| | | |
|---|---|---|
| | 10.0 ng/ml<br>200 ng/ml | 10.0 ng/ml<br>200 ng/ml |
| Precision of Standards (%CV) | 0.0%@0.1ng/ml<br>3.7@250 ng/ml | 0.0%@0.1ng/ml<br>2.0@250 ng/ml |
| Precision of QC Samples (%CV) | 8.7%@0.25 ng/ml<br>3.8%@10.0 ng/ml<br>2.9%@200 ng/ml | 9.4%@0.25 ng/ml<br>3.6%@10.0 ng/ml<br>3.5%@200 ng/ml |
| Accuracy of Standards | | |
| Accuracy of QC Samples | | |

20 out of 30 subjects had pre-dose concentrations for 9-hydroxyrisperidone. The firm was unable to explain this observation. There were no pre-dose concentrations for risperidone.

**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;
- $AUC_{\infty}$ area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of $AUC_{last}$ and $C_{last}/\lambda_z$ ($C_{last}$ is last quantifiable plasma concentration);
- $\lambda_z$ 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 ($\lambda_z$) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$;
- $\%AUC_{ex}$ percentage of $AUC_{\infty}$ 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 (i.e ———————— marketed tablet).

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

## RESULTS

Figure 2.Mean Plasma Concentrations- Time Profiles of Risperidone A- Reference, B- Test following a 4.0 mg dose

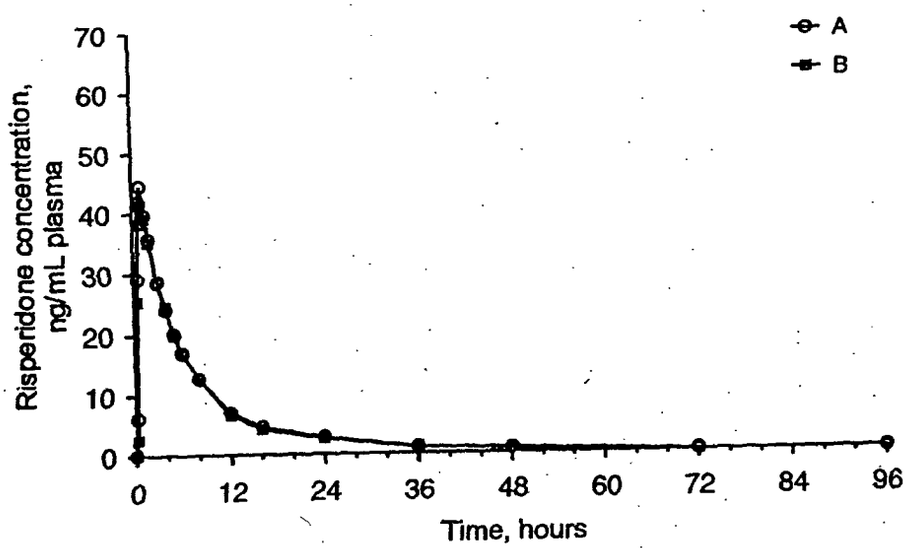



Table 3: Descriptive Statistics of the Pharmacokinetic Parameters of Risperidone and 9-hydroxy-risperidone

| PK Parameter | 4mgRisperdal marketed tablet(A) | 4 mg risperidone tablet (B) |
|---|---|---|
| **Risperidone** | | |
| $C_{max}$, ng/mL | 54.3 ± 30.7 | 51.8 ± 24.5 |
| $t_{max}$, h | 1.00 (0.25 - 3.00) | 1.00 (0.50 - 3.00) |
| $AUC_{last}$, ng.h/mL | 336 ± 291 | 321 ± 274 |
| $AUC_{\infty}$, ng.h/mL | 342 ± 300 | 329 ± 287 * |
| $t_{½,\lambda}$, h | 12.1 ± 9.2 | 13.6 ± 10.1 * |
| **9-hydroxy-risperidone** | | |
| $C_{max}$, ng/mL | 24.8 ± 15.1 | 25.0 ± 13.3 |
| $t_{max}$, h | 5.00 (0.50 - 24.05) | 5.00 (0.50 - 12.00) |
| $AUC_{last}$, ng.h/mL | 596 ± 259 | 579 ± 179 |
| $AUC_{\infty}$, ng.h/mL | 631 ± 268 | 611 ± 184 |
| $t_{½,\lambda}$, h | 23.8 ± 5.6 | 23.3 ± 5.1 |

Values are means ± SD, except for $t_{max}$: median (min-max), N=36 except *: N=35 (Subject A30047: not assessable)
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

| PK Parameter | 4mgRisperdal parameter marketed tablet(A) | 4 mg risperidone tablet (B) | Ratio(B/A) | 90% CI |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Risperidone** | | | | |
| $C_{max}$, ng/mL | 49.9 | 49.3 | 98.82 | 89.06 - 109.64 |
| $AUC_{last}$, ng.h/mL | 268 | 258 | 96.41 | 89.29 - 104.10 |
| $AUC_{\infty}$, ng.h/mL* | 270 | 256 | 94.94 | 88.14 - 102.27 |
| **9-hydroxy-risperidone** | | | | |
| $C_{max}$, ng/mL | 20.5 | 21.1 | 103.35 | 96.50 - 110.69 |
| $AUC_{last}$, ng.h/mL | 566 | 562 | 99.29 | 94.13 - 104.72 |
| $AUC_{\infty}$, ng.h/mL | 602 | 596 | 98.94 | 93.96 - 104.19 |

Values are based on the least-square means of the logarithmic transformed parameters (n=36; except for * where n=35: without Subject A30047 because $t_{\frac{1}{2}\lambda}$ and $AUC_{\infty}$ were not assessable).
Cross-reference: Attachment 2.15.

The treatment ratios of all pharmacokinetic

The firm conducted studies from April 22, 2002-July 10, 2002, however the batch of test they used had an expiration date of June 2002. The last dosing was done on June 20, 2000 so the firm was within the expiration window for the product.

## DISSOLUTION

Dissolution testing for the 1 mg and 4 mg tablets was performed on the bio-batches.

The NDA dissolution method and specifications used were:

USP Apparatus II
50RPM
500 ml of 0.1N HCL
Q= ———
Sampling at 15, 30, 45 and 60 min
Lots used in the study are presented in the following Table.

| Risperidone Dosage | Lots | |
|---|---|---|
| | Current Manufacturing Process | New Manufacturing Process |
| 1 mg | TS18801 | TS10901 |
| 4 mg | TS19101 | TS11401 |

**Table 1**: Dissolution Profile Results for Risperidone 1 mg FC Tablets lot TS18801- Current Process

| Tablet No. | Lot TS18801 Results (%) | | | |
|---|---|---|---|---|
| | 15 minutes | 30 minutes | 45 minutes | 60 minutes |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | | | | |
| Average | 72 | 90 | 96 | 97 |
| Std. Dev. | 8.9489 | 5.6642 | 4.0555 | 2.8110 |
| %RSD | 12.4 | 6.3 | 4.2 | 2.9 |

**Table 2**: Dissolution Profile Results for Risperidone 1 mg FC Tablets lot TS10901- New Process

| Tablet No. | Lot TS10901 Results (%) | | | |
|---|---|---|---|---|
| | 15 minutes | 30 minutes | 45 minutes | 60 minutes |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | | | | |
| Average | 92 | 100 | 100 | 100 |
| Std. Dev. | 4.0189 | 1.9069 | 1.5448 | 1.2060 |
| %RSD | 4.4 | 1.9 | 1.5 | 1.2 |

**Table 3**: Dissolution Profile Results for Risperidone 4 mg FC Tablets lot TS19101-Current process

| Tablet No. | Lot TS19101 | | | |
|---|---|---|---|---|
| | Results (%) | | | |
| | 15 minutes | 30 minutes | 45 minutes | 60 minutes |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | | | | |
| Average | 79 | 90 | 94 | 95 |
| Std. Dev. | 6.4544 | 4.3693 | 3.4772 | 2.9491 |
| %RSD | 8.2 | 4.9 | 3.7 | 3.1 |

**Table 4**: Dissolution Profile Results for Risperidone 4 mg FC Tablets lot TS11401-New process

| Tablet No. | Lot TS11401 Results (%) | | | |
|---|---|---|---|---|
| | 15 minutes | 30 minutes | 45 minutes | 60 minutes |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | | | | |
| Average | 95 | 99 | 99 | 100 |
| Std. Dev. | 2.1881 | 1.0445 | 0.9653 | 0.8348 |
| %RSD | 2.3 | 1.1 | 1.0 | 0.8 |

Dissolution testing for both strengths was faster for tablets made by ——— compared to those manufactured by ———

**Comments to Chemistry and Clinical Division:**

1.The firm has conducted acceptable bioequivalence studies on their 4 mg and 1 mg tablets manufactured by the ——— Therefore these studies have been found to be acceptable to OCPB. Comparative dissolution testing was performed on these bio-batches and the results indicate that these strengths meet the dissolution specification of Q= ——— minutes.

2. The firm did not provide the comparable comparative dissolution profiles for the 2 mg and 3 mg strengths for the ——— and ——— s. 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. During the course of these communications the FDA was also informed that the report title was misleading since it mentioned comparative dissolution was available for all strengths while only the 1 mg and 4 mg strengths had been tested. The absence of this data was also discussed with Division of Chemistry colleagues.

**Recommendation:**

1. Based upon comments 1 and 2 above, the manufacturing process change from _____ _____ should only be applicable to the 1 mg and 4 mg strengths (i.e., based upon BE results, comparative dissolution, and the new process meeting the NDA specifications).

2. The manufacturing process change can not be granted for the 2 mg and 3 mg strengths at this time. The firm is requested to provide comparative dissolution profiles using the NDA method and relevant chemistry information related to stability for approval of the manufacturing process change for the 2 mg and 3 mg strengths.

