NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Clinical Development

# Exelon® Oral Solution

## Study No. B153

# A Bioequivalence Study Comparing Single Doses of 3 and 6 mg of an Oral Solution of Exelon® with 3 and 6 mg Exelon® Capsules in Patients with Probable Alzheimer's Disease

| | |
|---|---|
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| Investigator(s) | Donald Hay, M.D.<br>Jameel Hourani, D.O.<br>Mark T. Leibowitz, M.D.<br>Steven Potkin, M.D. |
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# 1. Study synopsis

**Name of finished product:**
Exelon® Capsules, 3 mg and 6 mg
Exelon® Oral Solution, 2 mg/mL

**Name of active ingredient:**
rivastigmine tartrate

**Title of study:**

A bioequivalence study comparing single doses of 3 and 6 mg of an oral solution of Exelon® with 3 and 6 mg Exelon®. capsules in patients with probable Alzheimer's disease

**Investigators:**

Donald Hay, M.D.
Jameel Hourani, D.O.
Mark T. Leibowitz, M.D.
Steven Potkin, M.D.

**Study center(s):**

Three centers in the US

**Publication(s):**

None

**Study period:**
first subject enrolled: 29-Oct-97
last subject completed: 23-Dec-97

**Development phase:**
III

**Objective:**

The objective of this study was to compare the pharmacokinetics (PK) of single 3 mg and 6 mg doses of an Exelon® oral solution and 3 mg and 6 mg Exelon® capsules, respectively, in patients with probable Alzheimer's disease to test the hypothesis that the two formulations would be bioequivalent.

**Methodology:**

This was a multicenter, open-label, randomized (to sequence of oral solution and capsule), crossover, inpatient study comparing the PK of Exelon® oral solution to Exelon® capsules at two dose levels (3 and 6 mg).

**Number of subjects:**

The target enrollment was 60 patients, 30 at each dose level. The enrollment was terminated when 27 patients completed all procedures at the 3 mg dose level and 26 patients completed all procedures at the 6 mg dose level. There were no discontinuations. All patients were included in the safety and PK analyses. One patient in the 3 mg group was excluded from the statistical analyses for bioequivalence because of an incomplete PK profile.

**Indication and main criteria for inclusion:**

Males and females (non-child-bearing potential) less than 86 years of age with mild to moderately severe probable Alzheimer's disease participating in Exelon® Studies B353, B355, or B357 and receiving doses of 6, 8, 9, 10, or 12 mg/day were eligible provided that they were without any coexisting medical conditions that would put them at special risk.

**Investigational drug:**

| Dosage Form | Strength | Mode of Administration | Batch Numbers |
|---|---|---|---|
| Exelon® capsules | 3.0 mg | Oral | X1831296 |
| Exelon® capsules | 6.0 mg | Oral | X1851296 |
| Exelon® oral solution | 2 mg/mL | Oral | 00525 |

**Reference therapy:**

None

**Duration of treatment:**

Two single doses administered over 5 days; 3-day interval between doses

**Criteria for evaluation:**

**Efficacy:** None

**Safety:** Vital signs and adverse events

**Pharmacokinetics:** Blood samples were taken at 0.5 hours prior to dosing (pre-dose sample) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 15, and 24 hours post-dose for measurement of rivastigmine (Exelon®) and its decarbamylated metabolite, NAP 226-90, (formerly referred to as ZNS 114-666) in plasma. The patients' PK profiles were analyzed by standard non-compartmental methods yielding: $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, $t_{max}$, $t_{1/2}$, CL/F, and $V_z/F$ for rivastigmine; and $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, $t_{max}$, and $t_{1/2}$ for NAP 226-90. In addition, the relative bioavailability ($F_{rel}$) of rivastigmine was estimated for the capsules by comparison to the solution at the same dosage level.

**Bioanalytical methods:**

Plasma concentrations of rivastigmine and NAP 226-90 were determined using a ——— method. The limit of quantification (LOQ) for rivastigmine and NAP 226-90 ——— All plasma concentrations below the LOQ were reported ——— Details on the analytical methodology, precision and accuracy of the assay, and validation procedures are presented in the analytical report located in Appendix 9.3.

**Statistical methods:**

**Demographics and safety:** Summary statistics included means, Ns, standard deviations, medians, minimums, and maximums for continuous variables and frequencies and percentages for categorical variables. Demographics were summarized separately by dose and by sequence. Safety parameters were summarized by sequence within dose. To determine treatment-related abnormalities, comparison was made to baseline (or more generally, the last observation prior to the patient receiving study medication).

**Pharmacokinetics:** The PK parameters were summarized for rivastigmine and NAP 226-90 by treatment (solution or capsule) and cohort (3 mg or 6 mg dose). PK parameter comparisons of the solution and capsule formulations for rivastigmine and NAP 226-90 were performed for the 3 mg cohort and 6 mg cohort separately. An analysis of variance model was fitted to the raw and log-transformed PK parameters, $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$, to evaluate bioequivalence between solution and capsule. Decisions about bioequivalence were based on the analysis of log-transformed data. The bioequivalence between solution and capsule was assessed using the "ESTIMATE" statement of the ——— procedure. Based on the log-transformed data, the 90% confidence limits for the difference between the test and reference (least square) means were calculated and exponentiated to obtain the 90% confidence interval for the ratio (solution/capsule) of two (least squares) means. Bioequivalence between solution and capsule was declared if this 90% confidence interval fell within the 80 to 125% range. In addition, the

Wilcoxon signed rank test for paired differences of $t_{max}$ between solution and capsule was also performed for the equality of two treatment effects.

**Results:**

**Efficacy:** No efficacy evaluations were performed during the study.

**Safety:** No deaths, serious or severe adverse events, or discontinuations for any reason were reported during the study. Adverse events were reported in 26% of the patients during the 3 mg solution treatment, 37% of the patients during the 3 mg capsule treatment, 38% of the patients during the 6 mg solution treatment, and 27% of the patients during the 6 mg capsule treatment. The overall incidence of adverse events was similar for the solution and capsule formulations of Exelon®. The most frequently reported adverse events (occurring in >7% of the overall population, listed in order of decreasing frequency) were mild cases of headache, diarrhea, nausea, and insomnia. Clinically notable changes from baseline in blood pressure and/or pulse rate were reported for all treatments. Most of these vital sign abnormalities were asymptomatic fluctuations in systolic and diastolic blood pressure that resolved spontaneously. However, one female patient receiving Cardizem CD® for hypertension, had clinically notable low diastolic blood pressure values during the 3 mg capsule treatment that required a decrease in the patient's dose of Cardizem CD®. The low diastolic blood pressures were attributed to the patient's concomitant medication and pre-existing medical condition.

**Pharmacokinetics:**

Based on $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ of both rivastigmine and NAP 226-90, both the 3 mg and 6 mg doses of the solution dosage form (2 mg/mL) were found to be bioequivalent to the 3 mg and 6 mg strengths of the capsule dosage form, respectively.

The $t_{max}$ of rivastigmine following a 3 mg dose of the solution dosage form was not significantly different ($p=0.09$) from the $t_{max}$ following the same dose of the capsule dosage form. However, for the 6 mg cohort, the difference in $t_{max}$ between the solution and capsule form was statistically significant ($p=0.02$). On average, the arithmetic mean $t_{max}$ value for the 6 mg solution was 23.5% smaller (~16 minutes earlier) than the arithmetic mean $t_{max}$ value for the 6 mg capsule. The $t_{max}$ of NAP 226-90 following the 3 mg and 6 mg doses of the solution dosage form was not significantly different ($p=0.08$) than the $t_{max}$ following the respective doses of the capsule dosage form.

**Conclusions:**

- The 3 mg dose of the Exelon® oral solution (2 mg/mL) is bioequivalent to the oral 3 mg Exelon® capsule for the parent compound, rivastigmine, as well as the decarbamylated metabolite (NAP 226-90).
- The 6 mg dose of the Exelon® oral solution (2 mg/mL) is bioequivalent to the oral 6 mg Exelon® capsule for the parent compound, rivastigmine, as well as the decarbamylated metabolite (NAP 226-90).
- Single 3 and 6 mg doses of Exelon® oral solution and Exelon® capsules were safe and well tolerated by the patient population.

**Date of the report:** 22-Jul-98

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population than that used in the Phase 3 program is ongoing, with more than 2000 patients having been enrolled to date. In addition, studies investigating the effects of Exelon® in AD patients in long-term care facilities (Study B452: US; Study INT-02: non-US) and in patients with Lewy body dementia (INT-03) are also ongoing.

Exelon® capsules have been administered to over 3715 patients with AD during clinical trials worldwide. Of these, 3054 patients have been treated for at least 3 months, 2149 patients have been treated for at least 6 months, and 984 patients have been treated for 12 months or more. No pattern of drug-associated toxicity has been detected during long-term treatment with Exelon® in these studies.

For further information please refer to the Investigator's Brochure, 1997.[6]

### Rationale for developing Exelon® oral solution

Some patients with AD have difficulty swallowing or refuse to take capsules.[7] Therefore, an oral solution formulation of Exelon® would offer these patients a more acceptable alternative dosing form. In a study performed in non-patient volunteers (W251)[8], no adverse events were reported in subjects receiving a single dose of a drink solution containing 3 mg of Exelon®. In a pilot study (Amendment #1 to Study B353)[9], in which 18 patients with AD were treated at doses of 3 or 6 mg (nine patients at each dose) using a paradigm similar to this study, a 6 mg dose of the oral solution, but not a 3 mg dose, was found to be bioequivalent to the comparable capsule dose. In the pilot study, administration of the oral solution was not associated with any severe or serious adverse events or events not observed previously with Exelon® capsules.

## 4. Study objectives

The objective of this study was to compare the PK of single 3 mg and 6 mg doses of an Exelon® oral solution and 3 mg and 6 mg Exelon® capsules, respectively, in patients with probable Alzheimer's disease to test the hypothesis that the two formulations would be bioequivalent. The final market forms of Exelon® capsules and oral solution were tested.

## 5. Investigational plan

### 5.1. Overall study design

This was a multicenter, open-label, randomized (to sequence of oral solution and capsule), crossover, inpatient study. Patients were hospitalized for five days starting on Day -1, i.e., the evening preceding the first day of dosing, through completion of the final evaluations (Day 5). On Day -3 the patients ingested their morning dose of Exelon® capsules for Studies B353, B355, or B357 (referred to as the patients' core studies in this report) and came into the clinic for their screening visit. At this time, informed consent was obtained, vital signs were taken, and the patients' medication for their core study was confiscated to ensure that no additional doses of Exelon® were taken during their participation in this study. On Days -2 and -1, the patients' morning and evening doses of Exelon® capsules were withheld. Patients at a dose of 3 mg bid to 5 mg bid in their core study were assigned to receive single 3 mg doses of Exelon® oral solution

(6)

and capsule. Patients at a dose of 6 mg bid in their core study were assigned to receive single 6 mg doses of Exelon® oral solution and capsule. Patients were randomized to receive either the solution or capsule treatment first.

