CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20588/S002 AND 20272/S007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 8 1997

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA NUMBER: 20,272 **SPONSOR:** Janssen Research Foundation
Titusville, NJ 08560-0200

SUBMISSION DATE: November 26, 1996

OCPB RECEIPT DATE: December 6, 1996

DRUG NAME: Risperdal® (Risperidone)

DOSAGE FORM: Tablets (4 mg and 8 mg)

INDICATION: Psychosis **REVIEWER NAME:** Vijay K. Tammara, Ph.D.

SUBJECT: Label Change: Addition of QD Dosing Regimen

BACKGROUND:

Risperdal® (risperidone) is an anti-psychotic drug marketed by Janssen. It is currently available as 1 mg, 2 mg, 3 mg, and 4 mg tablets; although a 5 mg tablet has also been approved, it is not currently marketed (original OCPB review dated: Nov 12, 1993).

The current submission is a Supplemental Application to the original New Drug Application for Risperdal® (risperidone) Tablets. This application contains a bioequivalence study (RIS-BEL-33) involving an immediate release dosage formulation in two different strengths (new 8 mg tablet and 4 mg existing marketed tablet) to demonstrate bioequivalence between a once a day (Treatment A; QD new 8 mg) and twice a day (Treatment B; BID of existing 4 mg) dosing regimen of Risperdal for both rate and extent of absorption under steady-state conditions. It was an open two-way crossover study in 24 chronic schizophrenic patients stabilized on 4 mg risperidone bid for at least two weeks prior to the trial. Patients received treatments A and B each for one week according to a randomized crossover scheme. Blood samples prior to dosing on days 6 and 7 and at 0.5, 1, 2, 4, 8, 12, and 24 hours for treatment A; and at 0.5, 1, 2, 4, 8, and 12 hours for treatment B after dosing on day 7 were taken to measure the plasma concentrations of risperidone and the active moiety (risperidone plus 9-hydroxy risperidone) using radioimmunoassays.

The sponsor had also submitted three well-controlled clinical trials (RIS-USA-72, RIS-USA-60, and RIS-INT-10) to support the new QD dosing regimen.

RESULTS:

Only 23 subjects completed the study. Two patients had unusually low plasma levels for both risperidone and the active moiety. Hence, data from these patients was excluded in calculating relative bioavailability and average steady-state plasma concentrations. Further, the sponsor reported that 6 patients were classified as poor metabolizers and the other 15 as extensive metabolizers. The data of poor metabolizers was excluded to calculate mean steady-state pharmacokinetic parameters. However, the pooled data of 21 subjects (inclusive of poor and extensive metabolizers) was used to calculate relative bioavailability and average steady-state plasma concentration for both treatments. The relative bioavailabilities for risperidone and active moiety were 93% with 90% confidence intervals of 81-106% (risperidone) and 86-99% (active moiety) indicating comparable bioavailability of 8 mg once daily and 4 mg twice daily dosing regimen (Attachment 1). However, the two treatments can not be concluded as bioequivalent as steady state pharmacokinetic parameters such as Cmax, Cmin, and $AUC_{0-\tau}$ were not tested for bioequivalence.

Comment:

1) The sponsor should perform 90% confidence interval analysis using the two one-sided t-test procedure for all key pharmacokinetic parameters (Cmax, Cmin and $AUC_{0-\tau}$) of risperidone, its active metabolite, 9-hydroxy-risperidone, and the active moiety (risperidone+9-hydroxy-risperidone) to show bioequivalence between two treatments using log transformed values.

RECOMMENDATION:

From a pharmacokinetic standpoint, bioequivalency between 8 mg risperidone tablet given as once a day (QD) and 4 mg tablet given as twice a day (BID) has not been demonstrated.

Please, forward this **Recommendation** and **Comment 1** to the sponsor.

09/08/97

Vijay K. Tammara, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 9/8/97.

cc: NDA 20-272, HFD-120, HFD-860 (Tammara, Baweja, Malinowski), and CDR (Barbara Murphy for Drug files).

ATTACHMENT I

SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN RESEARCH FOUNDATION **Finished product:** Risperdal **Active compound:** (R064766)	
Title: A bioequivalence study comparing an 8-mg risperidone tablet with a 4-mg risperidone tablet in chronic schizophrenic patients. Part I: Pharmacokinetics	**Trial N.o.:** RIS-BEL-33 **Clinical phase:** III
Investigator: J. Pandraea, M.D.	**Country:** Belgium
Reference: JRF, Clinical Research Report RIS-BEL-33, February 1995	
Trial period: Start: 5 April 1994 End: 27 October 1994	**No. of investigators:** 3 **No. of subjects:** 24
Objectives: To compare the steady-state oral bioavailability of an 8-mg risperidone tablet with a 4-mg risperidone tablet in chronic schizophrenic patients.	
Trial design: open, randomized, two-way cross-over.	

Subject selection

- Inclusion criteria:
  - male or female between 18 and 65 years of age.
  - fulfilling the diagnostic criteria of chronic or subchronic schizophrenia as defined by DSM-III-R (295.21-295.22-295.11-295.12-295.31-295.32-295.91-295.92-295.61-295.62).
  - patients are stabilized on oral risperidone 4 mg twice daily for at least 2 weeks.
  - patients (or their legal guardians) give their informed consent prior to entry into the trial.
- Exclusion criteria:
  - female patients of reproductive age without adequate contraception.
  - female patients who are pregnant or lactating.
  - patients with mental disorders on Axis I (DSM-III-R) other than schizophrenia.
  - patients who have received a depot neuroleptic injection within one treatment cycle at the time of selection.
  - patients with clinically relevant organic or neurologic diseases.
  - patients with clinically relevant abnormal laboratory tests.
  - patients with clinically relevant abnormal ECG findings.
  - patients with a febrile illness 3 days prior to the first drug administration.
  - patients who have donated blood within 60 days prior to the trial.
  - patients who have been included in trials with investigational drugs during the 4 weeks preceding the trial.

Treatment	A	B
Dosage form	an 8-mg risperidone tablet	a 4-mg risperidone tablet
Dosing regimen	8 mg per os, once daily for one week	4 mg per os, twice daily for one week
Batch number	93K15/F64	93E13/F12
Disallowed medication	none	

Assessments	Plasma concentrations of risperidone and the active moiety (sum of risperidone and its active metabolite, 9-hydroxy-risperidone) prior to the morning drug intake on day 6 and day 7 of each treatment and at the following time points on day 7 after the morning drug intake: treatment A: 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose treatment B: 0.5, 1, 2, 4, 8 and 12 hours post-dose
Bioanalysis	Radioimmunoassay procedures (RIA I and II) were used to determine the plasma concentrations of risperidone (RIA I) and the active moiety (RIA II). The detection limits were 0.1 ng/ml (RIA I) and 0.2 ng/ml (RIA II).
Pharmacokinetic analysis	• C_{max}, C_{max}, T_{max}, AUC_{0-12h}, $AUC_{0-\infty}$, C_{ss} and F_{rel} based on actual plasma concentration-time curve and the non-compartmental analysis.
Statistical methods	• Descriptive statistics for the pharmacokinetic parameters and for the risperidone and active moiety plasma concentration at each blood sampling time-point. • Analysis of Variance for both C_{ss} (= $AUC_{0-\tau}/\tau$, τ is the dosing interval) and log of C_{ss} . • Classical 90%-confidence interval of the C_{ss} ratio (treatment A vs B).

Main features of the trial sample and summary of the results

Baseline characteristics - patient disposition	
Number of subjects entered (M/F)	13/11
Age: mean±SD (min-max), years	36 ± 7 (23-54) (excluding the drop-out)
Weight: mean±SD (min-max), kg	69 ± 15 (40-94) (excluding the drop-out)
Height: mean±SD min-max), cm	169 ± 11 (148-193) (excluding the drop-out)
Drop-outs: number / reason	1 / patient became uncooperative

Results: Pharmacokinetics

Table 1. Relative bioavailability

Parameters	Least-squares means (ANOVA)[a]		F_{rel}	90%
	-test (treatment A)- (8 mg once daily)	-reference (treatment B)- (4 mg twice daily)	(%)	C.I.
-Risperidone				
C_{ss} , ng/ml[b]	30.6	32.8	93	81-106
log C_{ss} [c]	19.5	21.9	89	79-100
-Active moiety				
C_{ss} , ng/ml	90.3	97.6	93	86-99
log C_{ss} [c]	81.3	90.3	90	85-96

[a] n=21, excluding two patients who had very low plasma levels due to either possible non-compliance (patient no. 2) or the concomitant intakes of carbamazepine (patient no. 12).