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
5/14/03 12:45:20 PM
BIOPHARMACEUTICS

Raman Baweja
5/14/03 01:57:44 PM
BIOPHARMACEUTICS

# Office of Clinical Pharmacology and Biopharmaceutics

*New Drug Application Filing Memorandum*

| | | | |
|---|---|---|---|
| **NDA:** | **N20-272/SE1-026 N20-588/SE1-017** | **Sponsor:** | **Johnson & Johnson** |
| **IND:** | | | |
| **Brand Name:** | Risperdal | **Priority Classification:** | S |
| **Generic Name:** | Risperidone | **Indication(s):** | Treatment of acute bipolar mania |
| **Drug Class:** | | **Date of Submission:** | December 13, 2002 |
| **Dosage Form:** | Tablets/Oral solution | **Route of Admin.:** | Oral |
| **Dosing Regimen:** | QD starting with 2 or 3 mg, titrated to 1-6 mg per day | **Due Date of Review:** | August 30, 2003 PDUFA date: October 15, 2003 |
| **Division:** | HFD-860 | **Medical Division:** | HFD-120 |
| **Reviewer:** | John Duan | **Team Leader:** | Ramana Uppoor |

| *Items included in NDA (CTD)* | *Yes* | *No* | *Request* |
|---|---|---|---|
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | |
| **Tabular Listing of All Human Studies** | X | | |
| **HPK Summary** | X | | |
| **Labeling** | X | | |
| **Reference Bioanalytical and Analytical Methods** | X | | |
| **Bioavailability and Bioequivalence Studies** | | - | |
| **Mass Balance Study** | | - | |
| **BA Studies** | | - | |
| **Absolute BA** | | - | |
| **Relative BA** | | - | |
| **BE Studies** | | - | |
| **Average BE** | | - | |
| **Population BE** | | - | |
| **Individual BE** | | - | |
| **Food-Drug Interaction** | | - | |
| **Dissolution Tests (In Vitro-In Vivo Comparison Studies)** | | - | |
| **Studies Using Human Biomaterials** | | - | |
| **Plasma Protein Binding Studies** | | - | |
| **Blood/Plasma Ratio** | | - | |
| **Metabolism Studies Using Hepatocytes, Microsomes,etc** | | - | |

| | | | |
|---|---|---|---|
| **In Vitro Drug Interaction Studies** | | - | |
| **Human Pharmacokinetics Studies** | | | |
| **PK, and Initial Safety and Tolerability in Healthy Volunteers** | | | |
| **Single Dose** | | | |
| **Multiple Dose** | | | |
| **PK, and Initial Safety and Tolerability in Patients** | | | |
| **Single Dose** | | | |
| **Multiple Dose** | | | |
| **Dose Proportionality** | | | |
| **Single Dose** | | | |
| **Multiple Dose** | | | |
| **PK in Population Subsets to Evaluate Effects of Intrinsic Factors** | | | |
| **Ethnicity** | | - | |
| **Gender** | | - | |
| **Pediatrics** | | - | |
| **Geriatrics** | | - | |
| **Renal Impairment** | | - | |
| **Hepatic Impairment** | | - | |
| **PK to Evaluate Effects of Extrinsic Factors** | | - | |
| **Drug-Drug Interaction: Effects on Primary Drug** | X | | |
| **Drug-Drug Interaction: Effects of Primary Drug** | X | | |
| **Population PK studies** | X | | |
| **Summary Table of PK/PD Studies** | X | | |
| **PK/PD studies in Volunteers** | | - | |
| **PK/PD studies in patients** | X | | |
| **Individual Datasets for all PK and PK/PD studies in electronic format** | X | | Yes |
| **Other** | X | | |
| **Genotype/Phenotype Studies** | | - | |
| **Chronopharmacokinetics** | | - | |
| **Literature review** | X | | |

| | |
|---|---|
| **Memo:** | **45-day filing review** |
| **Subject:** | **NDA 20-272/SE1-026//NDA 20-588/SE1-017, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS** |
| **Submission Date:** | December 13, 2002 |
| **Drug Name:** | RISPERDAL® (risperidone) |
| **Formulation & Strength:** | Tablets/Oral Solution |
| **Applicant:** | Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) |
| **Reviewer:** | John Duan, Ph.D. |
| **Type of Submission:** | Supplement New Drug Application |

## I. BACKGROUND

RISPERDAL® (risperidone), a benzisoxazole derivative with potent serotonin 5-$HT_{2A}$ and dopamine $D_2$ receptor-blocking properties, is an atypical antipsychotic approved for the treatment of schizophrenia. Risperidone is an antipsychotic, ameliorating both positive and negative symptoms of schizophrenia and exhibiting a low risk of extrapyramidal side effects (EPS). In this supplemental New Drug Application (sNDA), data collected by the applicant are presented to support the use of risperidone for the short-term treatment of acute manic episodes associated with Bipolar I disorder, either monotherapy or as adjunctive therapy to mood stabilizers.

Separate sNDAs for Risperidone tablets (N20-272) and Risperidone oral solution (N20-588) were submitted concurrently and cross-referenced to each other.

This sNDA includes the results of clinical studies that provide evidence of the efficacy and safety of risperidone for the treatment of acute manic episodes of Bipolar I disorder. The studies in which information on the pharmacokinetics of risperidone was obtained are included in the "hpbio" section of the current submission (Table 1 in Appendix). These include the studies described below.

- Four double-blind Phase-3 trials in Bipolar I disorder provide information on the pharmacokinetics of risperidone. All trials used a flexible risperidone dose range of 1 - 6 mg/day to optimize each patient's level of efficacy and tolerability. In all trials, a sparse sampling approach was followed. For each sample, the concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were determined.

- Pharmacokinetic data from the open-label extension study of RIS-USA-240, designated RIS-USA-241, are also included in this submission. Because RIS-USA-240 was terminated early, only a few patients entered RIS-USA-241.

- Eight pharmacokinetic trials, which were conducted in patients with Bipolar I disorder (RIS-CAN-27), patients with psychosis (RIS-FRA-4, RIS-GER-9, RIS-SUI-5, and RIS-RSA-1), or healthy subjects (RIS-USA-122, GAL-USA-19, and RIS-NED-26), provide data regarding potential drug interactions with mood stabilizers, antidepressants and Alzheimer's medication (cholinesterase inhibitors). The results of an interaction trial with the CYP3A4 inhibitor erythromycin is also given.

- Population pharmacokinetics of risperidone, in which the plasma concentration-time data of risperidone, 9-hydroxy-risperidone and the active moiety (i.e., the sum of risperidone and 9-hydroxy-risperidone) obtained in the monotherapy trials RIS-USA-239 and RIS-IND-2 and in the adjunctive trial RIS-INT-46, were combined and subjected to a population pharmacokinetic modeling approach using NONMEM. The structural model was built using data from four data-rich pharmacokinetic trials (JRD0001, JRD0002, RIS-FRA-4, and RIS-GER-9). The typical population values of basic pharmacokinetic parameters were estimated together with their inter- and intra-individual variability. The effects of demographics such as age, body weight, lean body mass, body surface area, height, sex, and other covariates (ALT, AST, and creatinine clearance) were explored, as well as possible influences of co-medication (carbamazepine, lithium, and valproate).

- A pharmacokinetic/pharmacodynamic evaluation for the Phase-3 clinical trials in patients with Bipolar I disorder.

- An overview of relevant published literature.

## II. COMMENTS AND RECOMMENDATION:

The Human Pharmacokinetics and Bioavailability section of this NDA appears to be filable from Clinical Pharmacology and Biopharmaceutics perspective. The NDA has been indexed and organized in a manner to allow substantive review to begin.

| | |
|---|---|
| Ramana Uppoor, Ph.D. | John Duan, Ph.D. |
| Team Leader | Reviewer |
| Division of Pharmaceutical Evaluation I | Division of Pharmaceutical Evaluation I |

cc: Orig 20,272
HFD-120 Division File
HFD-860 MMehta, CSahajwalla, RUppoor, JDuan
CDR

## Appendix

| Trial | Objective | Number of Patients |
|---|---|---|
| **COMPLETED TRIALS IN PATIENTS WITH BIPOLAR I DISORDER** | | |
| Phase 3, Double-blind, Placebo-controlled, 3-Week, Efficacy and Safety Trials | | |
| *Pivotal trials* | | |
| RIS-USA-239 | Flexible dose risperidone (1-6 mg daily) as monotherapy versus placebo. | Randomized: 262 patients with acute bipolar mania<br>Treated[a]: 259 patients |
| RIS-USA-102 | Flexible dose risperidone (1-6 mg daily) as adjunctive therapy to mood stabilizers (lithium or valproate) versus placebo plus mood stabilizers, followed by a 10-week, open-label phase. | Randomized: 158 patients with acute bipolar mania<br>Treated[a]: 156 patients<br>(85 patients entered the open-label extension phase) |
| *Supportive trials* | | |
| RIS-IND-2 | Flexible dose risperidone (1-6 mg daily) as monotherapy versus placebo. | Randomized: 291 patients with acute bipolar mania<br>Treated[a]: 290 patients |
| RIS-INT-46 | Flexible dose risperidone (1-6 mg daily) as adjunctive therapy to mood stabilizers (lithium, valproate, or carbamazepine) versus placebo plus mood stabilizers, followed by a 10-week, open-label phase. | Randomized: 151 patients with acute bipolar mania<br>Treated[a]: 150 patients<br>(124 patients entered the open-label extension phase) |
| *Terminated trial (safety only)* | | |
| RIS-USA-240[b] | Flexible dose risperidone (1-6 mg daily) as monotherapy versus placebo or divalproex sodium. | Planned: 432 patients with acute bipolar mania<br>Randomized: 39 patients<br>Treated[a]: 39 patients<br>(17 patients entered the open-label extension trial, RIS-USA-241) |
| **Phase 3, Open-Label Trial** | | |
| RIS-USA-241[a] (Open-label extension of terminated RIS-USA-240) | Flexible dose risperidone (1-6 mg daily) as monotherapy. | Planned: ≤432 patients with acute bipolar mania<br>17 patients entered |
| **COMPLETED DRUG-INTERACTION TRIALS** | | |
| RIS-CAN-27 | To assess the effect of repeated risperidone doses on valproate steady-state pharmacokinetics. | 22 patients with bipolar disorder in remission for at least 2 weeks |
| RIS-GER-9 | To assess steady-state pharmacokinetics of lithium in combination with risperidone and with other antipsychotics. | 13 patients with psychosis |
| RIS-FRA-4[c] | To assess the effect of repeated carbamazepine doses on risperidone steady-state pharmacokinetics. | 12 patients with (sub)chronic schizophrenia (11 analyzed) |
| RIS-SUI-5[c] | To assess the effect of repeated fluoxetine doses on risperidone steady-state pharmacokinetics. | 13 patients with psychosis |
| RIS-RSA-1 | To assess the effect of repeated amitriptyline doses on risperidone steady-state pharmacokinetics. | 12 patients with psychosis |
| RIS-USA-122 | To assess steady-state pharmacokinetics of both risperidone and donepezil when taken alone and taken together. | 24 healthy male subjects |
| GAL-USA-19 | To assess steady-state pharmacokinetics of both risperidone and galantamine when taken alone and taken together. | 16 healthy elderly (≥60 years) subjects |
| RIS-NED-26 | To assess potential effects of repeated doses of erythromycin on single-dose pharmacokinetics of risperidone. | 18 healthy subjects (12 EMs and 6 PMs) |

EM = CYP2D6 extensive metabolizers, as determined by dextromethorphan phenotyping; PM = CYP2D6 poor metabolizers, as determined by dextromethorphan phenotyping.

[a] All patients randomized who received at least 1 dose of study medication.

[b] RIS-USA-240 was terminated by sponsor for business reasons. all patients had the option to complete the open label extension trial RIS-USA-241.

[c] Clinical study report filed previously to RISPERDAL® NDA (20-272).