Following a 10 hour fast, each patient received a single dose of a 3 mg or 6 mg oral solution or capsule at ~0800 hours on Day 1. No food was allowed for 2 hours after dosing. Blood samples were taken at 0.5 hours prior to dosing (baseline sample) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 15, and 24 hours post-dose for measurement of rivastigmine and its decarbamylated metabolite, NAP 226-90 (formerly referred to as ZNS 114-666), in plasma. On Days 2 and 3 no medication was administered. On Day 4 a single dose of 3 mg or 6 mg of the other formulation of Exelon® was given and the blood sampling was repeated. Patients were discharged from the hospital following final safety evaluations on Day 5. On the evening of Day 5, patients restarted on or began titration up to the same dose of Exelon® capsules that they were taking prior to their participation in this study, provided that there were no tolerability problems. The decision to restart patients on their previous dose or perform dose titration was made by the Investigator using the guidelines for restarting dosing after missed doses specified in the core protocols. The enrollment was terminated when 27 patients completed all procedures at the 3 mg dose level and 26 patients completed all procedures at the 6 mg dose level.

Text Table 5.1-1. shows the schedule of hospitalization, dosing times, blood sample collection times, information regarding withholding of scheduled capsule doses for Studies B353, B355 and B357 and the administration of the study medication for Days -3 to 5.

Text Table 5.1-1. **Schedule of hospitalization, dosing, and blood sampling**

| Study Day | -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|
| Hospitalization | | | X[a] | X | X | X | X | X[b] |
| Dose Time[c] | | | | ~0800 h | | | ~0800 h | |
| Blood Sample Times (hours post-dose) | | | | -0.5, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 15 | 24 | | -0.5, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 15 | 24 |
| Comments on Dosing | Skip PM dose | Skip AM and PM doses | Skip AM and PM doses | Administer study drug; skip PM dose | Skip AM and PM doses | Skip AM and PM doses | Administer study drug; skip PM dose | Restart dosing with PM dose[d] |

a Patients were hospitalized in the evening before the first dose was administered

b Patients were discharged after the final evaluations were completed

c 24-hour clock

d Patients restarted participation in their core study at the same dose they were taking prior to entry into this protocol or at a lower dose if re-titration was deemed necessary

## 5.2. Discussion of design

To eliminate the need for dose titration, eligible volunteers were recruited from a pool of patients with AD participating in Exelon® Studies B353, B355 and B357 who were tolerating doses of Exelon® capsules at or above the doses planned for Study B153.

**Rationale for dose**

The doses evaluated in this study represented the middle and upper end of the single-dose range of Exelon® that has been investigated in clinical trials in AD patients. In a previous pilot relative bioavailability study in AD patients (Amendment #1 to Study B353[9]), single doses of an oral solution of Exelon® of 3 and 6 mg were well tolerated. A dose of 1.5 mg was not evaluated, as most patients will not remain at a dose of 1.5 mg bid and plasma levels of rivastigmine following this dose are often below the limit of quantification of the assay.

**Dose Withholding**

Patients were instructed not to take any of the Exelon® capsules for ~72 hours prior to administration of the first dose of oral solution or capsule in this study. Additionally, no dose of Exelon® was administered between the morning dose on Day 1 and the dose on Day 4. Based on the elimination half-lives for rivastigmine (~1 hour) and its major metabolite, NAP 226-90 (~5 hours), these drug-free periods should allow adequate time for these substances to be cleared from the plasma. Thus, levels of rivastigmine and its metabolite in the baseline (-0.5 hour) plasma samples on Days 1 and 4 were expected to be below the limit of quantification of the assay.

## 5.3. Study population

### 5.3.1. Target population

The study was to include up to 60 patients with mild to moderate probable AD who were being treated with Exelon® capsules at doses of 3-6 mg bid in Studies B353, B355, or B357 to ensure that 50 patients completed all study procedures at each dose level. As the study progressed, the pool of patients from the core studies who were eligible and willing to participate in the study at the three centers conducting the trial was depleted. Enrollment was terminated at 53 patients; 27 patients completed the 3 mg treatment and 26 completed the 6 mg treatment. According to the sample size calculation in the protocol, only 22 completed patients at each dose level were required to accomplish the objective of the study.

### 5.3.2. Inclusion and exclusion criteria

To participate in this study, patients had to satisfy the following criteria:

- patients had to be currently receiving a dose of Exelon® of 6-12 mg/day in Exelon® Studies B353, B355, or B357;
- patients had to be less than 86 years of age (older patients were allowed to participate if approved by the Novartis Medical Expert);
- patients or their legal representative, if they were not medically competent, and the responsible caregiver had to provide written informed consent prior to the performance of any study-related procedures including withholding of capsule doses.

Patients meeting any of the following criteria were excluded from participating in the study:

- patients with any medical condition that would put them at special risk for participating in the study;
- patients who lost or had one pint (approximately 450 mL) or more of blood withdrawn within one month before receiving study medication;
- patients with cardiac/renal/hepatic disease as evident from their last laboratory evaluation or other conditions which would be expected to alter the kinetics of Exelon®.

### 5.3.3. Interruption or discontinuation from treatment

To participate in Study B153, the patients' bid Exelon® regimen from their core studies was suspended for approximately 8 days.

Patients who discontinued from the study prematurely, and did not take both doses of study medication or failed to complete the blood sampling procedures as scheduled, were to be replaced so that the requisite number of patients (at least 22 at each dose level) were obtained for bioequivalence analyses. Patients discontinuing prematurely from this study were to be allowed to continue their participation in Study B353, B355, or B357.

## 5.4. Treatments

### 5.4.1. Investigational drug and reference therapy

#### Dosage forms

The following Exelon® formulations, dosage strengths, and batch numbers were supplied by the Sponsor for this study:

| | | |
|---|---|---|
| Exelon® capsules: | 3.0 mg rivastigmine tartrate | Batch X1831296, KN 3739059.01.009 |
| Exelon® capsules: | 6.0 mg rivastigmine tartrate | Batch X1851296, KN 3741204.01.010 |
| Exelon® oral solution: | 2 mg/mL rivastigmine tartrate aqueous solution | Batch 00525 |

#### Packaging

The Sponsor provided each site with the following bulk packages of medication:

3 mg Exelon® capsules: [redacted]

6 mg Exelon® capsules: [redacted]

2 mg/ mL Exelon® oral solution: [redacted]

The containers served as multi-dose bottles and were used for multiple patients.

#### Labeling and storage

Labels on the bottles of capsules contained the following information: Novartis logo and address, study drug name (Exelon® Capsules), study number (ENAB 153), capsule strength (3 mg or 6 mg), the batch number, expiration date, number of capsules in the bottle (325), Store

## 10.3. Pharmacokinetic results

### 10.3.1. Bioanalytical method performance

Plasma concentrations of rivastigmine and NAP 226-90 were determined using a ——— method. The concentrations of unknown samples were calculated from calibration curves generated using a $1/y^2$ weighted linear least-squares regression. All the concentrations were expressed as nanograms of rivastigmine and NAP 226-90 base per milliliter of plasma.

In order to determine the performances of the assay, quality control samples were prepared by spiking drug-free human plasma with known amounts of rivastigmine and NAP 226-90.

Plasma samples from one or two patients and for two treatments were analyzed within the same run. In each run, samples for one calibration curve and three quality control samples in duplicate were assayed with unknown samples.

Quality control and calibration samples accounted for about 25% of all determinations performed to obtain the concentrations of the unknown samples.

The results of between-run accuracy and precision obtained for the four quality control samples throughout the study are summarized in Text Table 10.3.1-1. and in the Analytical Report located in Appendix 9.3.

Text Table 10.3.1-1. Summary of bioanalytical assay precision and accuracy results for rivastigmine and NAP 226-90

| Nominal value (ng/mL) | Measured value (ng/mL) | n | Precision CV % | Accuracy % |
|---|---|---|---|---|
| Rivastigmine | | | | |
| 0.30 | 0.31 | 69 | 9.7 | 3.3 |
| 10 | 10.55 | 69 | 6.8 | 5.5 |
| 25 | 26.83 | 38 | 5.3 | 7.3 |
| 50 | 52.33 | 34 | 7.4 | 4.7 |
| NAP 226-90 | | | | |
| 0.30 | 0.30 | 70 | 10.0 | 0.0 |
| 10 | 10.64 | 70 | 6.2 | 6.4 |
| 25 | 25.04 | 38 | 7.1 | 0.2 |
| 50 | 47.87 | 34 | 7.8 | -4.3 |

Measured : Mean of n determinations
Accuracy : (Measured-nominal)/nominal x 100
Precision : CV % = (SD/Mean) x 100
Reference: Appendix 9.3.

As shown in Text Table 10.3.1-1, satisfactory accuracy and precision were achieved over the concentration range throughout the duration of the study.

The limit of quantitation (LOQ) of the method was estimated at ——— for both compounds from the results of the lowest calibration sample. The values ———

The performance of the method (accuracy and precision) confirmed the validity of the plasma concentrations of rivastigmine and NAP 226-90 measured during the study. Details on the analytical methodology, precision and accuracy of the assay, and validation procedures are presented in Appendix 9.3.

## 10.3.2. Pharmacokinetics of rivastigmine and NAP 226-90

For the 3 mg capsule treatment, Patient 1016 had no measurable plasma levels of either the parent compound or the metabolite, NAP 226-90. Since plasma levels of rivastigmine and NAP 226-90 were always observed following oral administration of a 3 mg dose of the capsule by all other patients in this study and in numerous studies conducted in support of the original NDA for rivastigmine capsule (NDA 20-823; Exelon®), it is possible that the capsule may not have been swallowed by this patient. Failure of drug release from the immediate release capsule dosage form is not expected since rivastigmine is a highly soluble (10 mg/mL in water) and a highly permeable compound (>90% absorbed). Patient 1016 had measurable levels of both the parent compound and the metabolite following the 3 mg solution treatment. Therefore, Patient 1016 was included in the pharmacokinetic analysis and in the statistical analysis for the purpose of calculation of summary statistics but excluded from all inferential statistics.

### Rivastigmine pharmacokinetics

The mean pharmacokinetic parameters of rivastigmine following oral administration of single doses of 3 mg and 6 mg of both the oral solution and the capsules are provided in Text Table 10.3.2-1.

Following oral administration of a 3 mg and 6 mg dose of Exelon®, either as a solution or capsule, rivastigmine was rapidly absorbed with an average $t_{max}$ of about 1 hour (Text Table 10.3.2-1.). The average peak plasma concentration of rivastigmine was about 9 ng/mL following a 3 mg dose of the solution and capsule, and about 25 ng/mL following a 6 mg dose of the solution and the capsule. The average terminal elimination half-life of rivastigmine ranged from 1.4 to 1.7 hours for all the treatments. The relative bioavailability of rivastigmine from the capsules compared to the solution ranged from 101 to 111%. Consistent with the known non-linear pharmacokinetics of rivastigmine following oral administration of the capsule[10,11], a more than proportional (about 2.8-3.5 fold) increase in $C_{max}$ and $AUC_{0-\infty}$ was observed with a doubling of the dose from 3 mg to 6 mg given either as a solution or a capsule. The apparent oral clearance (Cl/F) of rivastigmine was also reduced by about half when the dose was increased from 3 mg to 6 mg.

The intersubject variability for the pharmacokinetic parameters was high for rivastigmine (coefficient of variation, CV of 50-76% for $AUC_{0-\infty}$ and 77-105% for Cl/F). However, the intrasubject variability for rivastigmine has been found to be low in a previous study (CV of 23% for $AUC_{0-\infty}$ and 18% for $C_{max}$)[8].