[b] C_{ss} =AUC0-τ/τ (for treatment A, τ=24 hours; for treatment B, τ=12 hours).

[c] data analysed on log-scale but statistics transformed back to linear scale.

Table 6 Median steady-state fluctuation

Parameters (n=29)	test (treatment A) (8 mg once daily)	reference (treatment B) (4 mg twice daily)
Risperidone		
C_{av}, ng/ml[a]	13.6	17.3
C_{min}, ng/ml	2.4	7.2
C_{max}, ng/ml	76.3	48.2
Fluctuation, %[b]	382	183
Active moiety		
C_{av}, ng/ml	71.5	80.4
C_{min}, ng/ml	40	58.4
C_{max}, ng/ml	142	113
Fluctuation, %	145	66.4

[a] C_{av} = AUC0-τ/τ (for treatment A, τ = 24 hours; for treatment B, τ = 12 hours).
[b] Fluctuation, % = (C_{max}-C_{min})/C_{av} x 100%, n = 22, patient no. 2 was not included who showed little or no fluctuations.

Conclusions

There was no difference in the steady-state average plasma concentrations of risperidone and the active moiety (risperidone plus 9-hydroxy-risperidone) in schizophrenic patients following the 8-mg risperidone once-daily regimen and the 4-mg risperidone twice-daily regimen. The ratios of the steady-state average plasma concentrations of both risperidone and the active moiety following the two treatments fall within the acceptance range of bioequivalence. The median trough and peak levels of the active moiety under the 8-mg risperidone once-daily regimen were 68% and 126% of those seen under the 4-mg risperidone twice-daily regimen, respectively.

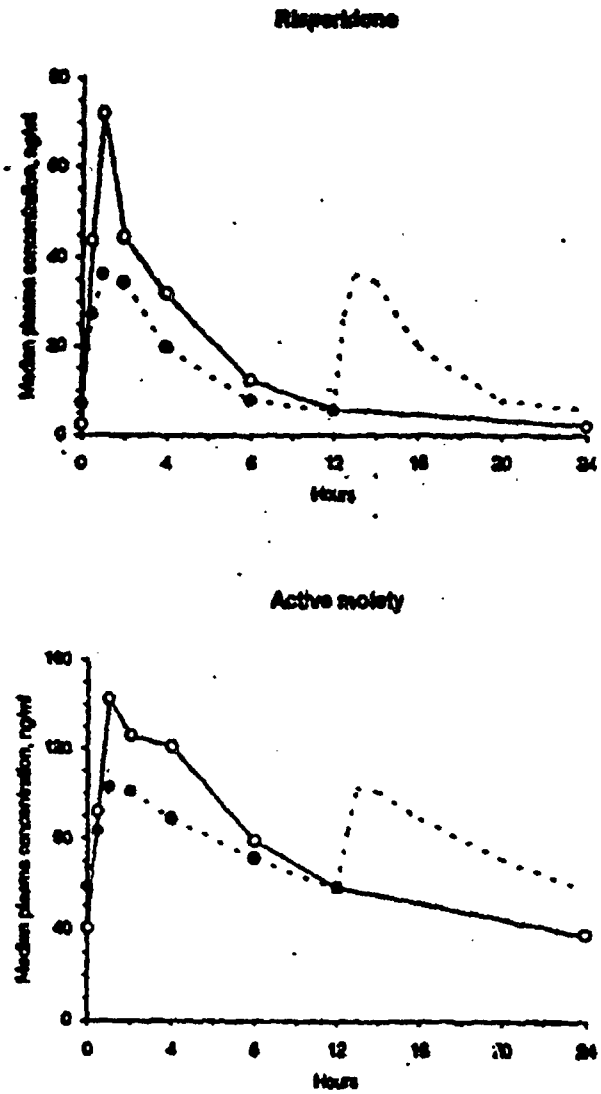


Figure 1: Plasma concentrations of risperidone (upper graph) and active moiety (lower graph) following the day 7 oral administration of 8 mg risperidone (open symbols: risperidone 8 mg once daily treatment) or 4 mg risperidone (closed symbols: risperidone 4 mg twice daily treatment). The dotted line without symbols corresponds to the predicted steady-state plasma drug concentrations after a second dose of the 4 mg bid treatment, which is identical to the profile observed after the first 4 mg dose of day 7.

Table 7: Steady-state pharmacokinetic parameters of risperidone in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment A: an 8-mg risperidone tablet once daily for one week

Patient	Day 6	Day 7				
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-24} ng.h/ml	F_{rel}[1] %
1						
2						
3						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
median	1.98	1.0	2.35	76.3	326	94.3
mean[3]	1.91	1.1	2.04	63.8	318	94.6
S.D.[3]	0.84	0.5	0.87	23.0	120	28.3
maximum						
minimum						

[1] Relative bioavailability (treatment A vs. treatment B). See section 3.5.3. for definition.
[2] No sample.
[3] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

Table 7: Continued
Steady-state pharmacokinetic parameters of risperidone in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment B: a 4-mg risperidone tablet twice daily for one week

Patient	Day 6	Day 7			
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-12h} ng.h/ml
1					
2					
3					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
median	5.62	1.0	7.23	48.2	208
mean[1]	5.00	1.5	5.89	37.9	181
S.D.[1]	2.87	1.1	3.62	17.6	78
maximum					
minimum					

[1] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

Table 9: Steady-state pharmacokinetic parameters of active moiety in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment A: an 8-mg risperidone tablet once daily for one week

Patient	Day 6	Day 7					
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-tau} ng.h/ml	F_{rel}[1] %	Metabolic[2] index
1							
2							
3							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
median	36.6	1.0	40.0	142	1715	95.6	0.23
mean[3]	39.4	1.3	41.8	155	1754	92.7	0.18
S.D.[3]	11.9	0.9	11.6	50	394	16.2	0.06
maximum							
minimum							

[1] Relative bioavailability (treatment A vs. treatment B).
[2] Metabolic index = AUC risperidone/AUC active moiety after the treatment A.
[3] No sample.
[4] Not calculated (see text for explanation).
[5] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

Table 9: Continued
Steady-state pharmacokinetic parameters of active moiety in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment B: a 4-mg risperidone tablet twice daily for one week

Patient	Day 6	Day 7				
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-12h} ng.h/ml	Metabolic index[1]
1						
2						
3						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
median	55.7	2.0	58.4	113	965	0.24
mean[3]	54.6	2.4	59.3	112	967	0.19
S.D.[3]	11.3	1.9	10.7	34	254	0.07
maximum						
minimum						

[1] Metabolic index = AUC risperidone/AUC active moiety after the treatment B.
[2] No. calculated (see text for explanations).
[3] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20, 272
Risperidone (Risperidal®)
0.25 mg Tablets

Janssen Pharmaceutical Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Reviewer: Vijay K. Tammara, Ph. D.

Submission Date:
December 28, 1998
April 6, 1999 (Fax)
April 19, 1999 (Fax)
April 20, 1999 (Fax)
April 21, 1999 (Fax)
April 27, 1999 (Fax)

Type of Submission: New NDA (New Dosage Strength)

Risperidone is a benzisoxazole derivative with potent serotonin type 2A (5-HT_{2A}) and dopamine type 2 (D_2) receptor-blocking properties.

Background: The original NDA 20-272 for Risperidal in dosage strengths 1, 2, 3, and 4 mg tablets was approved on December 29, 1993 for the management of the manifestations of psychotic disorders. Subsequently, supplemental NDA for the 0.5-mg tablet strength was approved in 1998. The effective dose range was 4-8 mg/day, and the maximum recommended daily dose was 16 mg. The purpose of this NDA is to include 0.25-mg tablets of risperidone, which can provide maximum flexibility for treating the elderly and those patients with hepatic and renal impairment. The composition for the 0.25-mg tablet is different from the existing marketed tablets. Therefore, a bioequivalence trial is conducted to demonstrate the bioequivalence of the 0.25-mg to-be-marketed tablets with the existing 1-mg marketed tablets.

In this submission, the sponsor has provided the final study report on bioavailability and bioequivalence of the 4 x 0.25-mg risperidone tablets (Study # NI30232) manufactured at ——— o 1 x 1-mg marketed risperidone tablets manufactured at the same site.

Bioequivalence Study NI30232:

Title: A bioequivalence trial of risperidone comparing 0.25 mg, 0.5 mg, and 1 mg risperidone tablets in healthy volunteers [NI30232, NDA 20-272; Vol. 14.5].

The objective of this study was to assess the bioequivalence of 4 x 0.25 mg to-be-marketed tablets and 2 x 0.5 mg research tablets to the 1 x 1 mg marketed tablets of risperidone.