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

/s/

John Duan
3/3/03 08:36:26 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/3/03 10:22:22 AM
BIOPHARMACEUTICS

**Clinical Pharmacology and Biopharmaceutics Review**

| | | |
|---|---|---|
| **NDA:** | 20-272/S-026<br>20-588/S-017 | **SUBMISSION DATES:** December 13, 2002<br>December 19, 2002<br>January 15, 2003 |
| **DRUG NAME:** | RISPERDAL® (risperidone) | |
| **DOSAGE STRENGTH:** | 0.25, 0.5, 1, 2, 3, and 4 mg tablets, 1 mg/mL oral solution | |
| **APPLICANT:** | Johnson & Johnson | |
| **REVIEWER:** | John Duan, Ph.D. | |
| **TEAM LEADERS:** | Ramana Uppoor, Ph.D, Joga Gobburu, Ph.D. | |
| **TYPE OF SUBMISSION:** | Supplemental New Drug Application | |

## I. Executive Summary

RISPERDAL® (risperidone), a benzisoxazole derivative with potent serotonin 5-$HT_{2A}$ and dopamine $D_2$ receptor-blocking properties, is an atypical antipsychotic for the treatment of schizophrenia. In this sNDA, data are presented to support the use of risperidone for the short-term treatment of acute manic episodes associated with Bipolar I disorder, as monotherapy or as adjunctive therapy to mood stabilizers. The clinical pharmacology section of this sNDA includes results from the trials in which information on the pharmacokinetics of risperidone was obtained. Four double-blind Phase III trials in Bipolar I disorder and eight pharmacokinetic trials that were conducted in patients with Bipolar I disorder, patients with psychosis, or healthy subjects provided information regarding potential drug interactions with risperidone and supportive safety data. In addition, a population pharmacokinetic analysis based on four phase III studies and a selection of phase I studies was conducted. These studies showed that the pharmacokinetic behavior of risperidone in bipolar I disorder patients was similar to that in schizophrenia patients obtained previously. Drug interaction information was obtained from three sources including analysis of adjunctive trial for bipolar I disorders, population pharmacokinetic analysis and formal drug interaction studies. Analysis of adjunctive trial with mood stabilizers showed that the plasma concentrations of the active moiety (the sum of risperidone and 9-hydroxy-risperidone), risperidone and 9-hydroxy-risperidone were not changed significantly when lithium or valproate was taken as concurrent mood stabilizers. However, when risperidone was co-administered with carbamazepine, plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were on average 50% lower. This finding is in line with population pharmacokinetic analysis and formal drug interaction study. The formal drug interaction studies with medications commonly used in the treatment of Bipolar I disorder (lithium, valproate or carbamazepine), Alzheimer's disease (donepezil and galantamine), psychiatric illnesses (fluoxetine and amitriptyline), and with the CYP3A4 inhibitor erythromycin were conducted. Important drug interactions include co-administration of carbamazepine that caused a reduction in the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone by about 50%, Co-treatment with fluoxetine increased the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. Dosing recommendations are made accordingly.

**RECOMMENDATIONS**

1. From Clinical Pharmacology and Biopharmaceutics perspective, this sNDA is acceptable provided the following comments and the labeling comments are adequately addressed by the applicant.

**Comments to the applicant**

In support of the label, the Sponsor is asked to describe CYP MP in a manner consistent with the currently used nomenclature for CYP isozymes, and to provide a summary of the data used to identify the specific P450 isozyme to which they refer (e.g. the inhibitor of that pathway may indicate which P450 is responsible).

Please make the requested changes before the labeling is finalized.

**LABELING RECOMMENDATIONS**

This labeling recommendation is based on the most recent proposed version in submission of N21-444 dated 8/13/2003. Only the subsections of the label that need to be revised from OCPB point of view are provided below.

1. In the CLINICAL PHARMACOLOGY section, the following additions are recommended.

Risperidone could be subject to two kinds of drug-drug interactions (see Drug Interactions under PRECAUTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \cong 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected.

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations ($C_{max}$) of lithium (n=13).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration ($C_{max}$) after concomitant administration of risperidone.

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see Drug Interactions under PRECAUTIONS).

2. The following changes are recommended for the section of Drug Interactions under PRECAUTIONS.

### Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration ($C_{max}$) after concomitant administration of risperidone.

### Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≅70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

*In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

### Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine.

3. In DOSAGE AND ADMINISTRATION section, a third heading is recommended as follows.

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone [redacted] in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (See CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. Dose of risperidone needs to be titrated accordingly when fluoxetine is co-administered (See CLINICAL PHARMACOLOGY and PRECAUTIONS).

Under the heading of Bipolar Mania, the following additions are recommended.

[redacted]

## II. Table of contents

## III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacokinetics of risperidone in healthy subjects as well as in patients with schizophrenia have been described in earlier submissions. Four double-blind Phase III trials in Bipolar I disorder and eight pharmacokinetic trials that were conducted in patients with Bipolar I disorder, patients with psychosis, or healthy subjects were submitted in this supplement.

### 1. Absorption

Following oral administration of either the solution or tablet formulation, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxy-risperidone occurred at about 3 hours in extensive metabolizers (for CYP2D6), and 17 hours in poor metabolizers. Plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone are dose-proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg b.i.d.). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to the solution. The absolute oral bioavailability of risperidone was 70% (CV=25%). Food does not affect either the rate or extent of absorption of risperidone.

### 2. Distribution

The plasma protein binding of risperidone is 90% and that of 9-hydroxy-risperidone is 77%. The extent of protein binding does not change with age. The binding of risperidone and 9-hydroxy-risperidone is not affected by the presence of each other. No clinically significant plasma protein binding interactions were demonstrated for risperidone.

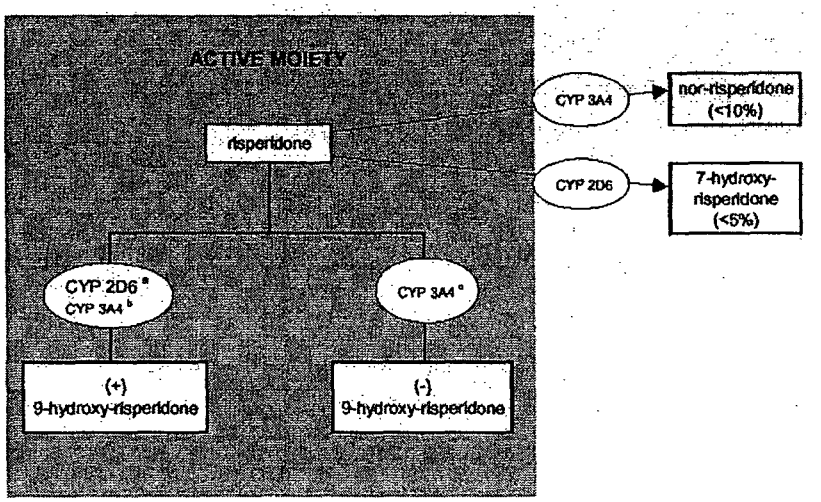
### 3. Metabolism

Risperidone is mainly metabolized by hydroxylation and N-dealkylation. The metabolism in vivo is predominantly mediated via CYP2D6 and, to a minor extent, also via CYP3A4. There is no evidence that other CYP isoenzymes affect the metabolism of risperidone. The 9-hydroxylation is the most important metabolic route. The sum of risperidone and 9-hydroxy-risperidone represents the active antipsychotic fraction (active moiety), since 9-hydroxy-risperidone is pharmacologically equipotent to the parent compound, both in vitro and in vivo.

Risperidone is subject to CYP2D6-mediated genetic polymorphism. Extensive metabolizers convert risperidone rapidly into 9-hydroxy-risperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolizers.

9-Hydroxy-risperidone contains [redacted]
hydroxy-risperidone, which are pharmacologically equipotent. It was reported that (+)-9-hydroxylation of risperidone is catalyzed predominantly by CYP2D6, and to a lesser extent by CYP3A4, whereas (-)-9-hydroxylation of risperidone is catalyzed by CYP3A4. As shown in the following Figure, it is apparent that the ratio of [redacted] will be higher in extensive metabolizers of CYP2D6 than in poor metabolizers due to the large difference in Km between CYP2D6 and CYP3A4. This was confirmed by results in psychotic patients and

an erythromycin-risperidone interaction study in healthy subjects. Other metabolites which were identified are 7-hydroxy-risperidone (<3% of total radioactivity in plasma; 1-5% of the dose recovered in urine) and acid metabolites of both risperidone and 9-hydroxy-risperidone (6-10% and 1-5% of the dose recovered in urine, respectively). 7-Hydroxy-risperidone showed a similar in vitro receptor binding profile as risperidone, but with a 2- to 3-times weaker affinity for the main target receptors.




[a] $K_m = 0.26 \pm 0.18$ µM
[b] $K_m = 42 \pm 14$ µM
[c] $K_m = 109 \pm 42.5$ µM (human liver microsomes, data from Furukori et al.[32])

**4. Elimination+**

Risperidone and its metabolites are primarily eliminated via the urine and to a much lesser extent via the feces. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxy-risperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

**5. Special populations**

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease.

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and $\alpha_1$-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease.

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients.
No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

**6. Drug interaction**

Drug interaction studies with medications commonly used in the treatment of Bipolar I disorder (lithium, valproate or carbamazepine), Alzheimer's disease (donepezil and galantamine), psychiatric illnesses (fluoxetine and amitriptyline), the erythromycin-risperidone interaction study in healthy subjects and other drug interaction studies previously conducted are summarized in QBR section of this review..

## IV. Question based review

### A. General Attributes

***1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?***

RISPERDAL® (risperidone) belongs to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. Risperidone is a white to slightly beige powder. It is insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl. RISPERDAL® tablets are available in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg strengths. RISPERDAL® is also available as a 1 mg/mL oral solution and as orally disintegrating tablets.

The mechanism of action of RISPERDAL® (risperidone) is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 ($D_2$) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than $D_2$ and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 ($D_2$), $\alpha_1$ and $\alpha_2$ adrenergic, and $H_1$ histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine $D_1$ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or $\beta_1$ and $\beta_2$ adrenergic receptors.

### B. General Clinical Pharmacology

***1. How does the PK of risperidone and its major active metabolites 9-hydroxy-risperidone in patients with bipolar I disorders compare to that in schizophrenia patients?***

The pharmacokinetics of risperidone in patients with acute manic episodes of Bipolar I disorder were studied in the following completed Phase-3 trials: the monotherapy trials RIS-USA-239 (pivotal), RIS-IND-2 (supportive), RIS-USA-240 (terminated for business reasons), and its open-label extension trial RIS-USA-241; and the supportive adjunctive therapy trial RIS-INT-46. In the pivotal adjunctive therapy trial RIS-USA-102, no samples to assess the pharmacokinetics of risperidone were collected.

Descriptive statistics of the plasma concentrations of the active moiety (the sum of risperidone and 9-hydroxy-risperidone), risperidone and 9-hydroxy-risperidone at each visit

are summarized for study RIS-USA-239 and study RIS-IND-2 (these two trials had identical dosing regimens and sampling schedule) as shown in the following table.

| Visit | Plasma concentrations normalized to a 4 mg dose (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| | Study RIS-USA-239 | | | Study RIS-IND-2 | | |
| | N | Mean ± SD | Median (min–max) | N | Mean ± SD | Median (min – max) |
| **Active moiety** | | | | | | |
| Day 7 predose | 87 | 20.8 ± 10.0 | 19.4 | 3 | 26.4 ± 17.9 | 22.8 |
| Day 7 postdose | 89 | 39.9 ± 20.1 | 37.1 | 7 | 57.3 ± 33.7 | 51.9 |
| Day 21 predose | 73 | 27.4 ± 15.7 | 24.3 | 1 | 34.4 ± 32.8 | 27.4 |
| **R** | | | | | | |
| Day 7 predose | 87 | 2.34 ± 5.04 | 0.37 | 3 | 5.51 ± 9.22 | 1.60 |
| Day 7 postdose | 89 | 15.7 ± 13.4 | 12.0 | 7 | 28.2 ± 25.7 | 19.3 |
| Day 21 predose | 73 | 4.99 ± 8.59 | 0.87 | 1 | 8.44 ± 24.48 | 1.81 |
| **9-hydro** | | | | | | |
| Day 7 predose | 87 | 18.4 ± 8.69 | 17.2 ( | 3 | 20.9 ± 13.3 | 19.0 |
| Day 7 postdose | 89 | 24.2 ± 10.3 | 23.2 ( | 7 | 29.1 ± 15.4 | 26.7 |
| Day 21 predose | 73 | 22.4 ± 13.0 | 19.6 ( | 1 | 25.9 ± 17.2 | 23.1 |

In general, the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were within the expected concentration range (for a 4-mg dose of risperidone o.d.: 25.6 ng/mL for the active moiety in a previous population pharmacokinetic analysis of data from schizophrenia patients).