**Text Table 10.3.2-1. Mean (±SD) pharmacokinetic parameters of rivastigmine following single oral administration**

| Parameter | Arithmetic mean±SD<br>Coefficient of variation (CV%)<br>(Range) | | | |
|---|---|---|---|---|
| | 3 mg solution (N=27)[a] | 3 mg capsule (N=26)[b] | 6 mg solution (N=26) | 6 mg capsule (N=26) |
| $AUC_{0-t}$ (ng.h/mL) | 22.71±17.36<br>76.44 | 22.77±15.9<br>69.85 | 74.65±37.69<br>50.48 | 80.84±43.6<br>53.93 |
| $AUC_{0-\infty}$ (ng.h/mL) | 23.62±17.85<br>75.57 | 23.64±16.34<br>69.12 | 76.24±38.19<br>50.10 | 82.25±44.02<br>53.52 |
| $C_{max}$ (ng/mL) | 8.69±4.41<br>50.75 | 9.09±4.33<br>47.61 | 24.93±11.44<br>45.88 | 25.23±11.9<br>47.14 |
| $t_{max}$ (h) | 0.98±0.294<br>29.59 | 1.1±0.35<br>32.3 | 0.91±0.24<br>26.75 | 1.19±0.53<br>44.50 |
| $t_{1/2}$ (h) | 1.40±0.45<br>32.14 | 1.40±0.5<br>35.80 | 1.67±0.4<br>24.06 | 1.70±0.36<br>21.16 |
| Cl/F (L/h) | 214.16±224.95<br>105.0 | 219.59±253.39<br>115.4 | 111.28±86.31<br>77.6 | 104.03±86.57<br>83.2 |
| $V_z/F$ (L) | 427.39±621.1<br>145.3 | 378.59±390.98<br>103.3 | 248.31±162.16<br>65.3 | 243.78±195.2<br>80.1 |
| $F_{rel}$ (Cap/Sol) (N=26) | | 1.01±0.21<br>21.2 | | 1.11±0.27<br>24.8 |

[a] Including Patient 1016.
[b] Excluding Patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90.
Reference: Section 15; Post-text Table 10.3.2-1., and Appendix 9.1.2.; Tables 9.1.2-1. & 9.1.2-3.

### NAP 226-90 pharmacokinetics

The mean pharmacokinetic parameters of NAP 226-90 following oral administration of single doses of 3 mg and 6 mg of both the oral solution and the capsules are provided in Text Table 10.3.2-2.

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Following oral administration of a 3 mg and 6 mg dose of Exelon®, either as a solution or capsule, the average time to peak plasma concentrations of NAP 226-90 ranged from 1.3 to 1.7 hours (Table 10.3.2-2.). The average peak plasma concentration of NAP 226-90 was about 6 ng/mL following a 3 mg dose of the solution and capsule, and between 10.5 and 11 ng/mL following a 6 mg dose of the solution and the capsule. The average terminal elimination half-life of NAP 226-90 ranged from 2.7 to 3.4 hours for all the treatments. Unlike rivastigmine, doubling the dose from 3 mg to 6 mg appears to increase the $AUC_{0-\infty}$ and $C_{max}$ of NAP 226-90 in a dose proportional manner when administered either as a solution or a capsule (Text Table 10.3.2-2.).

The intersubject variability for the pharmacokinetic parameters of NAP 226-90 was smaller than that of the parent compound (coefficient of variation, CV of 29-40% for $AUC_{0-\infty}$ and 25-33% for $C_{max}$). The intrasubject variability has been reported to be low for NAP 226-90 and is somewhat smaller (CV of 9% for $AUC_{0-\infty}$ and 12.5% for $C_{max}$) than that for rivastigmine[8].

**Text Table 10.3.2-2. Mean (±SD) pharmacokinetic parameters of NAP 226-90 following single oral administration**

| Parameter | Arithmetic mean±SD<br>Coefficient of variation (CV%)<br>(Range) | | | |
|---|---|---|---|---|
| | 3 mg solution (N=27)[a] | 3 mg capsule (N=26)[b] | 6 mg solution (N=26) | 6 mg capsule (N=26) |
| $AUC_{0-t}$ (ng h/mL) | 32.61±12.06<br>37.0 | 32.94±9.9<br>30.1 | 64.45±19.31<br>30.0 | 66.85±20.42<br>30.5 |
| $AUC_{0-\infty}$ (ng.h/mL) | 36.35±14.54<br>40.0 | 35.42±11.08<br>31.3 | 67.61±19.63<br>29.0 | 71.02±20.98<br>29.5 |
| $C_{max}$ (ng/mL) | 6.16±1.76<br>28.6 | 6.21±1.57<br>25.3 | 10.98±3.37<br>30.7 | 10.49±3.47<br>33.0 |
| $t_{max}$ (h) | 1.57±0.62<br>39.8 | 1.74±0.75<br>43.1 | 1.27±0.51<br>40.1 | 1.55±0.58<br>37.4 |
| $t_{1/2}$ (h) | 2.99±0.725<br>24.3 | 2.71±0.58<br>21.3 | 3.13±0.646<br>20.6 | 3.44±0.634<br>18.45 |

[a] Including Patient 1016.
[b] Excluding Patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90.
Reference: Section 15; Post-text Table 10.3.2-2. and Appendix 9.1.2.; Tables 9.1.2-2. and 9.1.2-4.

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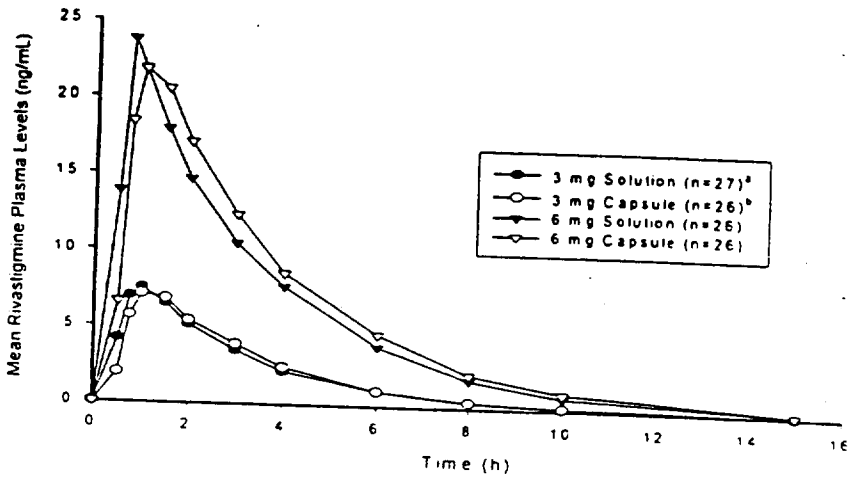
The mean plasma concentration-time profiles of rivastigmine and NAP 226-90 following single oral administration of 3 mg and 6 mg doses of the solution are almost superimposable on the corresponding dose-plasma concentration-time profiles of the capsule dosage form (Text Figures 10.3.2-1. and 10.3.2-2.).

**Text Figure 10.3.2-1. Mean plasma concentration-time profile of rivastigmine following single oral administration**




[a] Including Patient 1016.

[b] Excluding Patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90.

Reference: Section 15; Post-text Figure 10.3.2-1. and Appendix 9.1.1.; Tables 9.1 1-1, -2, -5, -6.

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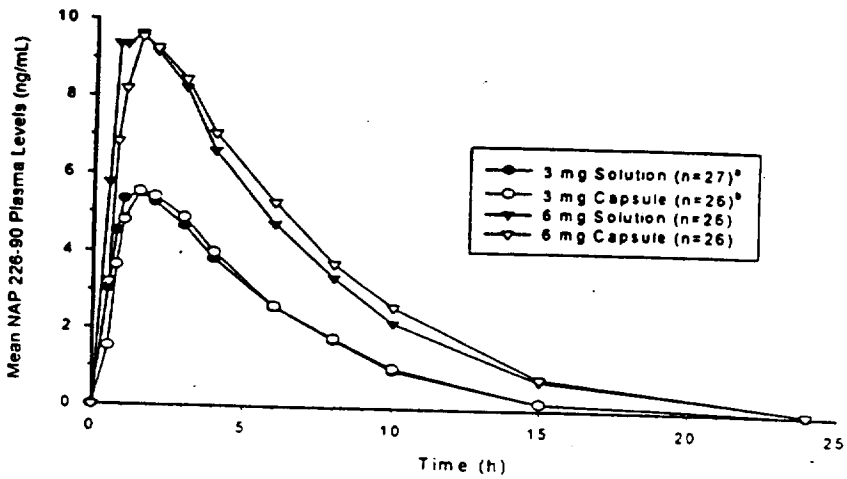
**Text Figure 10.3.2-2. Mean plasma concentration-time profile of NAP 226-90 following single oral administration**




[a] Including Patient 1016.

[b] Excluding Patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90

Reference: Section 15, Post-Text Figure 10.3.2-2. and Appendix 9.1.1., Tables 9.1.1-3, -4, -7, -8

## 10.3.3. Bioequivalence assessment between solution and capsule for rivastigmine

There were no statistically significant ($p \leq 0.05$) differences between the 3 mg solution and the 3 mg capsule treatments and between the 6 mg solution and 6 mg capsule treatments in $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ of rivastigmine (Text Table 10.3.3-1.). According to the Wilcoxon's signed rank test for paired differences of $t_{max}$, there was no statistically significant formulation effect for the 3 mg cohort ($p=0.09$). However, for the 6 mg cohort, the formulation effect was statistically significant ($p=0.02$). On average, the $t_{max}$ value for the solution was 23.5% smaller (~16 minutes earlier) than the value for the capsule (Text-Table 10.3.2-1.). The 90% confidence intervals provided in Text Table 10.3.3-1. were calculated using log transformed data.

Bioequivalence was found for $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ of rivastigmine for both the 3 mg and 6 mg dose. For the 3 mg dose group, the 90% confidence intervals for least square mean ratios of these three parameters were 90-107%, 94-109%, and 86-106%, and those for the 6 mg dose group were 87-99%, 87-100%, and 87-110%, respectively. These values all fell within the 80% to 125% bioequivalence range (Text Table 10.3.3-1.).

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**Text Table 10.3.3-1. Assessment of bioequivalence between solution and capsule for rivastigmine**

| Parameter | Geometric mean | | % Difference | p-value | 90% C.I. |
|---|---|---|---|---|---|
| | 3 mg Solution (N=26)[b] | 3 mg Capsule (N=26)[b] | | | |
| $AUC_{0-t}$ (ng.h/mL) | 17.65 | 17.90 | -1.39 | 0.74 | 90-107% |
| $AUC_{0-\infty}$ (ng.h/mL) | 19.01 | 18.84 | 0.90 | 0.85 | 94-109% |
| $C_{max}$ (ng/mL) | 7.60 | 8.0 | -4.97 | 0.44 | 86-106% |
| $t_{max}$[a] (h) | 1.0 | 1.0 | 0.0 | 0.09 | --- |
| **Parameter** | **Geometric Mean** | | **% Difference** | **p-value** | **90% C.I.** |
| | 6 mg Solution (N=26) | 6 mg Capsule (N=26) | | | |
| $AUC_{0-t}$ (ng.h/mL) | 64.14 | 69.06 | -7.13 | 0.06 | 87-99% |
| $AUC_{0-\infty}$ (ng.h/mL) | 65.69 | 70.53 | -6.85 | 0.08 | 87-100% |
| $C_{max}$ (ng/mL) | 22.24 | 22.65 | -1.78 | 0.80 | 87-110% |
| $t_{max}$[a] (h) | 0.75 | 1.0 | -25.0 | 0.02* | --- |

C.I. = Confidence Interval
[a] For $t_{max}$, median values were provided instead of geometric mean and the significance level was obtained from the Wilcoxon signed rank test.
[b] Excluding Patient 1016 who did not have complete pharmacokinetic profile for both periods of the study.
* = statistically significant, $p \leq 0.05$.
Reference: Section 15; Post-text Tables 10.3.3-1.1., 10.3.3-1.2., and Appendix 9.2.1.