Study Design: This was an open–label, randomized, balanced, three–period, single dose, cross–over study conducted in 30 healthy male subjects.

Treatment A: 2 x 0.5-mg risperidone research tablets (under fasting conditions)

Treatment B: 4 x 0.25-mg to-be-marketed risperidone tablets (under fasting conditions)

Treatment C: 1 x 1 mg marketed risperidone (under fed conditions).

Each treatment was separated by a seven-day washout period.
Subjects: A total of 30 healthy male subjects (mean age: 25 years; mean weight: 80 kg) participated and completed the study.

Formulations: 0.25-mg to-be-marketed tablets of risperidone (batch number 45021/F77); 0.5-mg research tablets of risperidone (batch number 97B24/F9); and 1-mg marketed tablets of risperidone (batch number 49935/F23) were used in this study.

RESULTS:
Pharmacokinetic Data Analysis: Pharmacokinetic parameters for risperidone and its active metabolite (9-hydroxy risperidone) were obtained by noncompartmental methods. The log-transformed pharmacokinetic parameters were statistically analyzed for both parent drug and the metabolite by the sponsor using Proc Mixed in SAS (ANOVA) for a three period crossover to account for period, sequence, and treatment (fixed effects) and subject within sequence (random effect) in the final model. The sponsor included the pharmacokinetic data from all 30 subjects in the analysis.

This reviewer performed the two one-sided t-test and calculated the 90% CI for Cmax and $AUC_{0-\infty}$ for treatment B vs C using WinNonLinPro® Software. The results obtained by the reviewer are in agreement with those reported by the sponsor. Since 0.5-mg tablet strength was a research formulation and not the to-be-marketed formulation, this reviewer did not review the results involved with this strength.

The mean plasma concentration time profiles are presented in Figure 1 and pharmacokinetic parameters for individuals are presented in Table 1. The mean pharmacokinetic parameters and geometric mean (GM) for all treatments are presented in the following table:

Treatment	$AUC_{0-\infty}$ (µg*hr/mL)				C_{max} (µg/mL)				T_{max} (hr)
	Mean ± SD	GM	Ratio	90 % CI	Mean ± SD	GM	Ratio	90% CI	Mean ± SD
Risperidone									
B (4 x 0.25 mg tablets)	64.2 ± 71.6	34.2	0.92	83, 102	7.1 ± 4.1	6.0	0.91	82, 95	1.3 ± 0.5
C (1 x 1 mg tablets)	63.8 ± 64.5	37.2	--	--	7.6 ± 3.8	6.6	--	--	1.1 ± 0.6
9-Hydroxy Risperidone									
Treatment	$AUC_{0-\infty}$ (µg*hr/mL)				C_{max} (µg/mL)				T_{max} (hr)
	Mean ± SD	GM	Ratio	90 % CI	Mean ± SD	GM	Ratio	90% CI	Mean ± SD
B (4 x 0.25 mg tablets)	124.4 ± 41.0	117	0.88	82, 95	5.08 ± 2.3	4.4	1.05	98, 115	4.5 ± 5.7

Treatment	$AUC_{0-\infty}$ (µg*hr/mL)				C_{max} (µg/mL)				T_{max} (hr)
	Mean ± SD	GM	Ratio	90 % CI	Mean ± SD	GM	Ratio	90% CI	Mean ± SD
C (1 x 1 mg tablets)	141.4 ± 51.6	133	--	--	5.05 ± 2.5	4.2	--	--	5.0 ± 4.7

Statistical analyses indicate that 4 x 0.25-mg risperidone tablets are bioequivalent to 1 x 1-mg risperidone tablets. The 90% confidence intervals for $AUC_{0-\infty}$ and Cmax were within 80-125 and no statistically significant difference in the mean Tmax was observed (Attachment 1).

Dissolution Method: Dissolution testing of risperidone tablets was performed using presently approved dissolution method and specification, which is as follows:

Apparatus : II (Paddle)
Speed : 50 rpm
Medium : 500 mL of 0.1 N HCl at 37°C
Specification :

Comment: The sponsor conducted this study only in healthy male subjects. In the future, the sponsor is requested to also include female subjects in such studies.

Recommendation: The marketed 1 mg risperidone and the 0.25 mg (to be marketed) risperidone tablets were found to be bioequivalent. The information provided is adequate to support its approval.

Please, forward this recommendation and the above **Comment** to the sponsor.

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

FT Initialed by C. Sahajwalla, Ph. D. _____

CC: N 20, 272 (SCM-014), HFD-120, HFD-860 (Tammara, Sahajwalla, Mehta), CDR (for Drug Files).

HFD-17
(FOI)
NOV 12 1993

NDA: 20-272

SUBMISSION DATES: April 15, 1992
March 29, 1993
May 17, 1993
May 24, 1993

GENERIC NAME: Risperidone

BRAND NAME: Risperdal®

DOSAGE FORM: Caplet

STRENGTHS: 1 mg, 2 mg, 3 mg, 4 mg and 5 mg

ROUTE OF ADMINISTRATION: Oral

SPONSOR: Janssen Research Foundation

REVIEWER: Mohammad Hossain, Ph.D.

TYPE OF SUBMISSION: Original NME

DRUG CLASSIFICATION: 1 P

SYNOPSIS:

The average absolute oral bioavailability of risperidone and the active moiety (risperidone plus 9-hydroxy-risperidone) was 70% and 100%, respectively, including extensive and poor metabolizers. The average relative oral bioavailability of risperidone tablet was 95% compared to a solution. Food does not affect either the rate or the extent of absorption of risperidone. The pharmacokinetics of risperidone and its equally active metabolite (9-hydroxy-risperidone) are linear over the dosing range of 1 to 16 mg daily (0.5 to 8 mg B.I.D.). The 1 mg, 2 mg and 4 mg market tablets have separately been shown to be bioequivalent to their corresponding research formulations. Bio-waiver for the 3 mg and 5 mg market tablets were granted based on the linear kinetics of the drug, compositional proportionality amongst all the tablet strengths, and on *in vitro* dissolution profiles submitted for this immediate release product.

The metabolism of risperidone, leading to the major metabolite, 9-hydroxy-risperidone, is subject to metabolic polymorphism of the debrisoquin and dextromethorphan phenotype (catalyzed by P450IID6 isozyme). Risperidone concentrations were lower and 9-hydroxy-risperidone concentrations were higher in extensive metabolizers, than those seen in

intermediate or poor metabolizers. As the formed 9-hydroxy-risperidone has the same activity as risperidone, and its formation is dependent on the debrisoquin hydroxylating status and/or dextromethorphan metabolic ratio of a subject, the presence of this equally active metabolite compensates for the difference in unchanged risperidone levels between extensive and poor metabolizers. For the active moiety (risperidone plus 9-hydroxy-risperidone), the pharmacokinetic parameters following single and multiple dose administration were similar between rapid and poor metabolizers.

Following a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers (slow, intermediate and rapid metabolizers), an average of 70% and 15% of the total radioactivity was recovered in the urine and feces, respectively, over a period of 7 days, for a combined recovery of 85%.

Following oral administration of risperidone in normal volunteers and psychotics, the apparent $T_{1/2}$ of risperidone was 3 hours in rapid metabolizers (n=27) and 20 hours in poor metabolizers (n=6). 9-hydroxy-risperidone $T_{1/2}$ averaged about 21 hours in rapid metabolizers and 30 hours in slow metabolizers. The apparent $T_{1/2}$ of the active moiety (risperidone plus 9-hydroxy-risperidone) averaged 22 hours including rapid and slow metabolizers (n=34). The coefficient of variation (CV) was about 30% in all instances.

No accumulation of risperidone is expected in rapid metabolizers. However, a 3-4 fold accumulation of risperidone is expected in poor metabolizers, with a similar accumulation also expected for 9-hydroxy-risperidone and the active moiety in both poor and rapid metabolizers. Steady-state concentrations of risperidone are reached within one day. 9-hydroxy-risperidone and the active moiety reached steady-state within 5-6 days.

In moderate to severe renally impaired subjects, total oral clearance decreased by 60% for the active moiety. The pharmacokinetics in subjects with liver disease were comparable to those in young healthy subjects although the mean free fraction of the active moiety in plasma was increased by 20% because of the diminished concentration of both albumin and α_1-acid glycoprotein. In the healthy elderly subjects, total oral clearance decreased by 40% for the active moiety. Based upon the pharmacokinetics of the active moiety, risperidone doses should be reduced in elderly subjects and in subjects with renal disease because of the diminished total oral clearance.