The predose plasma drug concentrations on Day 7 were lower than those on Day 21. This is related to the fact that steady state was not yet reached after 6 days of treatment, due to dose adjustment in the first days of the study. In addition, the median times after last drug intake were 22 hours on Day 7, and around 18 hours on Day 21.

The postdose samples on Day 7 were collected at a median time of 1 h after dosing, which corresponds to the expected tmax for risperidone. The postdose risperidone plasma concentrations were therefore much higher than the predose concentrations. This difference was less explicit for 9-hydroxy-risperidone, due to its later tmax as a result of its formation through metabolism of risperidone.

## C. Intrinsic Factors

***1. What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?***

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Risperidone is subject to CYP2D6-mediated genetic polymorphism. Extensive metabolizers convert risperidone rapidly into 9-hydroxy-risperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolizers.

## D. Extrinsic Factors

*1. Is risperidone a substrate of CYP enzymes?*

Yes. Risperidone is mainly metabolized by hydroxylation and N-dealkylation. The metabolism in vivo is predominantly mediated via CYP2D6 and, to a minor extent, also via CYP3A4. There is no evidence that other CYP isoenzymes affect the metabolism of risperidone. The 9-hydroxylation is the most important metabolic route. The sum of risperidone and 9-hydroxy-risperidone represents the active antipsychotic fraction (active moiety), since 9-hydroxy-risperidone is pharmacologically equipotent to the parent compound, both in vitro and in vivo.

Risperidone is subject to CYP2D6-mediated genetic polymorphism. Extensive metabolizers convert risperidone rapidly into 9-hydroxy-risperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolizers.

The action of CYP2D6 leads to the formation of 9-hydroxy-risperidone, the main metabolite of risperidone, which has a similar pharmacological profile as the parent drug. Hence, the sum of risperidone and 9-hydroxy-risperidone is responsible for the antipsychotic activity and constitutes the active moiety.

*2. Are there any in vivo drug-drug interaction studies that indicate the exposures are different when drugs are co-administered?*

Yes. Drug interaction information was obtained from three sources including analysis of adjunctive trial for bipolar I disorders, population pharmacokinetic analysis and formal drug interaction studies.

The adjunctive Phase-3 clinical trials in patients with Bipolar I disorder (RIS-USA-102 and RIS-INT-46) had a similar design, consisting of two phases. The first phase was a 3-week, double-blind treatment with parallel groups (placebo, risperidone and haloperidol for RIS-USA-102; placebo and risperidone for RIS-INT-46) during adjunctive mood stabilizer treatment (lithium and valproate in RIS-USA-102 and lithium, valproate or carbamazepine in RIS-INT-46). The second phase was a subsequent 10-week, open-label risperidone treatment. Both trials used a flexible o.d. risperidone dosage regimen (1-6 mg/day). The plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were only monitored in RIS-INT-46. Serum levels of the mood stabilizers were monitored in both RIS-USA-102 and RIS-INT-46.

The plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were similar when lithium or valproate were taken as concurrent mood stabilizer. However, when risperidone was co-administered with carbamazepine, plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were on average 50% lower as shown in the following table.

| | N | Actual plasma concentrations | | Normalized to a 4-mg dose | |
|---|---|---|---|---|---|
| | | Mean ± SD | Median (min – max) | Mean ± SD | Median (min – max) |
| **Lithium treatment group** | | | | | |
| *Active Moiety* | | | | | |
| Baseline | 9 | NQ* | NQ | NQ* | NQ |
| Endpoint DB | 23 | 28.9 ± 20.9 | 25.3 | 38.5 ± 24.8 | 36.2 ( |
| Endpoint OL | 19 | 38.6 ± 30.4 | 39.9 | 42.7 ± 28.1 | 39.8 |
| *Risperidone* | | | | | |
| Baseline | 9 | NQ | NQ | NQ | NQ |
| Endpoint DB | 23 | 5.85 ± 9.02 | 1.12 | 93 ± 13.12 | 1.46 |
| Endpoint OL | 19 | 9.33 ± 12.94 | 4.8 | 1 ± 17.0 | 3.33 |
| *9-hydroxy-risperidone* | | | | | |
| Baseline | 9 | NQ | NQ | NQ | NQ |
| Endpoint DB | 23 | 23.1 ± 14.8 | 22.0 | .6 ± 17.2 | 32.2 |
| Endpoint OL | 19 | 29.2 ± 23.3 | 19.2 | 31.6 ± 22.5 | 31. |
| **Valproate treatment group** | | | | | |
| *Active moiety* | | | | | |
| Baseline | 5 | NQ | NQ | NQ | NQ ( |
| Endpoint DB | 11 | 36.2 ± 20.3 | 30.2 | 40.4 ± 21.8 | 35.9 |
| Endpoint OL | 7 | 21.2 ± 6.2 | 19.8 | 37.8 ± 14.3 | 42.1 |
| *Risperidone* | | | | | |
| Baseline | 5 | NQ | NQ | NQ | NQ |
| Endpoint DB | 11 | 10.1 ± 10.0 | 8.38 | 15.0 ± 20.6 | 7.58 |
| Endpoint OL | 7 | 3.85 ± 6.01 | 1.41 | 7.76 ± 12.06 | 2.72 |
| *9-hydroxy-risperidone* | | | | | |
| Baseline | 5 | NQ | NQ | NQ | NQ |
| Endpoint DB | 11 | 26.1 ± 19.3 | 16.5 | 25.5 ± 10.9 | 26.8 |
| Endpoint OL | 7 | 17.3 ± 7.9 | 18. | 30.1 ± 14.8 | 36.7 |
| **Carbamazepine treatment group** | | | | | |
| *Active moiety* | | | | | |
| Baseline | 3 | NQ | NQ | NQ | NQ |
| Endpoint DB | 9 | 16.7 ± 9.1 | 14.3 | 18.8 ± 10.5 | 18.8 |
| Endpoint OL | 3 | 7.58 ± 4.36 | 10.0 | 12.4 ± 7.1 | 10.2 |
| *Risperidone* | | | | | |
| Baseline | 3 | NQ | NQ | NQ | NQ |
| Endpoint DB | 9 | 2.87 ± 4.62 | 0.67 ( | .29 ± 4.83 | 0.56 |
| Endpoint OL | 3 | 2.00 ± 3.15 | 0.23 ( | 99 ± 6.33 | 0.52 |
| *9-hydroxy-risperidone* | | | | | |
| Baseline | 3 | NQ | NQ | NQ | NQ |
| Endpoint DB | 9 | 13.8 ± 5.4 | 11.4 | 15.5 ± 7.0 | 17.5 ( |
| Endpoint OL | 3 | 5.58 ± 3.78 | 4.56 | 8.43 ± 1.68 | 9.10 |

Serum concentrations of lithium and valproate were similar between the three treatment groups for both treatment phases (double-blind and open-label) in RIS-USA-102 as shown in the following table.

| | Mood stabilizer + placebo | | Mood stabilizer + risperidone | | Mood stabilizer + haloperidol | |
|---|---|---|---|---|---|---|
| | N | Mean ± SE | N | Mean ± SE | N | Mean ± SE |
| **Lithium (mEq/L)** | | | | | | |
| Double-blind Baseline | 12 | 0.6 ± 0.09 | 14 | 0.7 ± 0.11 | 16 | 0.5 ± 0.06 |
| Double-blind Week 3 | 6 | 0.8 ± 0.13 | 11 | 0.7 ± 0.08 | 8 | 0.7 ± 0.07 |
| Open-Label Week 10 | 3 | 0.7 ± 0.20 | 6 | 0.6 ± 0.11 | 1 | 0.2 |

| Valproate (µg/mL) | | | | | | |
|---|---|---|---|---|---|---|
| Double-blind Baseline | 35 | 52.9 ± 4.97 | 37 | 53.4 ± 4.92 | 36 | 50.1 ± 5.67 |
| Double-blind Week 3 | 18 | 77.3 ± 6.43 | 26 | 65.4 ± 5.31 | 24 | 76.2 ± 5.22 |
| Open-label Week 10 | 11 | 66.6 ± 8.92 | 10 | 52.8 ± 9.24 | 11 | 70.3 ± 11.51 |

In the open phase of trial RIS-INT-46, serum concentrations of all three mood stabilizers were comparable between the double-blind randomization groups as shown in the following table.

| | Placebo-treated in DB* | | Risperidone-treated in DB | |
|---|---|---|---|---|
| | N | Mean ± SE | N | Mean ± SE |
| **Lithium (mEq/L)** | | | | |
| Week 1 | 9 | 0.71 ± 0.05 | 11 | 0.63 ± 0.05 |
| Week 10 | 22 | 0.79 ± 0.05 | 20 | 0.74 ± 0.05 |
| **Valproate (µg/mL)** | | | | |
| Week 1 | 4 | 42.75 ± 11.40 | 4 | 60.00 ± 7.69 |
| Week 10 | 8 | 79.25 ± 5.86 | 9 | 80.78 ± 9.74 |
| **Carbamazepine (µg/mL)** | | | | |
| Week 1 | 5 | 6.93 ± 0.85 | 2 | 6.39 ± 2.55 |
| Week 10 | 12 | 6.30 ± 0.31 | 7 | 6.13 ± 0.49 |

In the population pharmacokinetic study, the concomitant medication information of the three Phase 3 trials was analyzed to derive the list of the 10 most frequently used drugs. It contained the following drugs: lorazepam, temazepam, cogentin, ibuprofen, acetaminophen, chloral hydrate, amoxicillin, antacids, paracetamol and oxazepam. None of these drugs is expected to have influence on the pharmacokinetics of risperidone and/or 9-hydroxy-risperidone. On the other hand, carbamazepine co-administration was incorporated in the model as a singnificant covariate.

Formal drug interaction studies include the investigation of the interactions with medications commonly used in the treatment of Bipolar I disorder (lithium, valproate or carbamazepine), Alzheimer's disease (donepezil and galantamine), or psychiatric illnesses (fluoxetine and amitriptyline) and with the CYP3A4 inhibitor erythromycin were conducted.