## 10.3.4. Bioequivalence assessment between solution and capsule for NAP 226-90

There were no statistically significant ($p \leq 0.05$) differences between the 3 mg solution and 3 mg capsule treatments in $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ of NAP 226-90, and between the 6 mg solution and 6 mg capsule treatments in $AUC_{0-t}$ and $C_{max}$ of NAP 226-90 (Text Table 10.3.4-1.). For the 6 mg solution and capsule treatments, the difference in $AUC_{0-\infty}$ was statistically significant at the 0.05 level (Text Table 10.3.4-1), but the confidence interval (92 to 99%) was still within the 80-125% bioequivalence range. On average, the $AUC_{0-\infty}$ was only 4.8% lower for the solution compared to the capsule (Text Table 10.3.2-2.). The Wilcoxon's signed rank test for $t_{max}$ showed that there was no statistically significant formulation effect in either the 3 mg (p=0.28)

or the 6 mg cohort (p=0.08). The 90% confidence intervals provided in Text Table 10.3.4-1. were calculated using log transformed data.

Similar to the results for rivastigmine, bioequivalence was found for $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ of NAP 226-90 for both the 3 mg and 6 mg dose (Text Table 10.3.4-1.) according to the 90% C.I. calculation. For the 3 mg cohort, the 90% confidence intervals for least square mean ratios of these parameters were 92-102%, 95-106%, and 93-105%, and those for the 6 mg cohort were 93-100%, 92-99%, and 97-114%, respectively. These values all fell within the 80% to 125% bioequivalence range (Text Table 10.3.4-1.).

**Text Table 10.3.4-1. Assessment of bioequivalence between solution and capsule for NAP 226-90**

| Parameter | Geometric mean | | % Difference | p-value | 90% C.I. |
|---|---|---|---|---|---|
| | 3 mg Solution (N=26)[b] | 3 mg Capsule (N=26)[b] | | | |
| $AUC_{0-t}$ (ng.h/mL) | 30.69 | 31.60 | -2.86 | 0.31 | 92-102% |
| $AUC_{0-\infty}$ (ng.h/mL) | 34.06 | 33.85 | 0.60 | 0.95 | 95-106% |
| $C_{max}$ (ng/mL) | 5.95 | 6.0 | -0.80 | 0.77 | 93-105% |
| $t_{max}$[a] (h) | 1.5 | 1.5 | 0.0 | 0.28 | |
| Parameter | Geometric mean | | % Difference | p-value | 90% C.I. |
| | 6 mg Solution (N=26) | 6 mg Capsule (N=26) | | | |
| $AUC_{0-t}$ (ng.h/mL) | 61.81 | 63.94 | -3.34 | 0.08 | 93-100% |
| $AUC_{0-\infty}$ (ng.h/mL) | 64.97 | 68.10 | -4.59 | 0.03* | 92-99% |
| $C_{max}$ (ng/mL) | 10.51 | 9.97 | 5.34 | 0.27 | 97-114% |
| $t_{max}$[a] (h) | 1.25 | 1.5 | -16.67 | 0.08 | |

C.I. = Confidence Interval

[a] For $t_{max}$, median values were provided instead of geometric mean and the significance level was obtained from Wilcoxon signed rank test.

[b] Excluding Patient 1016 who did not have complete pharmacokinetic profile for both periods of the study.

* =statistically significant, p≤0.05.

Reference: Section 15; Post-text Tables 10.3.4-1.1., 10.3.4-1.2., and Appendix 9.2.2.

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## 11. Efficacy results

No efficacy evaluations were performed during this study.

## 12. Safety results

Data from all 53 patients who were randomized and received at least one dose of study medication were included in the safety analysis. There were 27 patients in the 3 mg cohort and 26 patients in the 6 mg cohort.

### 12.1. Overall experience of adverse events (AEs)

All treatment emergent adverse events that occurred within 48 hours after the administration of the study medication are summarized by formulation within dose, body system, and preferred term in Text Table 12.1-1 and in Section 15, Post-text Table 12.1-2. Treatment-emergent adverse events are also summarized by sex and severity in Section 15, Post-text Tables 12.1-2.1 and 12.1-3, respectively. Adverse events occurring during the 1-day washout (Day 3) are presented in listings, but not summarized. Individual patient listings of all adverse event data (including body system, preferred term, reported term, start and stop dates, duration, serious vs. not serious, severity, relationship to study medication, event causality, frequency, effect on study course, if therapy was prescribed) are presented in Appendix 8.1, Listing 12.1-1. Adverse events are listed by preferred term, body system, reported term, and patient number in Appendix 8.1, Listing 12.1-2.

Adverse events, regardless of relationship to trial drug, were reported for 7/27 patients (26%) during the 3 mg solution treatment, 10/27 patients (37%) during the 3 mg capsule treatment, 10/26 patients (38%) during the 6 mg solution treatment, and 7/26 patients (27%) during the 6 mg capsule treatment. The overall incidence of adverse events was similar for the solution and capsule formulations of Exelon® (Text Table 12.1-1). The two body systems most commonly affected were the gastro-intestinal system and the central and peripheral nervous system. The most frequently reported adverse events (occurring in >7% of the overall population, listed in order of decreasing frequency) were mild cases of headache, diarrhea, nausea, and insomnia. Of these, nausea occurred with equal frequency in both the 3 mg and 6 mg cohorts and for the solution and capsule formulations. However, the number of patients with adverse events in each treatment group was too small to detect any clinically relevant gender differences in the distribution of the most frequently reported adverse events (Post-text Table 12.1-2.1).

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**Text Table 12.1-1. Treatment emergent adverse events by body system and formulation within dose**

| Body System/ Preferred Term | 3 mg solution N=27 n (%) | 3 mg capsule N=27 n (%) | 6 mg solution N = 26 n (%) | 6 mg capsule N = 26 n (%) |
|---|---|---|---|---|
| At Least One Event | 7 (26) | 10 (37) | 10 (38) | 7 (27) |
| Any Drug Related Event | 2 (7) | 0 (0) | 3 (12) | 2 (8) |
| GASTRO-INTESTINAL SYSTEM DISORDERS | 4 (15) | 2 (7) | 3 (12) | 3 (12) |
| DIARRHEA | 2 (7) | 0 (0) | 1 (4) | 2 (8) |
| NAUSEA | 1 (4) | 1 (4) | 1 (4) | 1 (4) |
| CONSTIPATION | 0 (0) | 2 (7) | 0 (0) | 0 (0) |
| DYSPEPSIA | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| HICCUP | 0 (0) | 0 (0) | 1 (4) | 0 (0) |
| CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS | 2 (7) | 5 (19) | 2 (8) | 1 (4) |
| HEADACHE | 2 (7) | 4 (15) | 2 (8) | 1 (4) |
| DIZZINESS | 0 (0) | 1 (4) | 0 (0) | 0 (0) |
| PSYCHIATRIC DISORDERS | 3 (11) | 3 (11) | 1 (4) | 0 (0) |
| INSOMNIA | 1 (4) | 3 (11) | 0 (0) | 0 (0) |
| AGITATION | 1 (4) | 1 (4) | 1 (4) | 0 (0) |
| ANXIETY | 0 (0) | 1 (4) | 0 (0) | 0 (0) |
| CONFUSION | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| DEPRESSION | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| BODY AS A WHOLE - GENERAL DISORDERS | 1 (4) | 1 (4) | 3 (12) | 1 (4) |
| ACCIDENTAL TRAUMA | 0 (0) | 0 (0) | 2 (8) | 1 (4) |
| FEVER | 1 (4) | 1 (4) | 1 (4) | 0 (0) |
| MUSCULO-SKELETAL SYSTEM DISCRDERS | 2 (7) | 1 (4) | 1 (4) | 0 (0) |
| BACK PAIN | 1 (4) | 1 (4) | 0 (0) | 0 (0) |
| ARTHROSIS | 0 (0) | 0 (0) | 1 (4) | 0 (0) |
| PAIN | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| RESPIRATORY SYSTEM DISORDERS | 1 (4) | 1 (4) | 1 (4) | 1 (4) |
| RHINITIS | 0 (0) | 1 (4) | 1 (4) | 1 (4) |
| COUGHING | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| APPLICATION SITE DISORDERS | 0 (0) | 1 (4) | 1 (4) | 1 (4) |
| APPLICATION SITE REACTION* | 0 (0) | 1 (4) | 1 (4) | 1 (4) |
| HEARING AND VESTIBULAR DISORDERS | 0 (0) | 0 (0) | 1 (4) | 0 (0) |
| TINNITUS | 0 (0) | 0 (0) | 1 (4) | 0 (0) |
| RESISTANCE MECHANISM DISORDERS | 0 (0) | 0 (0) | 1 (4) | 0 (0) |
| UPPER RESP TRACT INFECTION | 0 (0) | 0 (0) | 1 (4) | 0 (0) |

Only adverse events on the day of dosing and the day after dosing are tabulated.

Patients having the same type of AE after the sol and cap treatments were included in the tabulations for both treatments.

*Application site reactions include: erythema or bruising at the sites were the PK blood samples were drawn.

Reference: Section 15 Post-text Table 12.1-2

Overall, no severe, serious, or unexpected adverse events were reported. All adverse events were classified as mild (91%) or moderate (9%) in severity (Section 15, Post-text Table 12.1-3). Drug-related adverse events (classified as possibly or probably related to the study medication by the investigators) were reported in 2/27 patients (7%) in the 3 mg solution group, in 3/26 patients (12%) in the 6 mg solution group, and in 2/26 patients (8%) in the 6 mg capsule group. The drug-related adverse events included diarrhea (3 mg solution, 6 mg solution, 6 mg capsule), nausea (3 mg solution, 6 mg solution, 6 mg capsule), and tinnitus (6 mg solution). All drug-related adverse events resolved within 1-2 days of onset. Data on adverse event drug relationships and duration are presented in Appendix 8.1, Listing 12.1-1.

None of the patients discontinued therapy because of adverse events.

## 12.2. Deaths, other serious adverse events (SAEs) and other significant adverse events

No deaths, serious adverse events or other significant adverse events were reported during the study.

## 12.3. Analysis and discussion of deaths, other serious adverse events (SAEs) and other significant adverse events

Not applicable.

## 12.4. Laboratory values

No laboratory data was collected during the 5-day treatment period.

## 12.5. Vital signs

Vital signs including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature were measured on Days 1 and 4 at 2 hours post-dose, on Day 3 at noon, and on Days 2 and 5 at 24 hours post-dose. Weight was measured at screening, baseline, and on Day 5 prior to discharge.