The plasma protein binding of risperidone was about 90% over the *in vitro* concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxy-risperidone was 77%. Neither parent nor the metabolite displaced each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μg/mL), warfarin (10 μg/mL) and carbamazepine (10 μg/mL) caused only a slight increase in the free fraction of risperidone (10 ng/mL) and 9-hydroxy-risperidone (50 ng/mL), a change unlikely to be of clinical significance.

No *in vivo* drug interaction study has been performed with risperidone. Three patients who received carbamazepine chronically as co-medication with a single dose of risperidone had high clearance of risperidone (225% increase) and a 45% increase in clearance for the active moiety suggesting enzyme-induction. A patient receiving clozapine chronically as co-medication had a 90% decrease in clearance of risperidone and a 55% decrease in the clearance for the active moiety.

Drugs, which are known to bind to cytochrome P450IID6 (debrisoquin 4-hydroxylase), were found to be potent inhibitors of the *in vitro* metabolism of risperidone and of the formation of the equiactive metabolite, 9-hydroxy-risperidone in human liver microsomes, (e.g., reduced haloperidol, chlorpromazine, fluoxetine, quinidine, haloperidol, orphenadrine, triphenitidyl and procyclidine). Drugs which bind to or are metabolized by other cytochromes P450 are only weak inhibitors of risperidone. Based on the kinetic parameters determined in the *in vitro* inhibition study, the effects of risperidone on the metabolism of drugs metabolized by cytochrome P-450IID6 is expected to be negligible. It appears that inter-individual variability by either a genetic deficiency in risperidone metabolism or by enzyme-inhibiting medication may not be clinically important when the active moiety is considered.

RECOMMENDATION:

This submission (NDA-20-272) has been reviewed by the Division of Biopharmaceutics and has been found to be acceptable for meeting the Biopharmaceutics requirements provided that the sponsor incorporates all the labeling changes and responds satisfactorily to all enclosed Comments.

NDA 20-272: RISPERDAL®
Risperidone Caplets

TABLE OF CONTENTS: Page No.

Note: The appendices contain more detailed data/information such as study results, dosage formulation, dissolution methodology and specification, assay validation, proposed labeling and *in vitro* protein binding and interaction studies. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request.

SUMMARY OF BIOAVAILABILITY AND PHARMACOKINETICS:

I. BIOAVAILABILITY:

A. Absolute Bioavailability:

Twelve dextromethorphan-phenotyped healthy males received single intravenous, intramuscular and oral solution doses of 1 mg risperidone (Study 6). In extensive metabolizers (n=9, dextromethorphan metabolic ratio, MR=0.0002-0.015), the average absolute bioavailability of risperidone alone, and risperidone plus 9-hydroxy-risperidone (active moiety) from the oral dosage form was found to be approximately 66% (CV=42%) and 107% (CV=21%), respectively. In poor metabolizers (n=2; MR=5.4-6.5), the mean absolute bioavailability of risperidone, and the active moiety was 82% (CV=30%) and 75% (CV=16%), respectively. The average absolute oral bioavailability of risperidone and the active moiety (risperidone plus 9-hydroxy-risperidone) in all the subjects was 69% (CV=25%) and 101% (CV=24%), respectively.

B. Relative Bioavailability:

Six healthy males received single oral doses of 2 mg risperidone given as a solution (4 mL of a 0.5 mg/mL) and as 2x1 mg tablets. The average bioavailability of risperidone from the tablets (fasting) relative to the solution (fasting) was 94% (CV=10%).

C. Bioequivalence:

Both $AUC_{0-\infty}$ and C_{max} of risperidone, 9-hydroxy-risperidone, and the active moiety (risperidone plus 9-hydroxy-risperidone) were shown to be equivalent based on 90% confidence interval analysis (two one-sided t-test procedure) using both untransformed and log transformed data for the following treatment comparisons in Studies 8, 9 and 10. Analysis of variance showed T_{max} not to be statistically significant.

(1) Bioequivalence of risperidone in healthy volunteers -
Two 1 mg market caplets (F23) were shown to be bioequivalent to 2 mg research tablets (F13 and F24) and 2 mg solution in 24 healthy male volunteers (Study 8). The 2 mg research tablet (F24) is identical to the to-be-market 2 mg (F37) tablet. F37 has the final coloring and lake. The 1 mg market caplet (F23) is identical to the 2 mg research tablet (F24). So, it can be said that in this study F24 represents F37, the 2 mg tablet to-be-marketed. The 2 mg tablet core is compositionally proportional with the other proposed market strengths of 3 mg, 4 mg, and 5 mg with only minor coloring differences in the film coating.

(2) Bioequivalence of risperidone in psychotic patients -
In Study 9, the 4 mg market caplet (F31) was shown to be bioequivalent to the 4 mg (F12) research tablet in 24 patients. The 4 mg market caplet (F31) is compositionally proportional with the other proposed strengths of 2 mg, 3 mg, and 5 mg with respect to both the tablet core and the film coating.
Study 10 compared 1x4 mg market (F31) and 4x1 mg (F23) market caplets with 4x1 mg (F05) research tablets in 36 psychotic patients. All the formulations were shown to be bioequivalent to each other.

(3) Bioequivalence of haloperidol in healthy volunteers - The research tablet of haloperidol used in the double-blind controlled clinical trials was compared to that of the market product in 24 healthy males according to a randomized crossover design (Study 11). The two formulations were equivalent ($AUC_{0-\infty}$ and C_{max}) based on 90% C.I. analysis (two one-sided t-test) using both untransformed and log transformed data. Analysis of variance showed T_{max} not to be statistically significant.

D. Formulations/Bio-waiver Request:

Risperidone caplets are film-coated. This Application describes, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg as dosage strengths proposed for marketing. The caplet cores for each of the five dosage strengths proposed for marketing are proportionally similar for all excipients. Risperidone comprises —— by weight of the 1 mg caplet core and — by weight of the cores of the other four strengths. There are minor differences in the film coating for each of the caplet strengths representing the different color additives. The sponsor requests for waiver of *in vivo* bioequivalence study for the 2 mg, 3 mg and 5 mg strength caplets manufactured at ———— because the caplet cores are compositionally proportional with minor differences in the film coating color additives, and based, on *in vitro* dissolution profiles submitted in this application.

E. Food Effect:

The bioavailability of the tablets after a standard breakfast was 104% (CV=16%) compared to the fasted state (n=6), indicating that food does not affect the extent of absorption of risperidone (Study 6). Average C_{max} and T_{max} were also similar. Patients in the clinical trials were allowed to take their daily medication with or without food. As this food interaction study was performed early in drug development, the plasma concentrations of 9-hydroxy-risperidone were not assayed. Because the disposition of risperidone is hardly affected by food, the kinetics of the active metabolite were assumed not to be altered.

II. PHARMACOKINETICS:

A. Absorption and Distribution:

Following oral administration as a solution or a tablet, average peak plasma risperidone, and active moiety concentrations occurred in about 1 hour in rapid and slow metabolizers. Following a 30-minute infusion of 1 mg risperidone in 12 dextromethorphan phenotyped volunteers (Study 4), risperidone volumes of distribution were not dependent on the subject's metabolic status: overall Vd_{ss} of 1.2 L/kg (CV=30%) and Vd_{area} of 1.4 L/kg (CV=30%).

Following a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers (slow, intermediate and rapid metabolizers using the urinary debrisoquin metabolic ratio), the slow metabolizer had a 3-fold higher C_{max}, a 6.5-fold longer $T_{1/2}$, a 12.5-fold higher AUC_{0-t} and a 8.5-fold larger urinary excretion of risperidone compared to the rapid metabolizer (Study 3). Similar values were observed with non-labelled solution dose. For the total radioactivity, there were no differences in $T_{1/2}$ and only a 1.5 to 2-fold difference in mean C_{max} and $AUC_{0-\infty}$ between the rapid and intermediate/slow metabolizers. For the active moiety, no difference was observed in mean C_{max} and $T_{1/2}$, and only a 1.5-fold difference was noted in mean $AUC_{0-\infty}$.

B. Metabolism and Elimination:

The main metabolic pathway of risperidone was hydroxylation and oxidative N-dealkylation in humans. Hydroxylation leading to the major active metabolite, 9-hydroxy-risperidone, is subject to metabolic polymorphism of the debrisoquin and dextromethorphan phenotype (catalyzed by P450IID6 isozyme) [Study 3 & 4]. Risperidone concentrations were lower and 9-hydroxy-risperidone concentrations were higher in extensive metabolizers, than those seen in intermediate or poor metabolizers. As the formed 9-hydroxy-risperidone has the same activity as risperidone, and its formation is dependent on the debrisoquin hydroxylating status and/or dextromethorphan metabolic ratio of a subject, the presence of this equally active metabolite compensates for the difference in unchanged risperidone levels between extensive and poor metabolizers. For the active moiety (risperidone plus 9-hydroxy-risperidone), the pharmacokinetic parameters following single and multiple dose administration were similar between rapid and poor metabolizers.