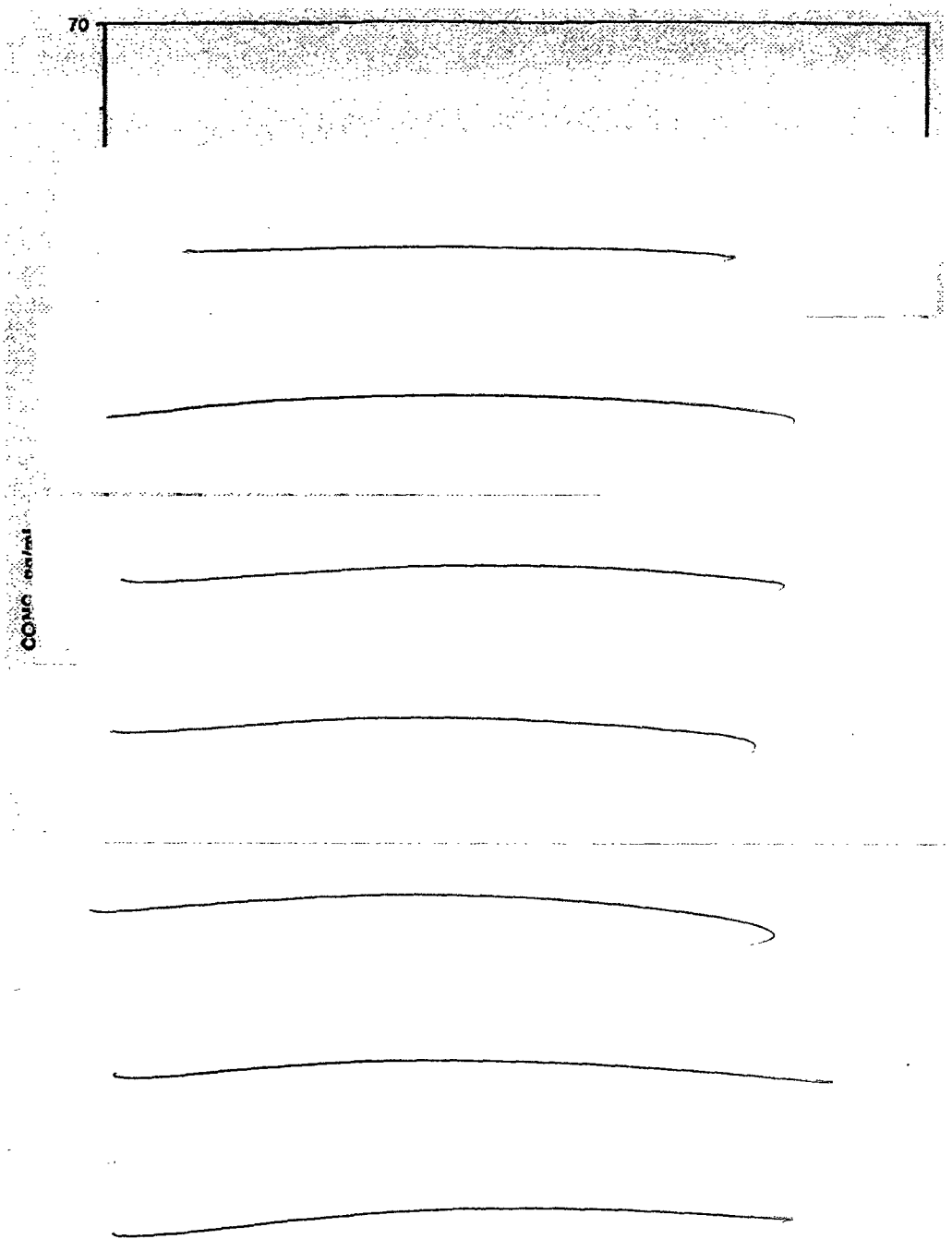
Repeated oral doses of risperidone did not affect the pre-dose or average plasma concentrations or AUC of valproate when compared to placebo. There was a 20% increase in valproate peak plasma concentration after concomitant administration of risperidone as shown in the following table.

| Parameter | Ratio (risperidone versus placebo treatment), % | 90% confidence intervals |
|---|---|---|
| $C_{predose}$ | 103.5 | 87.6 – 122.4 |
| $C_{max}$ | 119.9 | 97.1 – 148.0 |
| $AUC_{24h}$ | 95.6 | 84.0 – 108.9 |
| $C_{ss,av}$ | 95.7 | 84.0 – 108.9 |

No significant change in the steady-state pharmacokinetic parameters of lithium occurred after replacement of the concomitant neuroleptic with risperidone as summarized in the following table.

| Parameters (Mean ± SD; N=13) | Lithium + Risperidone | Lithium + Other antipsychotic | Treatment ratio (90% CI) Lithium+ Risperidone / Lithium + other |
|---|---|---|---|
| Tmax, h | 3.05 ± 0.94 | 2.37 ± 0.98 | - |
| Cmin, mmol/L | 0.58 ± 0.12 | 0.57 ± 0.07 | - |
| Cmax, mmol/L | 0.80 ± 0.16 | 0.71 ± 0.12 | 101 (94 – 110) |
| AUC12h, mmol.h/L | 7.80 ± 1.86 | 7.05 ± 1.50 | 103 (92 – 116) |

Co-administration of carbamazepine and risperidone for 3 weeks caused a reduction in the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The following figure shows the trough plasma concentrations of risperidone and 9-OH-risperidone measured on different days (carbamazepine administered on Day 22-42).




The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of

risperidone and 9-hydroxy-risperidone, which could lead to decreased efficacy of risperidone treatment.

Co-treatment with fluoxetine increased the plasma concentrations of risperidone and, to a lesser extent, those of the active moiety. The plasma levels of 9-hydroxy-risperidone were slightly reduced. The peak levels and AUC values increased by a factor of 2.5-2.8 for risperidone and by a factor of 1.5-1.4 for the active moiety, respectively as summarized in the following table.

| **Parameters (mean ± SD; N=10)** | **Risperidone + fluoxetine** | **Risperidone alone** | **Treatment ratio (90% CI) Risperidone + fluoxetine / Risperidone alone** |
|---|---|---|---|
| **Active Moiety** | | | |
| Cmin 0h, ng/mL | 51.2 ± 22.8 | 32.9 ± 12.9 | 158 (134-184) |
| Cmax, ng/mL | 86.7 ± 32.8 | 58.1 ± 20.6 | 148 (125-174) |
| AUC12h, ng.h/mL | 690 ± 220* | 491 ± 157 | 139 (126-153) |
| Cavg, ng/mL | 57.5 ± 18.3* | 41.0 ± 13.0 | 138 (126-153) |
| **Risperidone** | | | |
| Cmin 0h, ng/mL | 26.0 ± 16.6 | 7.19 ± 8.55 | 617 (333-1142) |
| Cmax, ng/mL | 55.0 ± 25.3 | 23.7 ± 16.5 | 260 (169-400) |
| AUC12h, ng.h/mL | 383 ± 164* | 144 ± 136 | 304 (201-458) |
| Cavg, ng/mL | 31.9 ± 13.6* | 12.0 ± 11.3 | 304 (201-458) |
| **9-hydroxy-risperidone** | | | |
| Cmin 0h, ng/mL | 25.3 ± 11.7 | 25.7 ± 13.5 | 103 (78-137) |
| Cmax, ng/mL | 34.5 ± 12.0 | 36.4 ± 15.1 | 96 (79-116) |
| AUC12h, ng.h/mL | 308 ± 112* | 348 ± 158 | 94 (75-118) |
| Cavg, ng/mL | 25.7 ± 9.3* | 29.0 ± 13.2 | 94 (75-118) |

In daily practice, a dose reduction of risperidone may be considered when fluoxetine is added to the risperidone therapy.

Amitriptyline co-administration increased the AUC of active moiety, risperidone and 9-hydroxy-risperidone by 15-20% as shown in the following table. However, this may not be clinically significant.

| **Parameters (mean ± SD; N=12)** | **Risperidone + Amitriptyline** | **Risperidone Alone** | **AUC ratio ± SD Risperidone + amitriptyline / Risperidone alone** |
|---|---|---|---|
| **Active moiety** | | | |
| tmax, h | 2.3 ± 0.5 | 1.9 ± 0.7 | - |
| Cmax, ng/mL | 74.6 ± 27.3 | 71.0 ± 27.5 | - |
| AUC12h, ng.h/mL | 650 ± 245 | 584 ± 245 | 1.16 ± 0.34 |
| **Risperidone** | | | |
| tmax, h | 2.0 ± 0.7 | 1.8 ± 0.6 | - |
| Cmax, ng/mL | 28.4 ± 24.0 | 25.0 ± 21.5 | - |
| AUC12h, ng.h/mL | 183 ± 189 | 152 ± 157 | 1.21 ± 0.35 |

| 9-hydroxy-risperidone | | | |
|---|---|---|---|
| tmax, h | 3.2 ± 1.4 | 3.1 ± 2.4 | - |
| Cmax, ng/mL | 49.9 ± 18.5 | 48.1 ± 19.2 | - |
| AUC12h, ng.h/mL | 475 ± 186 | 432 ± 187 | 1.15 ± 0.36 |

Upon co-administration of donepezil, a minor increase in risperidone parameters was observed. However, no effects of donepezil on the pharmacokinetic parameters of 9-hydroxy-risperidone and the active moiety were observed as shown in the following table. No effect of risperidone on donepezil pharmacokinetics was observed (table below).

| **Parameters (N=24)** | **Mean ± SD** | | **Treatment ratio (90% CI) Risperidone + Donepezil / Risperidone alone*** |
|---|---|---|---|
| | **Risperidone + Donepezil** | **Risperidone alone** | |
| **Active moiety** | | | |
| AUCτ, ng.h/mL | 109 ± 33 | 100 ± 36 | 110.36 (103.93 - 117.20) |
| Cmax, ng/mL | 12.7 ± 4.2 | 11.1 ± 3.8 | 114.61 (107.46 - 122.24) |
| Cmin, ng/mL | 6.38 ± 1.91 | 6.01 ± 2.38 | 108.22 (100.53 - 116.49) |
| Cavg, ng/mL | 9.10 ± 2.74 | 8.33 ± 3.02 | 110.44 (104.00 - 117.28) |
| Fluctuation Index | 0.69 ± 0.16 | 0.62 ± 0.13 | 110.97 (99.49 - 122.46) |
| **Risperidone** | | | |
| AUCτ, ng.h/mL | 31.3 ± 30.9 | 28.3 ± 32.9 | 114.54 (103.06 - 127.31) |
| Cmax, ng/mL | 4.84 ± 3.09 | 4.12 ± 3.29 | 120.67 (107.42 - 135.56) |
| Cmin, ng/mL | 1.23 ± 1.93 | 1.16 ± 1.94 | 108.74 (95.41 - 123.93) |
| Cavg, ng/mL | 2.61 ± 2.58 | 2.37 ± 2.76 | 114.50 (103.05 - 127.23) |
| Fluctuation Index | 1.80 ± 0.68 | 1.65 ± 0.60 | 108.73 (100.61 - 116.86) |
| **9-hydroxy-risperidone** | | | |
| AUCτ, ng.h/mL | 77.8 ± 18.7 | 71.6 ± 21.6 | 109.83 (103.86 - 116.14) |
| Cmax, ng/mL | 8.52 ± 2.69 | 7.42 ± 2.41 | 114.90 (106.91 - 123.49) |
| Cmin, ng/mL | 5.14 ± 1.39 | 4.85 ± 1.48 | 106.43 (97.63 - 116.04) |
| Cavg, ng/mL | 6.49 ± 1.56 | 5.97 ± 1.80 | 109.83 (103.89 - 116.12) |
| Fluctuation Index | 0.51 ± 0.25 | 0.43 ± 0.15 | 120.60 (94.72 - 146.48) |
| **Donepezil** | | | |
| | **Risperidone + Donepezil** | **Donepezil** | **Treatment ratio (90% CI) Risperidone + Donepezil / Donepezil alone*** |
| AUCτ, ng.h/mL | 437 ± 113 | 444 ± 93 | 97.03 (91.11 - 103.33) |
| Cmax, ng/mL | 22.3 ± 5.6 | 23.0 ± 4.7 | 96.06 (90.14 - 102.37) |
| Cmin, ng/mL | 14.9 ± 4.2 | 15.0 ± 3.4 | 97.92 (90.15 - 106.36) |
| Cavg, ng/mL | 18.2 ± 4.7 | 18.5 ± 3.9 | 96.96 (91.06 - 103.24) |
| Fluctuation Index | 0.41 ± 0.09 | 0.43 ± 0.08 | 95.53 (89.82 - 101.24) |