Changes from baseline for pulse and blood pressure (supine after 5 minutes, immediately upon standing, and after standing 3 minutes), respiratory rate, oral body temperature, and weight are summarized by study day, dose, and formulation in Section 15, Post-text Table 12.5-1.

Clinically notable vital sign changes from baseline in excess of the guidelines set by the FDA Division of Neuropharmacological Drug Products and/or vital sign values that were outside the core study protocol-specified ranges for pulse and blood pressure are presented in Section 15, Post-text Table 12.5-2. All values outside the core study protocol range (core study criteria) are flagged H/L (value higher/lower than upper/lower limit of protocol criteria). Clinically notable abnormalities were indicated with an asterisk (*). Values worse than baseline where the baseline values were abnormal are flagged as W/w. The number of patients with clinically notable pulse and blood pressure abnormalities are summarized by dose, formulation, and study day in Section 15, Post-text Table 12.5-2.2. and by sex in Post-text Table 12.5-2.1.

Individual patient vital sign listings for all pulse and blood pressure measurements conducted during the study are presented in Section 15, Post-text Listing 12.5-1. Individual patient vital sign listings for all weight, respiratory rate and oral body temperature measurements are presented in Section 15, Post-text Listing 12.5-2.

Mean changes from baseline to the final visit for all vital sign parameters were minor (Section 15, Post-text Table 12.5-1). A total of 6/27 patients (22%) during the 3 mg solution treatment, 7/27 patients (26%) during the 3 mg capsule treatment, 9/26 patients (35%) during the 6 mg capsule treatment, and 6/26 patients (23%) during the 6 mg solution treatment had a blood pressure and/or pulse value in excess of the FDA Division of Neuropharmacological Drug Products criteria for clinically notable vital sign abnormalities. For all treatment groups, the percentage of patients with clinically notable decreases in pulse rate, systolic blood pressure, and diastolic blood pressure ranged from 0-8%, 4-12% and 11-19%, respectively. Clinically notable increases in pulse rate and systolic blood pressure were reported in 4% of the patients in the 3 mg and 6 mg solution treatments, respectively (Text Table 12.5-1.).

**Text Table 12.5-1. Number of patients with clinically notable blood pressure and pulse abnormalities by treatment group**

| Variable | | 3 mg | | 6 mg | |
|---|---|---|---|---|---|
| | | solution n (%) | capsule n (%) | solution n (%) | capsule n (%) |
| Total no. patients studied | | 27 | 27 | 26 | 26 |
| Total no. patients with any clinically notable vital sign abnormality | | 6 (22) | 7 (26) | 9 (35) | 6 (23) |
| Pulse | high | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| | low | 0 (0) | 1 (4) | 1 (4) | 2 (8) |
| Systolic BP | high | 0 (0) | 0 (0) | 1 (4) | 0 (0) |
| | low | 2 (7) | 1 (4) | 3 (12) | 1 (4) |
| Diastolic BP | high | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | low | 3 (11) | 5 (19) | 4 (15) | 3 (12) |

Patients having the same type of vital sign abnormality after sol and cap treatments were included in the tabulations for both treatments.

Reference: B153 Clinical Trial Report, Section 15, Post-text Table 12.5-2.

Most vital sign abnormalities were asymptomatic fluctuations in systolic and diastolic blood pressure that resolved spontaneously. However, one female patient (2003) receiving Cardizem CD® (240 mg QD) for hypertension had clinically notable diastolic blood pressure values during the 3 mg capsule treatment on Day 4 (supine 32 mmHg; sitting 48 mmHg; after 3 minutes of standing 42 mmHg) and Day 5 (supine 50 mmHg; immediately on standing 44 mmHg; standing after 3 minutes 38 mmHg) that required a decrease in the patient's dose of Cardizem CD® to 120 mg QD on Day 4. The patient's primary care physician was notified to continue medical management. All of the patient's other vital sign parameters were within normal clinical limits during the study. The investigator attributed the low diastolic blood pressures to the patient's concomitant medication and pre-existing medical condition. (Details are provided in Section 15,

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**Text Table 12.5-2. Number of clinically notable pulse and BP abnormalities by treatment, study day, and position**

| Study Day | Position | Parameter | Result | 3 mg solution n (%) | 3 mg capsule n (%) | 6 mg solution n (%) | 6 mg capsule n (%) |
|---|---|---|---|---|---|---|---|
| Day 1: Initial Dose (measured 2 hours post-dose) | | | | N=14 | N=13 | N=13 | N=13 |
| | Supine | Systolic BP | High | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Supine | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| | Immediate Standing | Pulse | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 1 (8) | 0 (0) | 0 (0) |
| Day 2 (measured 24 hours post-dose) | | | | N=14 | N=13 | N=12 | N=13 |
| | Supine | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 1 (7) | 1 (8) | 1 (8) | 1 (8) |
| | Immediate Standing | Systolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 1 (8) | 1 (8) | 0 (0) |
| | Immediate Standing | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 1 (8) | 1 (8) |
| | Standing after 3 min. | Pulse | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| | Standing after 3 min. | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 2 (15) | 0 (0) | 0 (0) |
| Day 3 (measured at noon) | | | | N=14 | N=13 | N=13 | N=13 |
| | Supine | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| | Immediate Standing | Systolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 1 (7) | 0 (0) | 2 (15) | 0 (0) |
| Day 4 Final Dose (measured 2 hours post-dose) | | | | N=13 | N=14 | N=13 | N=13 |
| | Supine | Pulse | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| | Immediate Standing | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 1 (8) | 1 (7) | 0 (0) | 0 (0) |
| Day 5 (measured 24 hours post-dose) | | | | N=13 | N=14 | N=13 | N=13 |
| | Supine | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 1 (7) | 1 (8) | 0 (0) |
| | Immediate Standing | Pulse | High | 1 (8) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| | Immediate Standing | Systolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 1 (8) | 0 (0) | 0 (0) | 1 (8) |
| | Immediate Standing | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 1 (8) | 1 (7) | 0 (0) | 1 (8) |
| | Standing After 3 min. | Pulse | High | 1 (8) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Standing After 3 min. | Systolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| | Standing After 3 min. | Diastolic BP | High | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | | | Low | 0 (0) | 0 (0) | 0 (0) | 1 (8) |

Criteria: Pulse: >=120 bpm / <=50 bpm with increase / decrease from baseline of >=15 bpm
Systolic BP: >=180 mmHg / <=90 mmHg with increase / decrease from baseline of >=20 mmHg
Diastolic BP: >=105 mmHg / <=50 mmHg with increase / decrease from baseline of >=15 mmHg
Reference: Section 15, Post-text Table 12.5-2.2.

# 13. Discussion and overall conclusions

## 13.1. Discussion

Based on $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ of both rivastigmine and NAP 226-90, both the 3 mg and 6 mg doses of the solution dosage form (2 mg/mL) were found to be bioequivalent to the 3 mg and 6 mg strengths of the capsule dosage form, respectively.

The $t_{max}$ of rivastigmine following a 3 mg dose of the solution dosage form was not significantly different (p=0.09) from the $t_{max}$ following the same dose of the capsule dosage form. However, for the 6 mg cohort, the difference in $t_{max}$ between the solution and capsule form was statistically significant (p=0.02). On average, the arithmetic mean $t_{max}$ value for the 6 mg solution was 23.5% smaller (~16 minutes earlier) than the arithmetic mean $t_{max}$ value for the 6 mg capsule. The $t_{max}$ of NAP 226-90 following the 3 mg and 6 mg doses of the solution dosage form was not significantly different (p=0.08) than the $t_{max}$ following the respective doses of the capsule dosage form.

$T_{max}$ is a highly variable PK parameter because it is obtained from discrete time instances and is highly dependent on the blood sampling schedule. In this study, the interval between the sampling times up to one hour (i.e. 0, 0.5, 0.75, and 1 hour) is smaller than the interval between sampling points after 1 hour (ie., 1.5, 2, and 3 hours). For the 6 mg solution, 3/26 patients had $t_{max}$ values for rivastigmine that were greater than 1 hour, whereas for the 6 mg capsule, 9/26 patients had $t_{max}$ values greater than 1 hour. This distribution explains the higher variability associated with the mean $t_{max}$ value for rivastigmine in the 6 mg capsule treatment (CV% = 44.5%) compared with the 6 mg solution treatment (CV% = 26.75%) and may account for the statistically significant difference between the two formulation means that was reported for this variable.

In both the 3 and 6 mg cohorts, the plasma concentration of the solution peaked slightly earlier (7-16 minutes) than that of the capsule. This finding was expected since the solution by-passes the drug-dissolution step compared to the solid, capsule dosage form. In previous clinical studies (W104[12] and W361[13]) in which instantaneous absorption was achieved by intravenous administration to healthy young volunteers (single doses up to 2.7 mg infused over 1 h), rivastigmine was well tolerated without any signs of excessive cholinergic stimulation. Therefore, the slightly earlier peak observed after solution treatment is not expected to present a safety concern for a chronically administered drug that is gradually titrated to the patient's maximum tolerated dose.

The criteria for establishing bioequivalence of rivastigmine oral solution to the capsule are that the 90% confidence intervals for the ratios of log-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ values for each comparison are within the range of 80-125%. These criteria were met for all three of these parameters for both rivastigmine and NAP 226-90 for each comparison performed.

Adverse events were reported in 26% of the patients during the 3 mg solution treatment, 37% of the patients during the 3 mg capsule treatment, 38% of the patients during the 6 mg solution treatment, and 27% of the patients during the 6 mg capsule treatment. The overall incidence of adverse events was similar for the solution and capsule formulations of Exelon®. The two body

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systems most commonly affected were the gastro-intestinal system and the central and peripheral nervous system. The most frequently reported adverse events (occurring in >7% of the overall population, listed in order of decreasing frequency) included mild cases of headache, diarrhea, nausea, and insomnia. Of these, 6 drug-related episodes of diarrhea and nausea were reported in 4 patients (2 in each dose group). No severe, serious, or unexpected adverse events were reported. All adverse events were classified as mild or moderate in degree of severity and resolved within 1-2 days of onset. None of the patients discontinued therapy because of adverse events.

Clinically notable changes from baseline in blood pressure and/or pulse rate were reported for all treatments. Most of these vital sign abnormalities were asymptomatic fluctuations in systolic and diastolic blood pressure that resolved spontaneously. However, one patient, receiving Cardizem CD® for hypertension, had cynically notable low diastolic blood pressure values during the 3 mg treatment that required a decrease in the patient's dose of Cardizem CD®. The low diastolic blood pressure values were attributed to the patient's concomitant medication and pre-existing medical condition. None of these vital sign abnormalities caused a patient to discontinue from the study.