Following a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers (slow, intermediate and rapid metabolizers using the urinary debrisoquin metabolic ratio), an average of 70% (CV=2%) and 14% (CV=20%) of the total radio-activity was recovered in the urine and feces, respectively, over a period of 7 days, for a mean combined recovery of 84% (Study 3). Less than 1% of the fecal radioactivity was due to the parent compound, indicating essentially complete absorption. In the 0-168 hour urine, 4%, 11%

and 30% of the administered radioactive dose was recovered as risperidone in the extensive, intermediate and poor debrisoquin hydroxylator.

In plasma, the $AUC_{0-\infty}$ of risperidone and 9-hydroxy-risperidone represented 10% and 70% of the $AUC_{0-\infty}$ of the total radioactivity in the extensive metabolizer (Study 3). Risperidone, the 7- and 9-hydroxy-metabolites and the acid metabolites accounted for 51-56% of the dose excreted in the urine within the first 4 days after dosing, for a total urinary excreted radioactivity of 64%. Only 3-5% of the dose could be identified as glucuronides in the urine. In methanolic feces extracts, risperidone and four hydroxy-metabolites were found as cleavage products. Unchanged risperidone and its cleavage degradation product represented 3% of the dose in the feces of the poor metabolizer.

Following a 30-minute infusion of 1 mg risperidone in 12 dextromethorphan phenotyped volunteers (Study 4), renal clearance of risperidone represented only 3% (CV=73%) of total oral clearance (394 mL/min; CV=28%) in extensive metabolizers, and 22% (CV=9%) of total oral clearance in the intermediate (192 mL/min) and poor metabolizers (54 mL/min). Following oral administration of risperidone in normal volunteers (Study 4 & 7), the apparent $T_{1/2}$ of risperidone was 3 hours (CV=31%) in rapid metabolizers (n=27) and 20 hours (CV=38%) in poor metabolizers (n=6). After oral administration to psychotic patients, about 90% of risperidone was eliminated with an effective half-life of about 3 hours, and the remainder with a half-life of about 15 hours. 9-hydroxy-risperidone $T_{1/2}$ averaged about 21 hours (CV=22%) in rapid metabolizers and 30 hours (CV=26%) in slow metabolizers. The apparent $T_{1/2}$ of the active moiety (risperidone plus 9-hydroxy-risperidone) averaged 22 hours (CV=27%) including rapid and slow metabolizers (n=34).

C. Steady-State Kinetics:

The steady-state pharmacokinetics of 1 mg risperidone per day for 20 days in 10 normal male volunteers did not differ significantly from those seen after a single 2 mg dose given as an oral solution in rapid metabolizers (Study 7). For the active moiety, pharmacokinetic parameters following single and multiple dose administration were similar between the rapid and poor metabolizers.

No accumulation of risperidone is expected in rapid metabolizers. However, a 3-4 fold accumulation of risperidone is expected in poor metabolizers, with a similar accumulation also expected for 9-hydroxy-risperidone and the active moiety in both poor and rapid metabolizers. Steady-state concentrations of risperidone are reached within one day. 9-hydroxy-risperidone and the active moiety reached steady-state within 5-6 days (Study 7).

III. DOSE PROPORTIONALITY AND DOSAGE STRENGTH EQUIVALENCY:

A. Dose Proportionality:

The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active moiety are linear over the dosing range of 1 to 16 mg daily (0.5 to 8 mg B.I.D.) [Study 5, 6, 12, 13 and Clinical Research Report NB4410].

B. Dosage Strength Equivalency:

Dosage strength equivalency between the 1 mg tablet (F23) given as a 4x1 mg dose and the 4 mg tablet (F31) has been demonstrated in Study 10. Further, the 1 mg tablet (F23) given as a 2x1 mg dose and the 2 mg tablet (F24) have been shown to be dosage strength equivalent in Study 8. For the 3 and 5 mg tablets dosage strength equivalency studies are not available.

IV. SPECIAL POPULATIONS:

The pharmacokinetics of risperidone were investigated in healthy young subjects (n=8; 18-40 years), healthy elderly subjects (n=12; ≥65 years), subjects with liver disease (n=8), subjects with moderate renal impairment (n=7; 24 hour Cl_{cr}=30-60 mL/min/1.73 m^2) and subjects with severe renal disease (n=7; 24 hour Cl_{cr}=10-29 mL/min/1.73 m^2) after a single oral intake of 1 mg (F23) market tablet. The elimination profiles of risperidone in the elderly and subjects with renal and liver disease were more variable than the profiles in young subjects whereas the interindividual variability for the active moiety was much less for all the above groups.

A. Renal Impairment:

On an average, $AUC_{0-\infty}$ increased by about 2-5 fold, $T_{1/2}$ increased by 1.5-2.5 fold and renal clearance decreased by 2.5-4 fold for risperidone, 9-hydroxy-risperidone and the active moiety in renally impaired subjects compared to young, healthy subjects. Total oral clearance decreased by upto 60% for risperidone and the active moiety. The concentration of α_1-acid glycoprotein was significantly increased in moderate and severe renal disease resulting in about a 20% decrease in unbound fraction of the active moiety in these subjects.

B. Hepatic Impairment:

The pharmacokinetics of the active moiety in subjects with liver disease were comparable to those in young healthy subjects although the mean free fraction of the active moiety in plasma was increased by 20% because of the diminished concentration of both albumin and α_1-acid glycoprotein. In hepatically impaired subjects, the higher unbound fraction of the

active moiety probably compensated for the diminished intrinsic clearance, so that the total oral clearance in liver disease was comparable to the oral clearance in young subjects.

C. Healthy Elderly:

On an average, $AUC_{0-\infty}$ and $T_{1/2}$ increased by about 30-45%, and renal clearance decreased by about 40-50% for risperidone, 9-hydroxy-risperidone and the active moiety. Total oral clearance decreased by 40% for the active moiety.

D. Race and Gender Effects:

No specific PK study was conducted to investigate race and gender effects. However, using Generalized Additive Modeling approach, NONMEM did not show body weight and sex as significant predictors of clearance. Also, based on the median prediction errors and the 25-75% percentiles, there appear to be no great differences due to gender (whether corrected for body weight or not) and race (Asian, Caucasian, Hispanic and Negroid) [Clinical Research Report N84410].

V. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

As part of a single dose kinetic study (Study 4), PK/PD evaluation was attempted by the firm using safety measurements (prolactin rise) in a healthy population. Risperidone, 9-hydroxy-risperidone and active moiety plasma concentrations were not related to efficacy measurements related to control of symptoms of psychosis.

VI. DRUG INTERACTIONS:

No *in vivo* drug interaction study has been performed with risperidone. Three patients who received carbamazepine chronically as co-medication with a single 4 mg dose of risperidone had high clearances of risperidone (225% increase) and 45% increase for the active moiety suggesting enzyme-induction. A patient receiving clozapine chronically as co-medication had a 90% decrease in clearance of risperidone and a 50% decrease in the clearance of the active moiety (Clinical Research Report N84410).

Drugs, which are known to bind to cytochrome P450IID6 (debrisoquin 4-hydroxylase), were found to be potent inhibitors of the *in vitro* metabolism of risperidone and of the formation of the equiactive metabolite, 9-hydroxy-risperidone in human liver microsomes (e.g., reduced haloperidol, chlorpromazine, fluoxetine, quinidine, haloperidol, orphenadrine, triphenitidyl and procyclidine). Drugs which bind to or are metabolized by other cytochromes P450 are only weak inhibitors of risperidone. No interaction with *in vitro* risperidone metabolism could be observed for compounds that interact with cytochromes P450IA1 and P450IA2 (7,8-

benzoflavone), P450IIC9 (diazepam), $P450_{MP}$ (tranylcypromine) and P450IIIA4 (nifedipine). Based on the kinetic parameters determined in the *in vitro* inhibition study, the effects of risperidone on the metabolism of drugs metabolized by cytochrome P-450IID6 is expected to be negligible. It appears that inter-individual variability by either a genetic deficiency in risperidone metabolism or by enzyme-inhibiting medication may not be clinically important when the active moiety is considered.