Risperidone did not change the bioavailability of galantamine at steady state, as investigated in healthy elderly subjects shown in the following table.

| PK Parameters | Combination Treatment (C) | | Single Treatment (S) | | | Mean Ratio (C/S, %) | 90%CI |
|---|---|---|---|---|---|---|---|
| | N | LS Mean | N | LS Mean | MSE | | |
| AUCτ, ss, ng.h/mL | 16 | 674.3 | 16 | 691.7 | 5063.11 | 97.5 | 91.4-104.0 |
| Cmax,ss, ng/mL | 16 | 93.79 | 16 | 92.18 | 84.55 | 101.7 | 95.7-108.2 |

Systemic exposure of the risperidone active moiety was not affected by galantamine coadministration although a minor increase in risperidone AUC was observed as shown in the following table.

| PK Parameters | Combination Treatment (C) | | Single Treatment (S) | | | LS Mean Ratio (C/S,%) | 90%CI |
|---|---|---|---|---|---|---|---|
| | N | LS Mean[a] | N | LS Mean[a] | MSE | | |
| **Active moiety** | | | | | | | |
| **AUCτ, ss, ng.h/mL** | 16 | 99.3 | 15 | 106.1 | 147.55 | 93.6 | 86.6-101.1 |
| **Cmax,ss, ng/mL** | 16 | 11.30 | 15 | 12.57 | 7.99 | 89.9 | 77.0-105.0 |
| **Risperidone** | | | | | | | |
| **AUCτ, ss, ng.h/mL** | 16 | 16.1 | 15 | 14.6 | 10.99 | 110.6 | 96.4-127.0 |
| **Cmax,ss, ng/mL** | 16 | 3.16 | 15 | 3.27 | 0.75 | 96.7 | 81.3-115.0 |
| **9-OH-risperidone** | | | | | | | |
| **AUCτ, ss, ng.h/mL** | 16 | 80.5 | 15 | 89.3 | 111.02 | 90.2 | 83.1-97.9 |

After co-administration of the CYP3A4 inhibitor erythromycin at steady state in healthy subjects, no clinically relevant changes were observed in the pharmacokinetics of active moiety, risperidone and 9-hydroxy-risperidone after a single dose of 1 mg of risperidone as shown in the following table. This result was similar when considering the poor and extensive metabolizers of risperidone separately.

| Parameter | Mean (SD) | | | | Ratio RIS+ERY/RIS(%) | 90% CI | N |
|---|---|---|---|---|---|---|---|
| | RIS | N | RIS + ERY | N | | | |
| **Active moiety** | | | | | | | |
| Cmax, ng/mL | 9.41 (3.48) | 18 | 8.37 (2.07) | 17 | 94 | 84-105 | 17 |
| tmax, h | 1.6 (1.0) | 18 | 2.3 (1.2) | 17 | - | - | - |
| AUClast, ng.h/mL | 177 (69) | 18 | 186 (53) | 17 | - | - | - |
| $AUC_{\infty}$, ng.h/mL | 187 (73) | 18 | 195 (57) | 17 | 106 | 99-115 | 17 |
| t1/2 term, h | 22.6 (5.6) | 18 | 22.2 (4.5) | 18 | - | - | - |
| **Risperidone** | | | | | | | |
| Cmax, ng/mL | 6.78 (3.72) | 18 | 5.64 (2.73) | 18 | 85 | 76-95 | 18 |
| tmax, h | 1.5 (1.0) | 18 | 1.7 (0.9) | 18 | - | - | - |
| AUClast, ng.h/mL | 84.4 (85.9) | 18 | 88.6 (85.3) | 18 | - | - | - |
| $AUC_{\infty}$, ng.h/mL | 87.7 (88.6) | 18 | 91.9 (88.3) | 18 | 103 | 94-112 | 18 |
| t1/2 term, h | 10.4 (9.3) | 18 | 9.8 (8.0) | 18 | - | - | - |
| **9-hydroxy-risperidone** | | | | | | | |
| Cmax, ng/mL | 3.23 (2.75) | 18 | 3.23 (3.00) | 17 | 95 | 84-108 | 17 |
| tmax, h | 11.6 (10.5) | 18 | 15.8 (15.7) | 17 | - | - | - |
| AUClast, ng.h/mL | 91.3 (54.6) | 18 | 90.6 (56.2) | 17 | - | - | - |
| $AUC_{\infty}$, ng.h/mL | 106 (52) | 17 | 110 (53) | 15 | 101 | 93-110 | 15 |
| t1/2 term, h | 27.6 (7.9) | 17 | 28.1 (9.9) | 16 | - | - | - |

Plasma concentration-time profiles of erythromycin were analyzed and the treatment ratios for Cmin, Cmax and AUC5h showed a shift upwards as shown in the following table.

| Treatment | Mean (SD) | | Ratio[a] | 90% |
|---|---|---|---|---|
| Parameters | ERY (n=17)[b] | RIS + ERY (n=18) | RIS+ERY/ERY (%) (n=17) | Confidence Interval (n=17) |
| Cmin, ng/mL | 236 (376) | 216 (191) | 114 | 93-140 |
| Cmax, ng/mL | 788 (478) | 820 (454) | 107 | 83-138 |
| tmax, h | 1.3 (0.6) | 1.2 (0.4) | - | - |
| AUC5h, ng.h/mL | 2548 (2144) | 2521 (1682) | 105 | 83-134 |

## E. Analytical methods

There were two assays used in the studies. All bioanalyses conducted before June 2000 used the radioimmunoassay (RIA). The bioanalyses after June 2000 were conducted using the LC-MS/MS assay. The RIA includes two different methods. The first RIA method measured the active moiety, i.e., the sum of risperidone and 9-hydroxy-risperidone, with a quantification limit of ——— The second RIA method specifically measured unchanged risperidone with a quantification limit of ——— The plasma concentrations of 9-hydroxy-risperidone were calculated by subtracting the risperidone concentrations from those of the active moiety. The LC-MS/MS assay was developed and validated as a robust alternative assay for the RIAs. The LC-MS/MS assay quantifies risperidone and 9-hydroxy-risperidone individually, with a quantification limit of ——— for both compounds. Plasma concentrations of the active moiety are calculated as the sum of the corresponding risperidone and 9-hydroxy-risperidone plasma concentrations.

A cross-validation was conducted with subject samples. This cross-validation revealed that the results for the active moiety, obtained by summation of the LC-MS/MS results for risperidone and 9-hydroxy-risperidone were comparable to the results, obtained with the RIA (mean accuracy: 100%). As to the unchanged risperidone, quantified by RIA, an overestimation was noted in the lower concentration range in the presence of high concentrations of 9-hydroxy-risperidone. Since the risperidone overestimation was $\leq$ 3% of the 9-hydroxy-risperidone concentrations, it was considered not to impact the conclusions of any of the trials because the overestimation only contributed to the risperidone AUC values to a minor extent. Moreover, for all comparative trials the pharmacokinetic samples were analyzed using the same analytical technique, resulting in a similar overestimation for all treatments.

The RIA method for the active moiety showed cross-reactivity to the metabolite 7-hydroxy-risperidone. The concentration ratio of 7-hydroxy-risperidone versus 9-hydroxy-risperidone observed in human plasma is reported to be less than 7%. The results for the active moiety and consequently also for 9-hydroxy-risperidone may be overestimated by not more than 5%, since the binding affinity of the antiserum for 7-hydroxy-risperidone relative to 9-hydroxy-risperidone is 1.44 (being the ratio of ID50 values reported for both compounds). This is considered to be not significant compared to the overall inaccuracy and variability of the assay.

The LC-MS/MS assay was applied at two different sites. The interlaboratory reliability was established through an inter-laboratory study with spiked quality control samples.

ATTACHMENT B

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

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## Appendix II.

**PHARMACOMETRICS REVIEW**

| | | |
|---|---|---|
| **NDA:** | 20-272/S-026<br>20-588/S-017 | **SUBMISSION DATES:** December 13, 2002<br>December 19, 2002<br>January 15, 2003 |
| **DRUG NAME:** | RISPERDAL (risperidone - R064766) | |
| **DOSAGE STRENGTH:** | 0.25, 0.5, 1, 2, 3, and 4 mg tablets, 1 mg/mL oral solution | |
| **APPLICANT:** | Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica N.V. | |

| | |
|---|---|
| **REVIEWER:** | John Duan, Ph.D. |
| **TEAM LEADER:** | Joga Gobburu, Ph.D |
| **TYPE OF SUBMISSION:** | Supplemental New Drug Application |

RISPERDAL (risperidone - R064766), a benzisoxazole derivative, is an effective antipsychotic agent with potent combined serotonin 5HT2A and dopamine D2 antagonistic properties for the treatment of schizophrenia. This sNDA is seeking the approval for the indication for the treatment of acute manic episodes associated with Bipolar I disorder, as monotherapy and as adjunctive therapy to mood stabilizers. This review evaluates the results of a population pharmacokinetics analysis, including 3 Phase III trials with plasma concentration information, and a selection of Phase 1 trials.

## OBJECTIVES

The current review is to answer the following questions.

1. Is the pharmacokinetics of risperidone similar between patients with schizophrenia and bipolar mania?

2. Is there a need for dose adjustment when risperidone is given with carbamazepine? If yes, how should it be done?

## DATA

The database used for the population pharmacokinetic analysis of risperidone and 9-hydroxy-risperidone consisted of 74 patients with schizophrenic or schizoaffective disorder (JRD0001, JRD0002, RIS-GER-9, RIS-FRA-4) and of 333 patients with bipolar I disorder (RIS-USA-239, RIS-IND-2 and RIS-INT-46). Most patients were between 18 and 65 years of age. Patients randomized to the placebo treatment groups in RIS-USA-239 and RIS-IND-2 were not taken into account for the population pharmacokinetics database. Information about the trials used in the risperidone and 9-hydroxy-risperidone pharmacokinetic modeling is summarized below.

