included above	DSI will make full inspections of the clinical and bioanalytical sites used for the pivotal bioequivalence studies (RIS-NED-25 & RIS-USA-125). The sponsor has also provided background information on the pharmacokinetics of risperidone (basic properties, DDIs, special populations) from earlier risperidone NDAs (oral formulations: solution & tablets)	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

cc: NDA 21-444, HFD-850 (Electronic Entry /Lee), HFD-120 (Hardeman), HFD-860 (Mehta, Uppoor, Sahajwalla, Sunzel)

Table 1: Clinical trials of the risperidone [redacted] Quicklet development program

Trial	Study population	Dose	Objective	Discussed in summary
RIS-BEL-40[PK 1]	Volunteers	0.5 mg	bioavailability	Yes
RIS-BEL-47[PK 2]	Volunteers	0.5 mg	bioavailability	Yes
RIS-USA-125[PK 3]	Volunteers	2 x 0.5 mg	bioequivalence	Yes
RIS-NED-25[PK 4]	Volunteers	2 mg	bioequivalence	Yes
RIS-BEL-39	Patients	4 mg	taste	No
RIS-BEL-48[PK 5]	Patients	4 mg	bioavailability	No
RIS-BEL-51[PK 6]	Patients	0.5, 1, 2 and 4 mg	taste	No
RIS-BEL-52	Patients	4 mg	bioequivalence	No

Table. Overview of the clinical trials of Risperdal [redacted] tablets

Trial	Study Phase	Primary Aim	R[redacted] dose	Treatment Duration	Number of volunteers/ patients
RIS-BEL-40	I	PK (Rel BA)	1x0.5 mg R[redacted]*; 1x0.5 mg tabl. (commerc. available)	Single dose	8 (4F/4M, Cauc) Volunteers
RIS-BEL-47	I	PK (Rel BA, taste)	1x0.5 mg R[redacted]*; 1x0.5 mg tabl. (commerc. available)	Single dose	6 (2F/4M, Cauc) Volunteers
RIS-USA-125	I	PK (bioequivalence)	2x0.5 mg R[redacted]#; 2x0.5 mg tabl. (commerc. available)	Single dose	50 (14F/36M, 12% Cauc; 78% Hisp; 10% Black) Volunteers
RIS-NED-25	I	PK (bioequivalence)	1x2 mg R[redacted]#; 1x2 mg tabl. (commerc. available)	Single dose	40 (18F/22M, 97.5% Cauc) Volunteers
RIS-BEL-39	*I*	**No PK** *Taste, texture, tolerability*	*1x4 mg R[redacted]**	*Single dose*	*12 (6F/6M, 83.3% Cauc, 16.7% Asian) Patients*
RIS-BEL-48	I	PK (Rel BA, taste)	1x4 mg R[redacted]*; 1x4 mg tabl. (commerc. available)	Single dose	6 (1F/5M, Cauc) **Patients**
RIS-BEL-51	*I*	**No PK** *Taste of R[redacted] (4 strengths R[redacted] compared to IR)*	*0.5, 1, 2 & 4 mg R[redacted]* w or w/o food & beverage; 0.5, 1, 2 & 4 mg tabl. (commerc. available)*	*Single dose*	*60 (22F/38M, 93.3% Cauc, 1.7% Oriental, 5% other) Patients*
RIS-BEL-52**	I	PK (bioequivalence)	1x4 mg R[redacted]#; 1x4 mg tabl. (commerc. available)	Single dose	32 (14F/18M, 96.9% Cauc, 3.1% Hisp) **Patients**

Pilot formulation; # to-be-marketed formulation; ** PK results not available at filing

3.2. Composition

3.2.1. QUANTITATIVE INGREDIENT STATEMENT PER UNIT

The quantitative composition per unit dose of the proposed Risperidone — Tablets is as follows.

Table 3.2.1-1: Risperidone — Tablet Composition

Component	Unit Quantity (mg per Tablet)			Function	Quality Standard
	0.5 mg	1 mg	2 mg		
Formulation Number	F554	F555	F556		
Risperidone	0.5	1.0	2.0	Drug Substance	DMF
— Resin					DMF
Gelatin Type A					NF
Mannitol					USP
Glycine					USP
Simethicone					USP
Carbomer —					NF
Sodium Hydroxide					NF
Aspartame					NF
Ferric Oxide					NF
Peppermint Oil					NF
Total Table Weight (mg)	*14.3*	*28.6*	*57.1*		

TM = Trademark of Janssen Pharmaceutica

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/s/

Brian Booth
7/26/02 03:56:40 PM
BIOPHARMACEUTICS

Patrick Marroum
7/26/02 04:00:23 PM
BIOPHARMACEUTICS

22 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Russell Katz
4/2/03 08:31:08 AM