VII. *IN VITRO* STUDIES:

A. Plasma Protein Binding:

The plasma protein binding of risperidone was about 90% (CV=2%) over the *in vitro* concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein (Study 15). The plasma binding of 9-hydroxy-risperidone was 77% (CV=2%). Neither parent nor the metabolite displaced each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μg/mL), warfarin (10 μg/mL) and carbamazepine (10 μg/mL) caused only a slight increase of the free fraction of risperidone (10 ng/mL) and 9-hydroxy-risperidone (50 ng/mL), a change unlikely to be of clinical significance.

B. Blood:Plasma Partitioning:

In human blood, the blood to plasma concentration ratio of risperidone at 10 ng/mL amounted up to 0.67 (CV=2%). In human blood cell suspensions, the fraction of risperidone distributed to blood cells was about 74% (CV=3%).

VIII. DISSOLUTION:

IX. ASSAY:

X. MULTIPLE MANUFACTURING SITES:

All the drug products used in the pharmacokinetic studies were manufactured by Janssen Pharmaceutica, NV in Beerse, Belgium. However, the sponsor proposes in the NDA that all five strengths of Risperdal Caplets will also be manufactured by The sponsor requests for waiver of *in vivo* bioequivalence studies for the 2 mg, 3 mg, and 5 mg caplets manufactured at Beerse, Belgium and also for all the five caplet strengths manufactured by based on *in vitro* dissolution profiles submitted in this application for both the manufacturing sites. An "interim" dissolution specification is being set based on the available *in vitro* dissolution data for all the caplet strength lots manufactured in Beerse, Belgium and thereby allowing the inclusion of the new manufacturing site based on *in vitro* dissolution data for this immediate release product.

GENERAL COMMENTS (Need not be sent to the firm):

1. The reviewing Chemist is requested to note that both the drug substance and drug product will be manufactured by Janssen Pharmaceutica, NV in Beerse, Belgium and Evidently, there is an additional manufacturing site to the already existing one.

2. The reviewing Medical Officer is requested to note that chronic administration of carbamazepine with a single 4 mg dose of risperidone in a few patients has been shown to increase clearances of risperidone by 225% and that of the active moiety by 45%, suggesting enzyme-induction. Also, a patient receiving clozapine concurrently with risperidone had a 90% decrease in clearance of risperidone and a 55% decrease in clearance of the active moiety suggesting enzyme-inhibition. Therefore, caution should be exercised when carbamazepine and clozapine are co-administered with risperidone.

Dosing could be modified accordingly, such as, increasing the dose by 50% in patients receiving carbamazepine as co-medication, and decreasing the dose by half in patients receiving clozapine as co-medication. For patients receiving carbamazepine as co-medication, the dosing interval could also be reduced by about 50% (i.e., instead of a B.I.D. dosing regimen, it could be Q.I.D.).

COMMENTS TO BE SENT TO THE FIRM:

1. ***In Vitro* Dissolution:**

   (a) **Recommended "Interim" Dissolution Specification:**
   The Agency recommends the following "interim" dissolution specification for all strengths of Risperdal® caplets:

   Method: USP Apparatus II (Paddle) at 50 rpm
   Media: 500 mL of 0.1 N HCl

   (b) The firm is requested to submit dissolution data on 12 individual tablets, for each strength of Risperdal caplets manufactured at both the sites (Beerse, Belgium and) according to the dissolution method specified below:

   USP Apparatus (Paddle method) at 50 rpm in 500 mL of simulated gastric fluid (without pepsin and a pH of 1.2) at 37±0.5°C.

   The firm apparently has conducted some dissolution using this method. Based on limited data generated by the firm, it appears that simulated gastric fluid may reduce the variability and accelerate drug release for all the caplet strengths as compared to the current medium which is 0.1 N HCl. This may allow for setting of a more appropriate dissolution specification.
   The sponsor is requested to submit all requested information within 3 months of receiving this Comment.

2. **Bio-Waiver:**

   The caplet cores for each of the five dosage strengths proposed for marketing are proportionally identical for all excipients. There are minor differences in the film coating for each of the caplet strengths representing the different color additives. Therefore, a waiver of *in vivo* bioequivalence study for the 2 mg, 3 mg and 5 mg strength caplets manufactured at Beerse, Belgium and also *in vivo* bioequivalence study between the two manufacturing sites (Beerse, Belgium and) for all

the caplet strengths (1-, 2-, 3-, 4-, and 5- mg) are granted, based on the linear kinetics of the drug and on *in vitro* dissolution profiles submitted in this application for this immediate release product.

3. **Analytical Method:**

The sponsor is requested to follow-up on patients #0210, #0248 and #0702 receiving placebo treatment who apparently had reported levels of the active moiety in their plasma samples. The sponsor should verify whether this may be due to cross-reactivity of the RIA assay with concomitant medications taken by these patients during the study period (Study JRD 6476/20).

4. **NONMEM Population Analysis:**

The sponsor is requested to use standardized prediction errors (SPE) and/or standardized mean prediction errors (SMPE) in determining predictive performance of the population model developed using the NONMEM software. The sponsor is encouraged to contact the Division of Biopharmaceutics for any assistance regarding the design and analysis of future population pharmacokinetic studies.

5. **Design of Food Effect Study:**

Ideally, drug-food interaction study should be conducted using the highest strength of the to be marketed product with the FDA recommended "high fat meal".

LABELING COMMENTS:

The firm is requested to perform the following revisions on the submitted annotated draft labeling:

1. The bioavailability and pharmacokinetic information for the Risperdal® caplets provided in the pharmacokinetic portion of the Clinical Pharmacology section should be replaced with the following:

PHARMACOKINETICS

ATTACHMENT A
DRAFT LABELING

3 page(s) of revised draft labeling has been redacted from this portion of the review.

4. The following information should be included under the "Dosage and Administration" section of the proposed labeling:

DOSAGE AND ADMINISTRATION

[redacted]

Biopharm Day April 19, 1993 (Attendees: J. Collins, Ph.D.; T. Ludden, Ph.D.; H. Malinowski, Ph.D., N. Fleischer, Ph.D. and R. Baweja, Ph.D.)

/S/

Mohammad Hossain, Ph.D.
Pharmacokinetics Evaluation Branch

First Draft Prepared On October 7, 1993

RD/FT initialed by Raman Baweja, Ph.D. /S/

cc: NDA 20-272 (orig.), HFD-120, HFD-426 (Hossain, Ette, Baweja, Fleischer), HFD-340 (Viswanathan), Chron, Drug, Reviewer, FOI (HFD-19) and F files.

Note: Dr. Ene Ette of the Division of Biopharmaceutics reviewed and provided the comment involving NONMEM analysis.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Risperdal ® (Risperidone)
NDA:20-272 /SCM-028(AZ)
FORMULATION: Oral Tablet
APPLICANT: Johnson & Johnson
INDICATIONS: Schizophrenia
Generic Name: Risperidone

PRIMARY REVIEWER: Andre Jackson
TYPE: Chemistry Supplement
STRENGTH:1 mg, 2 mg, 3 mg, 4 mg
Submission Date: June 23, 2003
OCPB Receipt Date: October 22, 2003

Review of Additional Dissolution Data

Background

The firm submitted a chemistry supplement on February 24, 2003 which contained bioequivalence data for their 1 mg and 4 mg tablets. The submission contained:

A 1.0 mg single dose fasting study comparing the currently marketed risperidone tablet with a new formulation manufactured by [redacted]

A 4.0 mg single dose fasting study comparing the currently marketed risperidone tablet with a new formulation manufactured by [redacted]

Dissolution and formulation data for the 4 mg and 1 mg tablets and only formulation data for the 2 mg and 3 mg tablets.

The BE study and the dissolution data comparing the [redacted] and [redacted] was found to be acceptable. However, the firm did not provide the comparable comparative dissolution profiles for the 2 mg and 3 mg strengths for the original [redacted] The FDA was informed by the firm during the review process that there was no comparative dissolution data using the different processes for the 2 mg and 3 mg strengths. A comment was sent to the firm stating that a waiver of BE for the manufacturing process change could not be granted for the 2 mg and 3 mg strengths without comparative dissolution data.

The current submission contains the comparative dissolution data for the 2 mg and 3 mg dosage strengths requested by the FDA.

Dissolution Results

The NDA dissolution method and specifications used were:

USP Apparatus II
50RPM
500 ml of 0.1N HCL
Q: [redacted]

Sampling at 15, 30, 45 and 60 min

Lots used in the study are presented in the following Table.