| Trial No. | Subjects (M/F) | Age (years) Median (range) | Weight (kg) Median (range) | Design |
|---|---|---|---|---|
| R064766 JRD0001 | 24 M Psychotic patients | 38 (22, 45) | 100 (61, 112) | Open; cross-over; single 4 mg p.o.; 4-mg market tablet; 4-mg research tablet; bioequivalence. Sample till 96 h |
| R064766 JRD0002 | 36 M Psychotic patients | 34.5 (19, 44) | 91 (56, 113) | Open; cross-over; single 4 mg p.o.; 4-mg market tablet; 1-mg market tablet; 1-mg research tablet; bioequivalence. Sample till 96 h post dosing. |
| RIS-GER-9 | 4M/9F Psychotic patients | 53 (22, 62) | 73.0 (59, 148) | Open; sequential; repeated dosing 3 mg b.i.d.; interaction of risperidone on lithium. titrated to 3 mg bid. Sample till 12 h post dose. |
| RIS-FRA-4 | 8M/3F Psychotic patients | 35 (26, 52) | 72.0 (37, 99) | Open; sequential; repeated dosing 3 mg b.i.d.; interaction of carbamazepine on risperidone |
| RIS-USA-239 | Risperidone 134 (71/63) Placebo 125 (76/49) Patients with acute bipolar mania | Risperidone 37.0 (18, 69) Placebo 39.0 (18, 69) | Risperidone 82.1 (48, 154) Placebo 85.9 (48, 143) | 3-week, randomized, double-blind, parallel-group, multicenter clinical efficacy trial: efficacy of risperidone as monotherapy in the treatment of the manic phase of Bipolar I Disorder; flexible o.d. dose, 1-6 mg. Plasma samples were drawn on Day 7 predose and postdose (at least 1 hour after the predose sample) and on Day 21 predose. |
| RIS-IND-2 | Risperidone 146 (100/46) Placebo | Risperidone 32.0 (18, 70) Placebo | Risperidone 53.0 (33, 95) Placebo | 3-week, randomized, double-blind, parallel-group, multicenter clinical efficacy trial: efficacy of risperidone as monotherapy in the treatment of the |

| | | | | |
|---|---|---|---|---|
| | 144 (81/63) Patients with acute bipolar mania | 32.0 (18, 65) | 53.5 (30, 92) | manic phase of Bipolar I Disorder; flexible o.d. dose, 1-6 mg. Sample on Day 7 predose and postdose (at least 1 hour after the predose sample) and on Day 21 predose. |
| RIS-INT-46 | Risperidone 75 (32/43) Placebo 75 (31/44) Patients with acute bipolar mania | Risperidone 37 (20, 63) Placebo 42 (19, 65) | Risperidone 74 (46, 128) Placebo 73.5 (45, 123) | Clinical efficacy trial: efficacy of risperidone as adjunctive therapy to mood stabilizers in the treatment of the manic phase of Bipolar I Disorder; flexible o.d. dose, 1-6 mg. include a 3-week, double-blind (DB) phase with parallel treatment groups (placebo and risperidone), followed by a 10-week, open-label (OL) risperidone treatment phase. During the DB and OL phases, patients received either lithium, valproate or carbamazepine as a mood stabilizer. Predose plasma samples were drawn at baseline, at endpoint of the 3-week double-blind phase and endpoint of the 10-week open-label phase. |

In pivotal trial RIS-USA-102, no blood sampling for the determination of risperidone and 9-hydroxy-risperidone concentrations was scheduled.

R064766/JRD0001 and R064766/JRD0002 were "data-rich" pharmacokinetic trials with full characterization of the single-dose plasma concentration-time profiles. RIS-GER-9 and RIS-FRA-4 were "data-rich" pharmacokinetic trials with full characterization of the steady-state plasma concentration-time profiles. In the phase III clinical efficacy and safety trials (RIS-USA-239, RIS-IND-2, RIS-INT-46), pharmacokinetic information was obtained by limited blood sampling at "predose" and "intermittent" time points throughout the trial. Per protocol, three plasma samples could be obtained per patient under active treatment.

The plasma concentrations of the risperidone and the active moiety or 9-hydroxy-risperidone were determined using either a combination of two radioimmunoassay (RIA) methods or an LC-MS/MS assay method. A cross-validation revealed that the results for the active moiety, obtained by summation of the LC-MS/MS results for risperidone and 9-hydroxy-risperidone were comparable to the results obtained with the RIA (mean accuracy: 100%). As to the unchanged risperidone, quantified by RIA, an overestimation of 3% was noted in the lower concentration range in the presence of high concentrations of 9-hydroxy-risperidone.

Data sets were prepared separately for each trial according to the NONMEM format. They were stored as S-PLUS data frames, and were exported to ASCII files before fitting models.

The entire data set was randomly split into an index and a qualification data set, which consisted of 70% and 30% of the data per trial, respectively. The index data set was used for model building purposes, the qualification data set for model qualification. After the model passed qualification, both data sets were combined and the final model was fitted to it in order to obtain final estimates of parameters and their asymptotic standard errors.

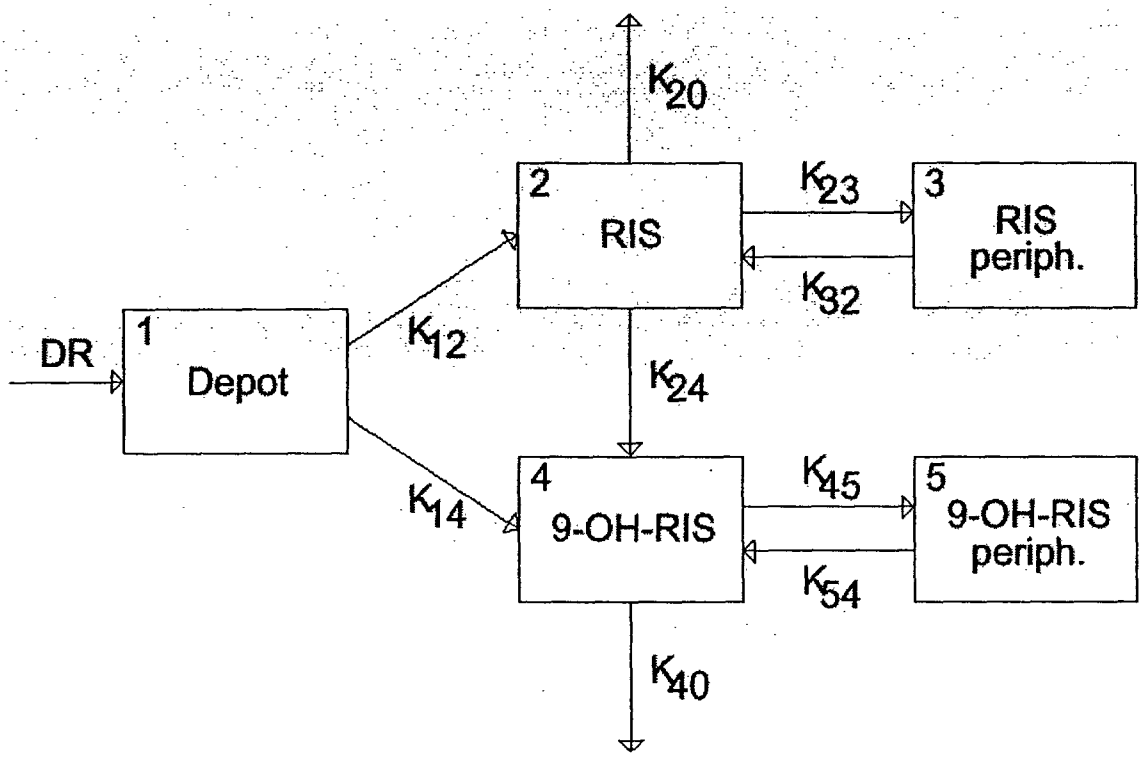
## METHOD

### 1. Structural Pharmacokinetic Model

Visual examination of risperidone and 9-hydroxy-risperidone plasma concentration-time profiles in single-dose trials revealed bi-exponential profiles of risperidone and its metabolite, which

supports the use of two-compartment disposition models for both compounds. A flexible absorption model that included consecutive zero- and first-order processes, and a lag time was selected as it allowed proper fitting of variable risperidone absorption profiles.

By contrast to the parent compound, 9-hydroxy-risperidone pharmacokinetics cannot be adequately modeled independently since it is formed via first-pass metabolism and also via systemic biotransformation of risperidone. An integrated compartmental model was therefore developed, which incorporated two-compartment submodels for risperidone and 9-hydroxy-risperidone as shown in the following Figure.




The first (depot) compartment (1) serves for both compounds. It receives the risperidone dose via a zero-order process with the dosing rate (DR) as a parameter. The ultimately absorbed amount of the drug is split into systemically available risperidone and 9-hydroxy-risperidone entering central compartments 2 and 4 with absorption rate constants K12 and K14, respectively. The distribution of the compounds is modeled through inclusion of peripheral compartments 3 and 5. Rate constants K23 & K32, and K45 & K54 represent the distribution of risperidone and 9-hydroxy-risperidone, respectively. Systemically available risperidone is partly hydroxylated to 9-hydroxy-risperidone (K24) and partly converted into other metabolites (K20). Its renal excretion is known to be negligible. 9-hydroxy-risperidone formation (first-pass and systemic) is known to be mediated primarily by CYP2D6. The metabolite is eliminated by further biotransformation and via renal excretion of unchanged compound. K40 is a common rate constant describing both processes.

Fitting the above model to data allows estimation of the risperidone central volume of distribution (V2) over the (unknown) systemically available fraction (F), V2/F. The central

volume of distribution of the metabolite V4 is not identifiable without independent pharmacokinetic information after metabolite administration. An arbitrarily assumption was made that V4 is equal to V2/F in every patient.

An alternative parameterization of the model via clearances, volumes of distribution and intercompartmental exchange flow rates was used in the current analysis. The disposition parameters are defined below.

Risperidone:

V2 = V2/F: central volume of distribution;

CLP = K20*V2/F: elimination clearance outside the system;

CLPM = K24*V2/F: clearance associated with conversion to 9-hydroxy-risperidone;

V3 = V2/F*K23/K32: peripheral volume of distribution;

QP = K23*V2/F: intercompartmental exchange flow;

F1: relative bioavailability.

9-hydroxy-risperidone:

V4 = V2/F: central volume of distribution;

CLM = K40*V4: elimination clearance;

V5 = V4*K45/K54: peripheral volume of distribution;

QM = K45*V4: intercompartmental exchange flow.

The absorption submodel included three basic parameters: DR, K12 and K14. The alternative parameterization was used as follows.

D1: duration of the zero-order process;

FP: apparent fraction of the bioavailable dose absorbed as 9-hydroxy-risperidone; this fraction is conditional on the assumption of equal central volumes of distribution for risperidone and 9-hydroxy-risperidone;

KA: total absorption rate constant.

With this parameterization, basic absorption parameters are expressed as follows.

DR = DOSE/D1 where DOSE is the risperidone dose;

K12 = (1 - FP) * KA; (please see Comments)

K14 = FP * KA. (please see Comments)

## 2. Random effect model

Interindividual variability (IIV) was initially assumed for all pharmacokinetic parameters and was implemented as a diagonal variance matrix for random effects. Individual values of most pharmacokinetic parameters were assumed to follow the log-normal distribution, which was implemented as follows.

$P = TP * \exp(\eta_P)$

where P is an individual parameter value, TP is a typical population value and $\eta_P$ is a normal random variable with mean zero and standard deviation $\omega_P$. Individual values of the fraction parameter, FP, was constrained to fall within the 0 to 1 range by applying the following transformation.

$FP = \exp(LTFP + \eta_F)/[1+\exp(LTFP + \eta_F)]$

where FP is an individual fraction and $\eta_F$ is a random variable with mean zero and standard deviation $\omega_F$. LTFP is the logit of a typical population fraction TFP:

$LTFP = \ln[TFP/(1-TFP)]$.

Interoccasion variability (IOV) was tested for those parameters where sufficient data to support the estimation were available and where graphical examination revealed the most substantial within-patient variability. It was implemented as a second-level random effect as shown below:

$P = TP * \exp(\eta_P + O1*\eta_{P,O1} + O2*\eta_{P,O2} + O3*\eta_{P,O3})$

where O1, O2, O3 are binary index variables taking the value of 1 in case of occasion 1, 2 and 3, respectively, and 0 otherwise. The parameters $\eta_{P,O1}$, $\eta_{P,O2}$ and $\eta_{P,O3}$ are identically normally distributed independent random variables with mean zero and common standard deviation $\eta_{P,O3}$ They are also independent of $\eta_P$.