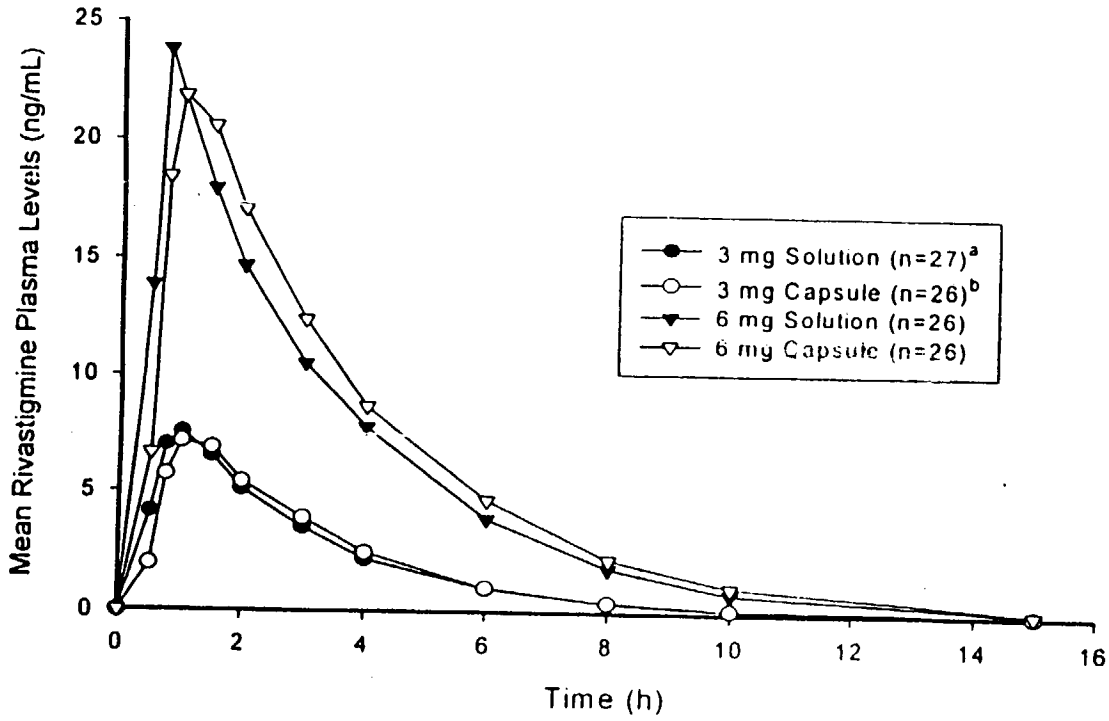
The occurrence of adverse events and vital sign abnormalities reported during this study may be due to the following aspects of the study design: (1) the patients' Exelon® dosing regimen from their core study was stopped for 3 days and was restarted for the bioequivalence study without titration; (2) similarly, no doses were administered between Days 1 and 4; and (3) the study medication was administered without food after a 10-hour fast during the bioequivalence study, whereas Exelon® was administered with food in the patients' core study.

## 13.2. Conclusions

- The 3 mg dose of the Exelon® oral solution (2 mg/mL) is bioequivalent to the oral 3 mg Exelon® capsule for the parent compound, rivastigmine, as well as the decarbamylated metabolite (NAP 226-90).
- The 6 mg dose of the Exelon® oral solution (2 mg/mL) is bioequivalent to the oral 6 mg Exelon® capsule for the parent compound, rivastigmine, as well as the decarbamylated metabolite (NAP 226-90).
- Single 3 and 6 mg doses of Exelon® oral solution and Exelon® capsules were safe and well tolerated by the patient population.

APPEARS THIS WAY
ON ORIGINAL

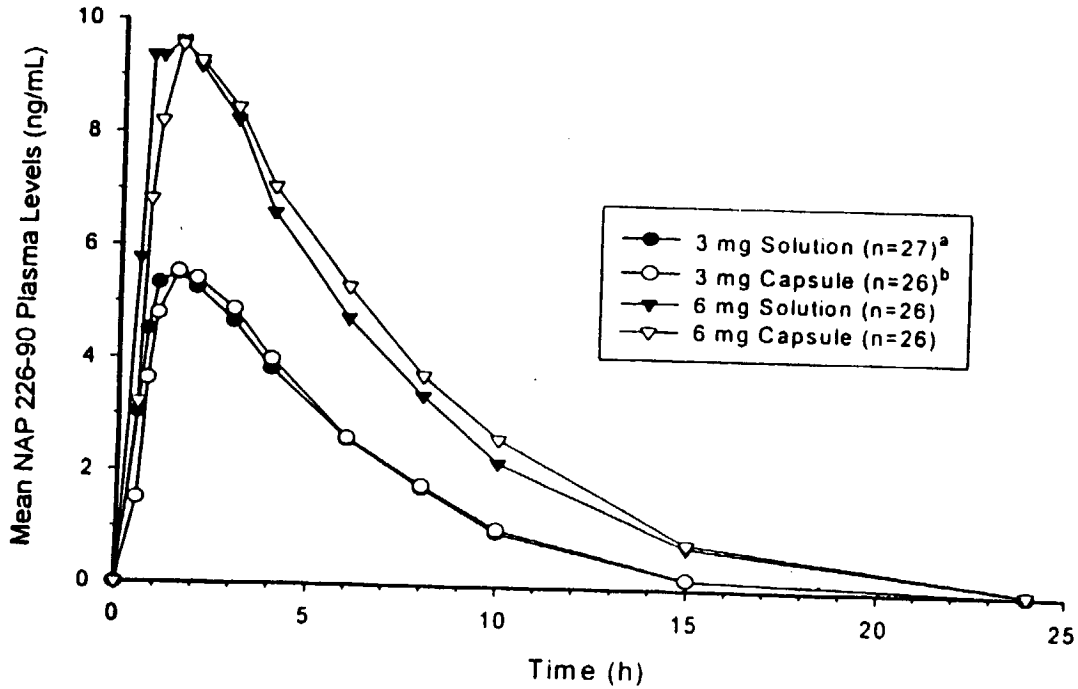
**Post-text Figure 10.3.2-1. Mean plasma concentration-time profile of rivastigmine following single oral administration of 3 mg and 6 mg dose of solution and capsule**




[a] Including patient 1016.

[b] Excluding patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90.

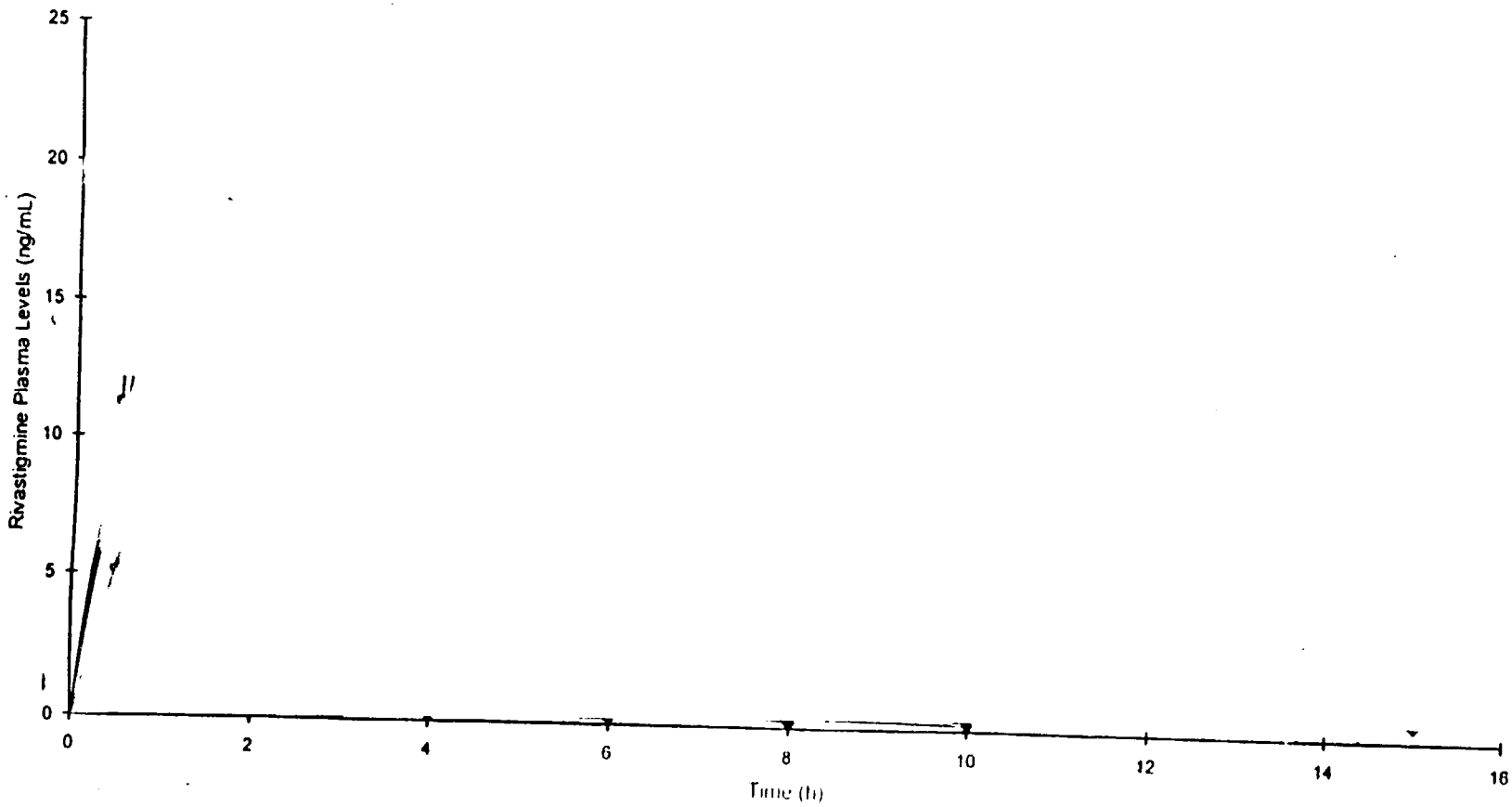
**Post-Text Figure 10.3.2-2. Mean plasma concentration-time profile of NAP 226-90 following single oral administration of 3 mg and 6 mg dose of solution and capsule**




[a] Including patient 1016.