The following lots of Risperidone FC Tablets from each manufacturing process were evaluated in this study:

Risperidone Dosage	Lots	
	Current Manufacturing Process	New Manufacturing Process
2 mg	TS18901	TS11201
3 mg	TS19001	TS11301

Table 1: Dissolution Profile Results for Risperidone 2 mg FC Tablets lot TS18901- Current Process

Tablet No.	Lot TS18901 Results (%)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	76	91	95	96
Std. Dev.	9.5853	6.0378	4.5017	3.3699
%RSD	12.7	6.7	4.8	3.5

Table 2: Dissolution Profile Results for Risperidone 2 mg FC Tablets lot TS11201- New Process

Tablet No.	Lot TS11201 Results (%)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	93	98	98	98
Std. Dev.	3.3155	1.0836	1.0299	0.7538
%RSD	3.6	1.1	1.0	0.8

5.1.2 Dissolution Profile Results – Risperidone 3 mg FC Tablets

Table 3: Dissolution Profile Results for Risperidone 3 mg FC Tablets lot TS19001-Current process

Tablet No.	Lot TS19001 Results (%)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	77	89	93	95
Std. Dev.	4.6024	2.8920	2.2563	2.2088
%RSD	6.0	3.2	2.4	2.3

Table 4: Dissolution Profile Results for Risperidone 3 mg FC Tablets lot TS11301-New process

Tablet No.	Lot TS11301 Results (%)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	94	99	99	99
Std. Dev.	4.0862	1.8340	1.3707	1.5374
%RSD	4.4	1.9	1.4	1.6

Comments:

1. Based upon the submitted data for the 2 mg and 3 mg tablets, the manufacturing process [redacted] ıould be applicable to the 2 mg and 3 mg strengths (i.e., based upon BE results for the 4 mg tablet, comparative dissolution profiles, formulation proportionality to the 4 mg strength which had a BE study and the new process meeting the NDA specifications).

PLEASE FORWARD THESE RECOMMENDATIONS TO THE SPONSOR

Andre Jackson_____

RD/FT Initialed by Raman Baweja, Ph.D._____

Cc-NDA 20272, HFD-860(Jackson, Baweja, Mehta), Central Documents Room(Biopharm-CDR)

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

/s/

Andre Jackson
10/22/03 10:56:54 AM
BIOPHARMACEUTICS

Raman Baweja
10/22/03 11:17:40 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Risperdal ® (Risperidone)
NDA:20-272 /SCM-028
FORMULATION: Oral Tablet
APPLICANT: Johnson & Johnson
INDICATIONS: Schizophrenia
Generic Name: Risperidone

PRIMARY REVIEWER: Andre Jackson
TYPE: Chemistry Supplement
STRENGTH:1 mg, 2 mg, 3 mg, 4 mg
Submission Date: February 24, 2003

Executive Summary

Risperidone tablets were approved for the treatment of schizophrenia. The firm has recently changed from [redacted] to a [redacted]. The proposed tablet strengths of 4 mg, 3 mg and 2 mg are [redacted] and are compositionally proportional for the new manufacturing procedure. The 1 mg tablet is not proportional to the 4 mg, 3 mg and 2 mg tablets. The current submission contains 2 studies to show that the [redacted] is bioequivalent to the currently marketed [redacted] The submitted studies were:

1. RIS-NED-27- 1 mg tablet
2. RIS-RSA-5- 4 mg tablet

The important findings were for the 90% CI:

	Cmax	AUClast	AUCinf
1 mg Tablet	87.9-100.9	96.8-109.9	96.4-109.7
4 mg Tablet	89.06-109.6	89.2-104.1	88.1-102.7

Submission Content:

A 1.0 mg single dose fasting study comparing the currently marketed risperidone tablet with a new formulation manufactured [redacted]

A 4.0 mg single dose fasting study comparing the currently marketed risperidone tablet with a new formulation manufactured [redacted]

Dissolution and formulation data for the 4 mg and 1 mg tablets and only formulation data for the 2 mg and 3 mg tablets.

Single-dose Fasting Bioequivalence Study 1.0 mg Tablet

Study Information

Study Number: RIS-NED-27
Study Dates: March 18, 2002-May 1, 2002

Analysis Dates: May 15, 2002-June 14, 2002
Storage Period: ——

The following batch numbers were used:
Treatment A: Risperdal marketed tablet:
Batch TS18801 -Expiry date: October 2002- F23;

Treatment B: ———————— risperidone tablet:
Batch TS10901 -Expiry date: June 2002- F134.

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Washout Period**	14 days
Blood Sampling Times	0,0.25,0.5,0.75,1,1.5,2,3,4,5,6,8,12,16,24,36,48,72, and 96 hrs		
Blood Volume Collected	5 mL		
Blood Sample Processing/Storage	-22^0 C		

Fasting Study-Demographics

	Risperdal® marketed N=15	Risperdal® marketed / ——— N=15	Total N=30
Age, years			
Mean (SD)	31.5 (5.72)	37.7 (10.22)	34.6 (8.72)
Median	31.0	38.0	33.0
Range	19-39	23-55	19-55
Sex, n (%)			
Male	7 (47)	8 (53)	15 (50)
Female	8 (53)	7 (47)	15 (50)
Race, n (%)			
Caucasian	14 (93)	15 (100)	29 (97)
Oriental	1 (7)	0	1 (3)
Weight, kg			
Mean (SD)	72.4 (13.05)	74.7 (13.58)	73.5 (13.14)
Median	69.0	75.0	70.0
Range	55-105	54-99	54-105
Height, cm			
Mean (SD)	177.3 (9.17)	174.7 (9.60)	176.0 (9.32)
Median	179.0	177.0	177.0
Range	160-194	160-188	160-194
Smoking habit, n (%)			
Light smoker	2 (13)	4 (27)	6 (20)
Non smoker	13 (87)	11 (73)	24 (80)
Pregnancy result, n (%)			
Negative	8 (53)	7 (47)	15 (50)
Not applicable	7 (47)	8 (53)	15 (50)

Cross-reference: Attachment 1.5.

Quantitative formulation for Risperdal 1 mg, 2 mg, 3 mg, and 4 mg tablets for the proposed

TABLET COMPONENT	COMPOSITION (mg per core tablet)
TABLET CORE	
Theoretical (core tablet) Weight	

Level 2 change.

The amount per tablet in the film-coating composition is only intended to be used to calculate the amount of the ingredient needed in the preparation of the [redacted] Therefore, it does not represent an exact amount per tablet.

Study Results

Clinical

Analytical Method Validation

No stability experiments were conducted in this study. The Sponsor demonstrated that risperidone and 9-hydroxyrisperidone were stable in human heparinized plasma/blood for at least:
72 hours at 4 °C in blood;
24 hours at room temperature in blood;
2 hours at 37 °C in blood;
72 hours at room temperature in plasma;
during 3 freeze/thaw cycles in plasma;
6 days in re-dissolved (in 300 µl of 50/50 0.01 M ammonium formate (pH 4.0 with HCOOH) / acetonitrile) extraction residue of 0.5 ml of plasma (stored at room temperature);
284 days at ≤ -18 °C in plasma (stability experiment on-going at Johnson and Johnson Pharmaceutical Research & Development).

In method validation study with code PBRL-RD-416 (Study PBR-000673) it was demonstrated that risperidone and 9-hydroxyrisperidone were stable for at least 112 hours in processed sample at 4 °C.

The Sponsor has demonstrated that risperidone and 9-hydroxyrisperidone were stable in methanol for at least:
6 months at ≤ -18 °C
1 month at 2–6 °C
3 days at room temperature (dark)
3 days at room temperature (light).

The stability data covered the conditions used in this study. Stock solutions were stored at –20 °C (target temperature) for less than 6 months, standard dilutions at 4 °C (target temperature) for less than 1 month. The study samples were stored a [redacted] for a maximum of 49 days before analysis at –20 °C (target temperature).

Parameter	Risperidone	9-hydroxyrisperidone
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	[redacted]	
Linearity (Standard curve samples)	[redacted]	
Quality Control (QC) Samples	0.25 ng/ml 10.0 ng/ml 200 ng/ml	0.25 ng/ml 10.0 ng/ml 200 ng/ml
Precision of Standards (%CV)	2.0%@0.1ng/ml 2.55@250 ng/ml	4.1%@0.1ng/ml 2.5@250 ng/ml
Precision of QC Samples (%CV)	9.5%@0.25 ng/ml 4.7%@10.0 ng/ml 3.0%@200 ng/ml	6.1%@0.25 ng/ml 4.5%@10.0 ng/ml 3.3%@200 ng/ml
Accuracy of Standards	[redacted]	
Accuracy of QC Samples	[redacted]	

Pharmacokinetic/Statistical Analysis

Pharmacokinetic analyses were performed by

Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone and the active moiety (calculated as the sum of the risperidone and 9-hydroxy-risperidone concentrations) were determined after a single oral intake of 1 mg risperidone:

- C_{max} maximum plasma concentration, determined by visual inspection of the data;
- t_{max} time to reach the maximum plasma concentration, determined by visual inspection of the data;
- AUC_{last} area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear trapezoidal summation;
- AUC_{∞} area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of AUC_{last} and C_{last}/λ_z (C_{last} is last quantifiable plasma concentration);
- λ_z first-order rate constant associated with the terminal portion of the curve, determined by linear regression of the terminal points of the semilogarithmic drug concentration-time curve;
- $t_{1/2,\lambda}$ elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$;
- $\%AUC_{ex}$ percentage of AUC_{∞} obtained by extrapolation, calculated by the following equation: $\frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}} * 100$.