As concentrations are distributed log-normally rather than normally, the transform-both-sides approach was applied. All measured concentrations were converted into natural logarithms, and the same was done to individual model predictions. The residual random error model in the log domain was additive:

$\ln(C) = \ln(Cp) + \varepsilon$

where C and Cp are measured and model-predicted concentrations, respectively, and $\varepsilon$ is an independent random variable with zero mean and standard deviation $\sigma$. Since risperidone and 9-hydroxy-risperidone concentrations were fitted simultaneously, two residual error parameters were included in the model: $\sigma_{RIS}$ and $\sigma_{9OH}$, respectively.

## 3. Mixture Model

Three phenotypes [poor (PM), intermediate (IM) and extensive (EM) metabolizers] may have different typical values of model parameters referring to the risperidone conversion to 9-hydroxy-risperidone (FP and CLPM). The phenotypic differences between patients were considered as prior information and were implemented using the mixture model option of NONMEM. The patient population was assumed to consist of three subpopulations with different typical values of FP and CLPM. The interindividual variability within each subpopulation was assumed to be the same. The program assigns each individual to one of the subpopulations and also estimates probabilities associated with each subpopulation, PPM, PIM and PEM, respectively, coded as P(1), P(2) and P(3).

## 4. Covariate Model

The covariates listed below were included in the database for analysis. Abbreviations used in NM-TRAN control files and data sets, and units are given in parentheses. In case of missing covariates, median values for that covariate in that trial were calculated and imputed. In case of missing height (HT) in the presence of weight (WT) and gender (SEX) information, a linear regression of HT versus WT (HT= a×WT + b) was performed for each gender using the available data and the obtained slopes and intercepts were used to calculate HT from WT and SEX. The calculated values were imputed.

Gender (SEX), males: 0, females:1

Race (Caucasians/others), Caucasian 1 Black 2 Oriental 3 Hispanic 4 Other 6

Age (AGE), years

Body weight (WT), kg

Height (HT), cm

Serum creatinine (CRT), μmol/L

Creatinine clearance (CRCL, mL/min), calculated as:

CRCL=WT*(140-AGE)/72/(CRT/88.4), for males

CRCL=0.85*WT*(140-AGE)/72/(CRT/88.4), for females

Total protein (TP), g/L

Alanine aminotransferase (ALT), U/L

Aspartate aminotransferase (AST), U/L

Total bilirubine (TB), μmol/L

Alkaline phosphatase (ALP), U/L

Albumin (ALB), g/L

glutamyl transferase (GGT), U/L

Lean body mass (LBM, kg), calculated as:

LBM=1.10*WT-128*($WT^2/HT^2$), for males

LBM=1.07*WT-148*($WT^2/HT^2$), for females

Body mass index (BMI, $kg/m^2$), calculated as: $BMI=WT/(HT/100)^2$

Body surface area (BSA, $m^2$) calculated from WT and HT using the height-weight formula: $BSA=WT^{0.5378}*HT^{0.3964}*0.024265$

Study (STU): R064766/JRD0001: 1; R064766/JRD0002: 2; RIS-GER-9: 3; RIS-FRA-4: 4; RIS-INT-46: 5; RIS-IND-2: 6; RIS-USA-239: 7.

Concurrent intake of carbamazepine (CARB): No carbamazepine comedication: 0 Carbamazepine comedication: 1.

The concomitant medication information of the three Phase 3 trials was analyzed to derive the list of the 10 most frequently used drugs. It contained the following drugs: lorazepam, temazepam, cogentin, ibuprofen, acetaminophen, chloral hydrate, amoxicillin, antacida, paracetamol and oxazepam. None of these drugs is expected to have any influence on the pharmacokinetics of risperidone and/or 9-hydroxy-risperidone.

A list containing both inducers and inhibitors of CYP450s was also prepared, and it contained the following drugs: amitryptiline, erythromycin, fluoxetine, fluvoxamine, ketoconazole, metoprolol, omeprazole, paroxetine, propranolol, valpromide and verapamil. The mood stabilizers valproate, lithium and carbamazepine were allowed per protocol in the RIS-INT-46 trial. Since for the above drugs only very limited information is available in the database (number of patients taking these medications is 6 or lower), and since formal interaction trials have been executed with erythromycin and with each of the mood stabilizers, no further analysis of the effect of comedication was performed, besides the effect of carbamazepine.

The process of covariate selection was guided by visual inspection of posterior Bayes estimates of random effects ($\eta_P$) produced by the POSTHOC step of a NONMEM run plotted versus all available patient characteristics. To accelerate the model development process, only effects for which a clear trend could be observed visually that could be confirmed by fitting a linear regression line were tested through inclusion in a NONMEM model. Mainly, effects of covariates on the clearance parameters were tested, since these are most relevant from a labeling perspective. Effects of continuous covariates such as WT were included as below:

$TP = \theta_{P,1} * (WT/WT_M)^{\theta P,2}$

where TP is a typical value of a pharmacokinetic parameter P; WT and $WT_M$ are subject's and median body weight, respectively. $\theta_{P,1}$ and $\theta_{P,2}$ are fixed-effects parameters to be estimated.

Effects of binary covariates such as SEX were implemented as follows:

$$TP = (1\text{-}SEX) * \theta_{P,1} + SEX * \theta_{P,2}$$

Particularly, the effect of carbamazepine comedication was implemented this way. Carbamazepine is a well-known inducer of the cytochrome P450 3A4 activity. It induces the metabolism of risperidone and perhaps also 9-hydroxy-risperidone. The effect of carbamazepine on CLP and CLM was therefore tested.

The statistical significance of fixed effects was assessed using the likelihood ratio test. Effects which had P-values associated with the likelihood ratio test < 0.01 (drop in minimum objective function by at least 6.6 units, 1 degree of freedom, $\chi^2$ distribution) were considered as statistically significant and were included in the model. NONMEM minimum objective function (MOF) is up to a constant an approximate log-likelihood of the data given the model. A conservative P-value was selected to avoid the inclusion of weak and clinically not relevant effects.

After inclusion of an effect into the model, new estimates of random effects (ETAs) were obtained and plotted and the next covariate was tested.

The significance of fixed effects in the final model was then checked by backward elimination of covariates from the model. An effect was excluded if the increase in MOF was more than 7.9 units (P = 0.005 at 1 degree of freedom, $\chi^2$ distribution).

## 5. Model qualification

The model developed with the index data set was qualified based on its predictive performance. Population predictions and empirical Bayesian (individual) predictions for all concentrations in the qualification data set were obtained using the POSTHOC option of NONMEM without fitting the model. Measured risperidone and 9-hydroxy-risperidone concentrations were plotted against population and individual predictions, respectively. Population and individual residuals returned by NONMEM after convergence was plotted versus population and individual predictions. The plots were examined for the bias and scatter. Other diagnostic plots were generated as well.

Statistical analysis of population and individual prediction errors was based on mean prediction errors (MPE) and root mean squared prediction errors (RMSE) (Sheiner & Beal, 1981). Population and individual residuals served as prediction errors. Since prediction errors within each individual are known to be correlated, MPE and RMSE are valid statistics for a single observation per individual. A method based on resampling was used to break the correlation. Six thousand random samples from prediction errors were drawn. In each draw, one number was sampled per patient, and MPE and RMSE were calculated for each sample. Median values were considered as the final statistics, and 2.5 –97.5 percentile intervals were used as 95-% confidence limits for the statistics.

Before starting the analysis, some outlying data points were discarded from the index data set. The following approach was used:

- the base model was fitted to the index data set;
- plots of WRES versus measurements were prepared;
- all data points with $-6 < WRES < 6$ or were identified and explored individually;
- identified data points were only excluded if they represented real aberrant points judged from graphical analysis of individual concentration-time profiles;
- before the decision was taken to exclude the data point, it was explored if comedication might account for the outlying.

The model diagnostics were based on visual exploration of the following plots prepared after fitting the model to the index data set:

- Population weighted residuals computed by NONMEM (WRES) versus population predicted concentrations;
- WRES versus time;
- WRES versus quantiles of standard normal.

The same set of plots was prepared for individual residuals based on empirical Bayes predictions.

## 7. Final Model Diagnostics and Parameter Estimates

The population model developed on the basis of the index data set and qualified using the qualification data set was fitted to the entire data set and final parameter estimates were obtained. The covariance step was implemented at this stage and standard errors of estimates were produced.

A series of diagnostic plots including the plots of WRES versus patient characteristics were prepared to check for potential effects not incorporated in the model.

To check a potential impact of outliers on parameter estimates, the final model was also fitted to the whole data set containing all outliers.

Since the active moiety, which is responsible for the effect, is the sum of risperidone and 9-hydroxy-risperidone, no separate population pharmacokinetic model was developed. The analysis was based on predicted individual active moiety concentrations at steady-state, which were obtained using the final model for risperidone and 9-hydroxy-risperidone. These predictions were converted into quasi-clearances of the active moiety. Potential impact of patient characteristics on these parameters was explored graphically and using regression analysis.

Practically, after the final model was fitted to the full data set and the individual Bayes empirical estimates of risperidone and 9-hydroxy-risperidone parameters were obtained, a data set that included these parameters was prepared. Dosing records implementing a steady-state infusion with a unit infusion rate into the depot compartment were included in the data set. The control stream without random effects was prepared with only the simulation step implemented. After completion of the NONMEM run, simulated risperidone and 9-hydroxy-risperidone concentrations at steady-state were summed up and the reciprocals of the sum were used as the quasi-clearances of the active moiety.

### 8. Software

The NONMEM V level 1.1 (GloboMax LLC, Hanover, MD, USA) was used for all model fittings. The modeling was performed on a PC platform using Microsoft Fortran Powerstation version 4.0 under Microsoft Windows 2000. The first-order (FO) approximation method was used throughout the analysis. Data set preparation, exploration and visualization was performed using S-PLUS 2000 release 3 for Windows (Insightful, Seattle, WA, USA). This package was also used for the statistical and graphical analysis of all NONMEM output.

## RESULTS

### 1.Data analyzed

From the 498 actively treated patients in the database, 407 (82%) were included in the population pharmacokinetic analysis. Reasons for exclusion of data were lacking information on date and time of drug intake or plasma sampling, lacking plasma concentration values, lacking information on the dose administered or aberrant plasma concentration-time profiles. The whole data set was randomly splitted into the index (283 patients) and the qualification (124 patients) data sets. The second index data set (247 of 283 patients) to be used for testing effects of laboratory variables was prepared by omitting two single dose trials where no laboratory variables were collected. Finally, the data set used for the simulation of active moiety concentrations was prepared. It contained dosing information and individual predictions of parameters obtained after fitting the final model to the whole data set.

### 2. Base model

From visual inspection of individual plasma concentration-time profiles after single oral intake, a two-compartment disposition model for both risperidone and 9-hydroxy-risperidone was selected. The 9-hydroxy-risperidone formation during the first pass of the parent drug through the liver, and also systemically, was taken into account in the model. A fraction of the risperidone dose is assumed to be metabolized to 9-hydroxy-risperidone during the first pass. However, this fraction is not estimable since the 9-hydroxy-risperidone central volume of distribution is unknown. An apparent fraction, FP, conditional on the assumption of equal volumes of distribution for both compounds, is estimable.

The elimination of risperidone from the circulation is controlled by two clearances: CLPM, which reflects the formation of 9-hydroxy-risperidone, and CLP, which represents all other elimination pathways of risperidone. The elimination of 9-hydroxy-risperidone is represented by CLM.