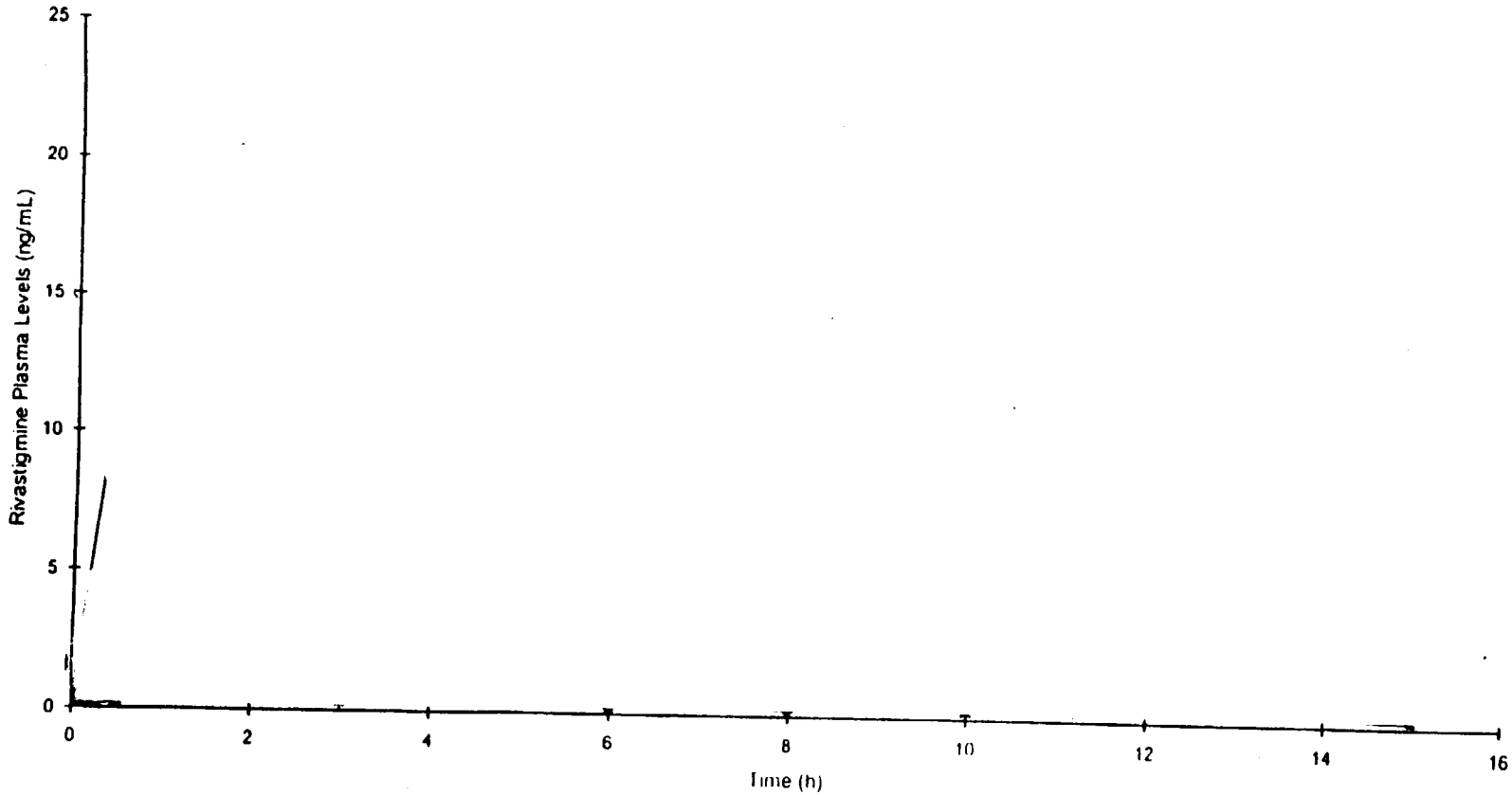
[b] Excluding patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90

**Post-Text Figure 10.3.2-3. Individual plasma concentration-time profiles of rivastigmine following a single 3 mg oral dose of solution (n=27)**



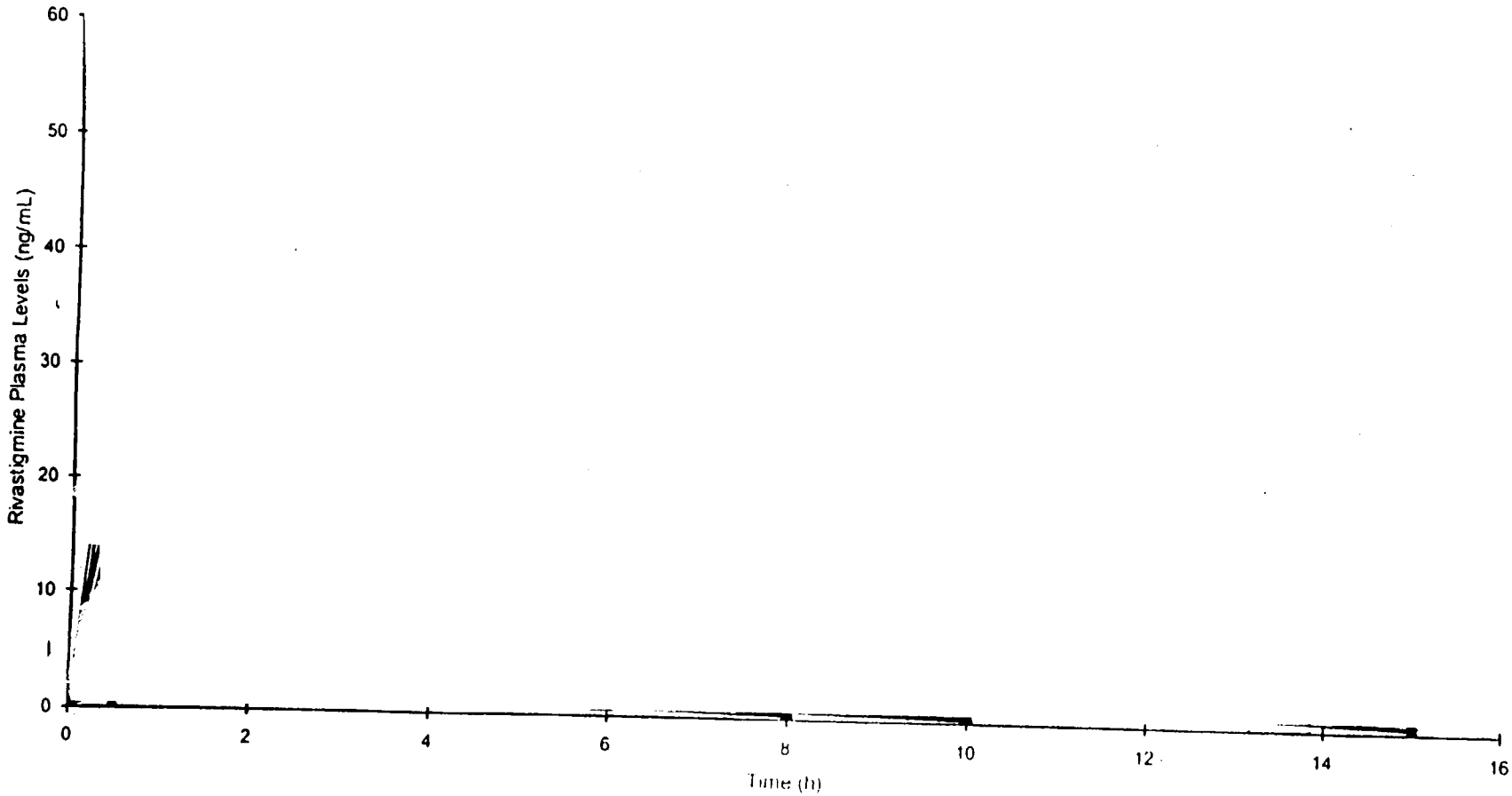

Note: Including patient 1016.

**Post-Text Figure 10.3.2-4. Individual plasma concentration-time profiles of rivastigmine following a single 3 mg oral dose of capsule (n=26)**

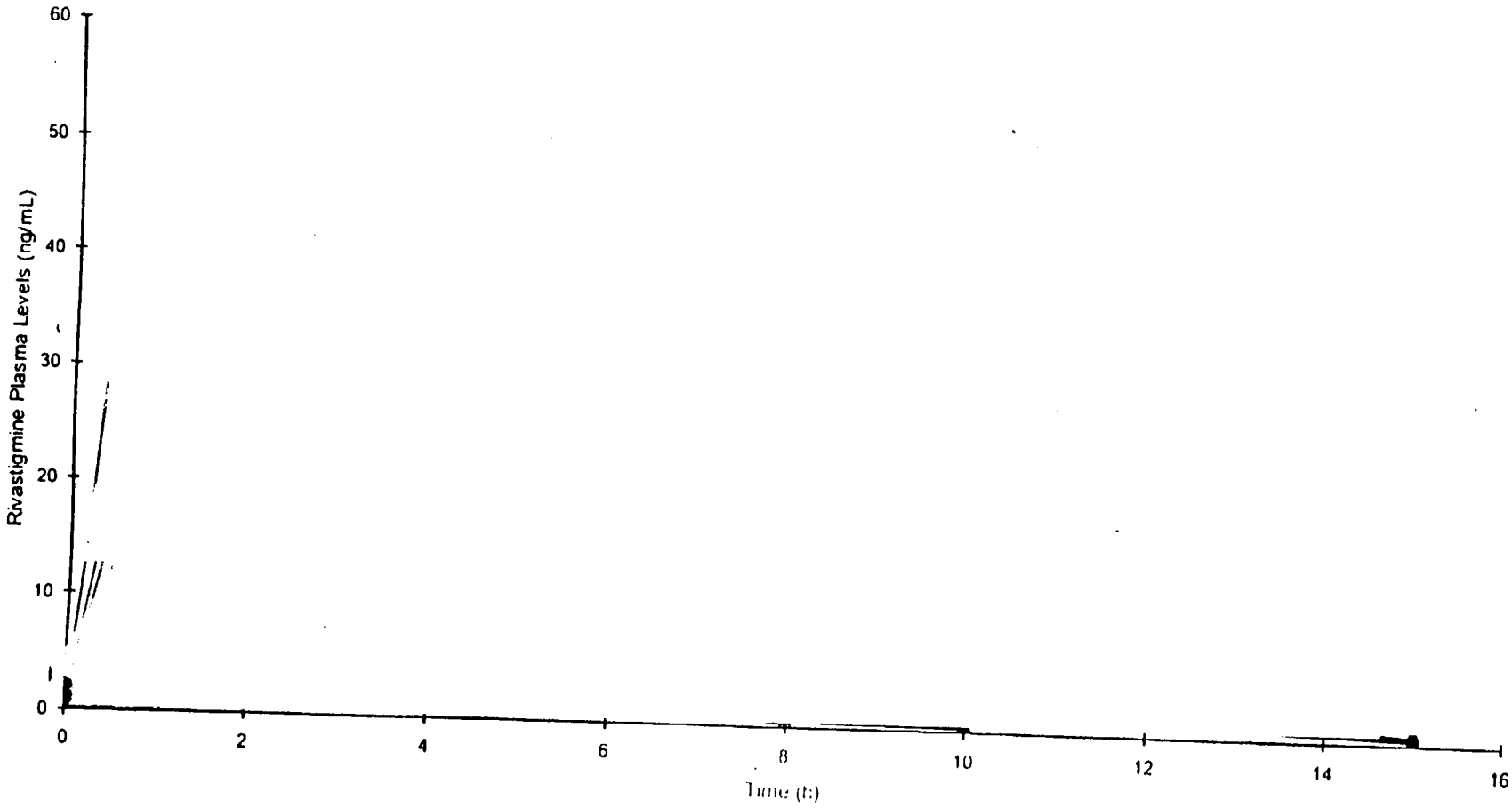



Note: Excluding patient 1016 who had no measurable plasma levels of either rivastigmine or NAP 226-90.