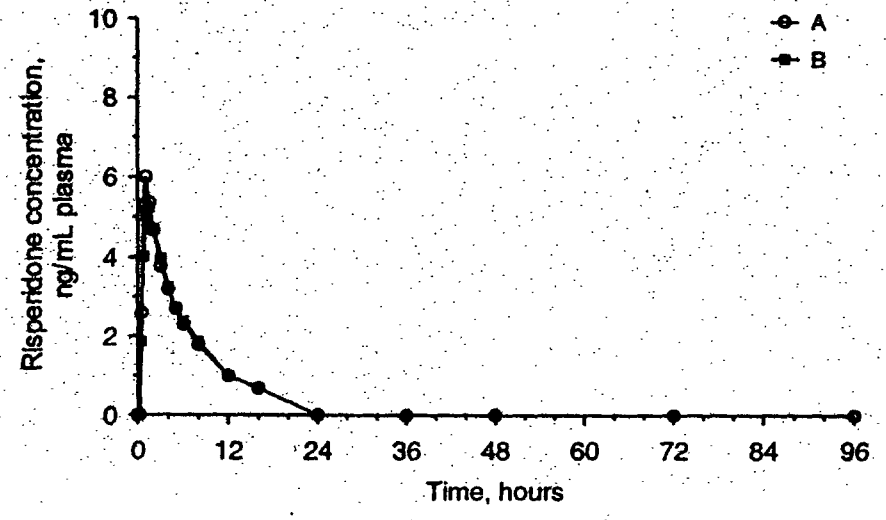
The relative bioavailability of risperidone, 9-hydroxy-risperidone and the active moiety (F_{rel}) were calculated as the C_{max}- and AUC-ratios of risperidone Treatments B/A (/marketed tablet).

Data of all subjects who received at least one dose of the study medication were tabulated and included in the analysis. Subjects could be excluded from the statistical analysis because of vomiting or too few data. This is clearly documented in Section 4. Descriptive statistics were calculated for the plasma concentrations of risperidone, 9-hydroxy-risperidone and the active moiety at each sampling time point and for the pharmacokinetic parameters. The pharmacokinetic parameters Cmax, AUC1ast and AUCinf were analyzed descriptively on both the original and the logarithmic scale. The summary statistics of the log transformed data were transformed back to the original scale when reported. T max and t1/2 were analyzed

descriptively on the original scale only. An analysis of variance (ANOVA) was performed to generate appropriate estimates allowing for the calculation of the 90% confidence intervals and to compare the pharmacokinetic parameters Cmax, AUClast and AUCinf for treatments B versus A. A general linear model (GLM) which includes factors of sequence and sex), subjects (nested in gender and sequence), period and treatment was used.

RESULTS

Figure 1.Mean Plasma Concentrations- Time Profiles of Risperidone A- Reference, B- Test following a 1.0 mg dose



Pharmacokinetic parameters for the marketed 1 mg tablet A versus the [illegible]. Values are mean (± SD).

	A	B
Risperidone		
C_{max}, ng/mL	6.79 ± 3.02	6.33 ± 3.04
t_{max}, h	1.00 (0.50 - 2.00)	1.00 (0.75 - 3.00)
AUC_{last}, ng.h/mL	44.0 ± 47.9	43.9 ± 47.8
AUC_{∞}, ng.h/mL	45.4 ± 49.2	45.4 ± 49.5
$t_{½,\lambda}$, h	5.1 ± 5.0	5.3 ± 5.6
9-hydroxy-risperidone		
C_{max}, ng/mL	4.40 ± 1.92	4.50 ± 1.82
t_{max}, h	5.00 (0.75 - 24.07)	5.00 (0.75 - 24.08)
AUC_{last}, ng.h/mL	122 ± 42.5	125 ± 42.6
AUC_{∞}, ng.h/mL	131 ± 45.4	134 ± 44.9
$t_{½,\lambda}$, h	25.3 ± 5.6	24.9 ± 8.9

Values are means ± SD, except for t_{max}: median (min-max)
Cross-reference: Attachments 2.11 through 2.13

Table 4: Summary of Statistical Analyses Regarding Assessment of Relative Bioavailability of Risperidone and 9-hydroxy-risperidone for the marketed 1 mg tablet A versus the new ———— tablet B.

	Ratio(B/A)	90% CI
Risperidone		
C_{max}, ng/mL	94.22	87.96 - 100.91
AUC_{last}, ng.h/mL	102.81	96.18 - 109.90
AUC_{∞}, ng.h/mL	102.87	96.43 - 109.73
9-hydroxy-risperidone		
C_{max}, ng/mL	101.66	97.94 - 105.53
AUC_{last}, ng.h/mL	101.14	96.49 - 106.01
AUC_{∞}, ng.h/mL	101.56	96.65 - 106.72

[a] Based upon log transformed LSMeans: Treatment A: N=29; Treatment B: N=30.

Comments:

1.The study results supports the bioequivalence of the new ———— 1.0 mg tablet to the currently marketed 1.0 mg tablet.

Single-dose Fasting Bioequivalence Study 4.0 mg Tablet

Study Information

Study Number: RIS-RSA-5
Study Dates: April 22, 2002-July 10, 2002

Analysis Dates: July 11, 2002-August 14, 2002
Storage Period: [redacted]

The following batch numbers were used:
Treatment A: Risperdal marketed tablet:
Batch TS19101 -Expiry date: November 2002

Treatment B [redacted] risperidone tablet:
Batch TS11401 -Expiry date: June 2002.

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Washout Period**	10 days
Blood Sampling Times	0,0.25,0.5,0.75,1,1.5,2,3,4,5,6,8,12,16,24,36,48,72, and 96 hrs		
Blood Volume Collected	5 mL		
Blood Sample Processing/Storage	-22^0 C		

Demographics

Table 2: Demographics and Baseline Characteristics
(Protocol: RIS-RSA-5)

	Risperdal marketed N=18	Risperdal® marketed / N=18	Total N=36
Age, years			
Mean (SD)	38.6 (10.08)	42.6 (8.47)	40.6 (9.39)
Median	39.5	42.5	41.5
Range	20 - 54	26 - 60	20 - 60
Sex, n (%)			
Male	12 (67)	13 (72)	25 (69)
Female	6 (33)	5 (28)	11 (31)
Race, n (%)			
Black	14 (78)	14 (78)	28 (78)
Caucasian	3 (17)	2 (11)	5 (14)
Other	1 (6)	2 (11)	3 (8)
Weight, kg			
Mean (SD)	63.6 (13.41)	64.7 (10.48)	64.1 (11.88)
Median	62.0	63.0	62.5
Range	42 - 91	53 - 92	42 - 92
Height, cm			
Mean (SD)	163.8 (7.11)	167.6 (8.50)	165.7 (7.96)
Median	164.0	167.5	165.5
Range	150 - 178	153 - 184	150 - 184
Smoking habit, n (%)			
Light smoker	4 (22)	7 (39)	11 (31)
Moderate to heavy	9 (50)	3 (17)	12 (33)
Non smoker	5 (28)	8 (44)	13 (36)
Pregnancy result, n (%)			
Negative	6 (33)	5 (28)	11 (31)
Not applicable	12 (67)	13 (72)	25 (69)
Diagnosis, n (%)			
Schizoaffective disorder (295.70)	2 (11)	2 (11)	4 (11)
Schizophrenia, paranoid (295.30)	2 (11)	0	2 (6)
Schizophrenia, residual (295.60)	10 (56)	16 (89)	26 (72)
Schizophrenia, undifferentiated (295.90)	4 (22)	0	4 (11)

Cross-reference: Attachment 1.5.

Study Results

Clinical

Analytical Method Validation

Parameter	Risperidone	9-hydroxyrisperidone
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples	0.25 ng/ml	0.25 ng/ml