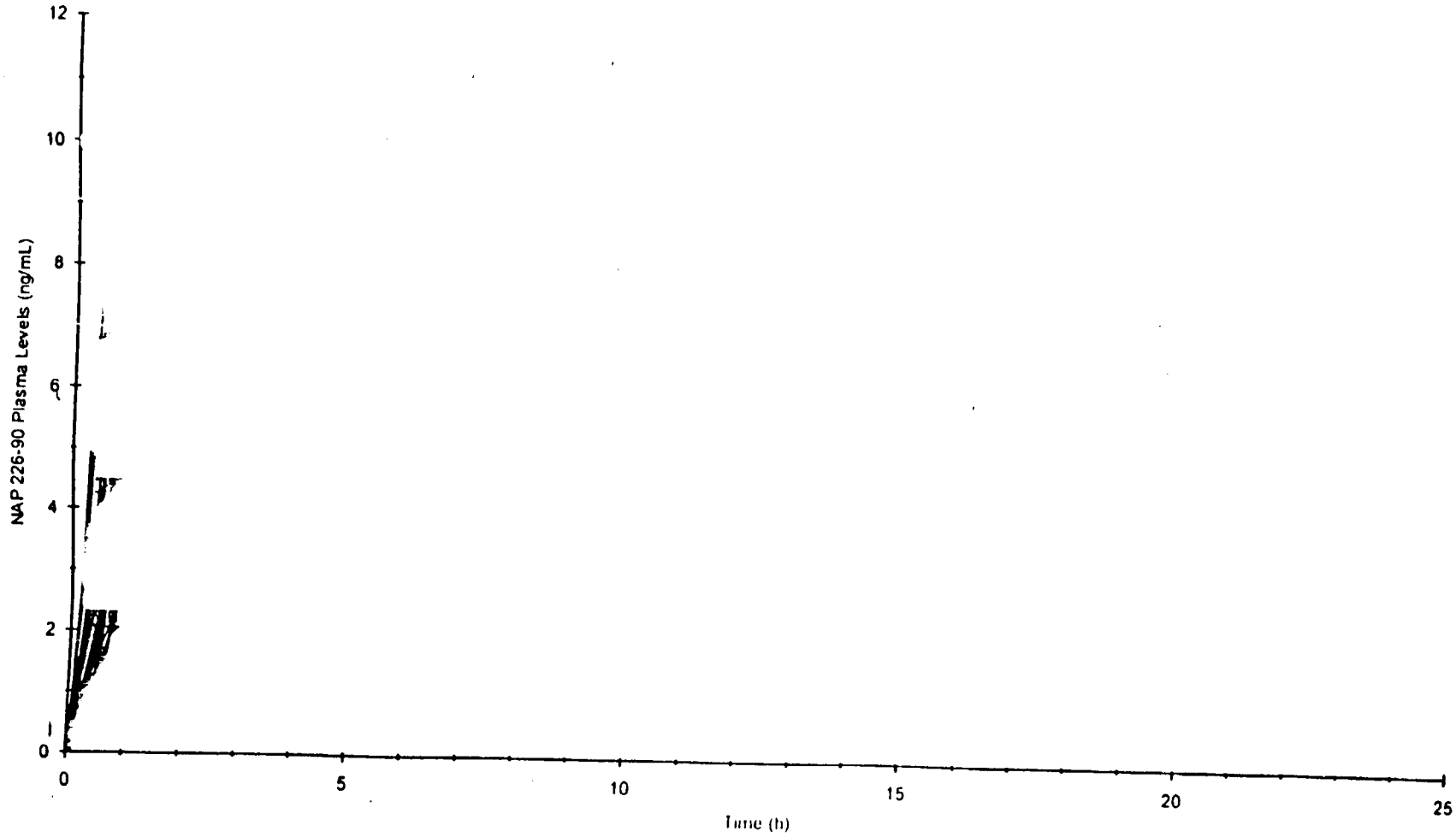
**Post-Text Figure 10.3.2-5. Individual plasma concentration-time profiles of rivastigmine following a single 6 mg oral dose of solution (n=26)**



**Post-Text Figure 10.3.2-6. Individual plasma concentration-time profiles of rivastigmine following a single 6 mg oral dose of capsule (n=26)**

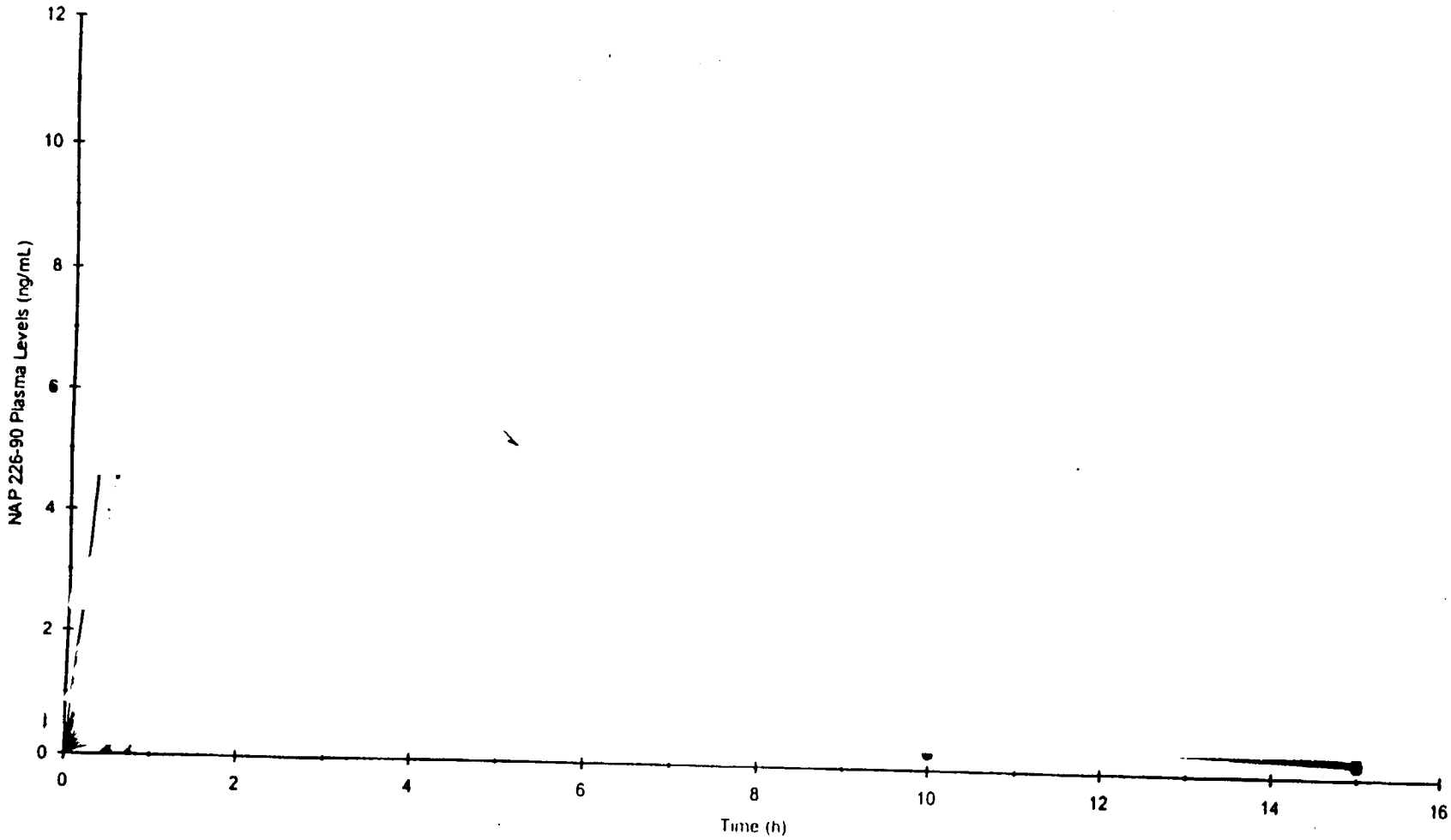


**Post-Text Figure 10.3.2-7. Individual plasma concentration-time profiles of NAP 226-90 following a single 3 mg oral dose of solution (n=27)**



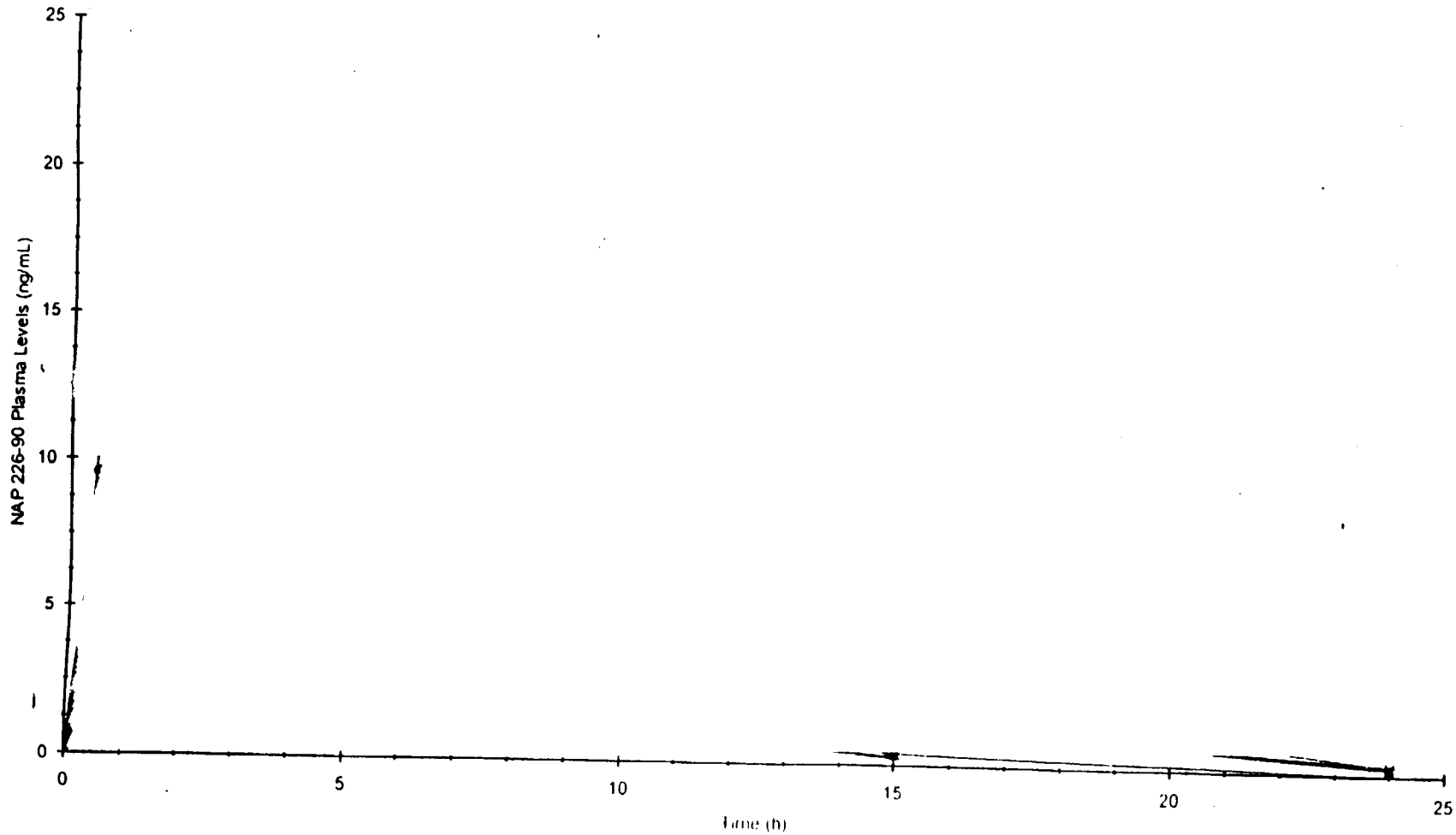

Note: Including patient 1016.

**Post-Text Figure 10.3.2-8. Individual plasma concentration-time profiles of NAP 226-90 following a single 3 mg oral dose of capsule (n=26)**

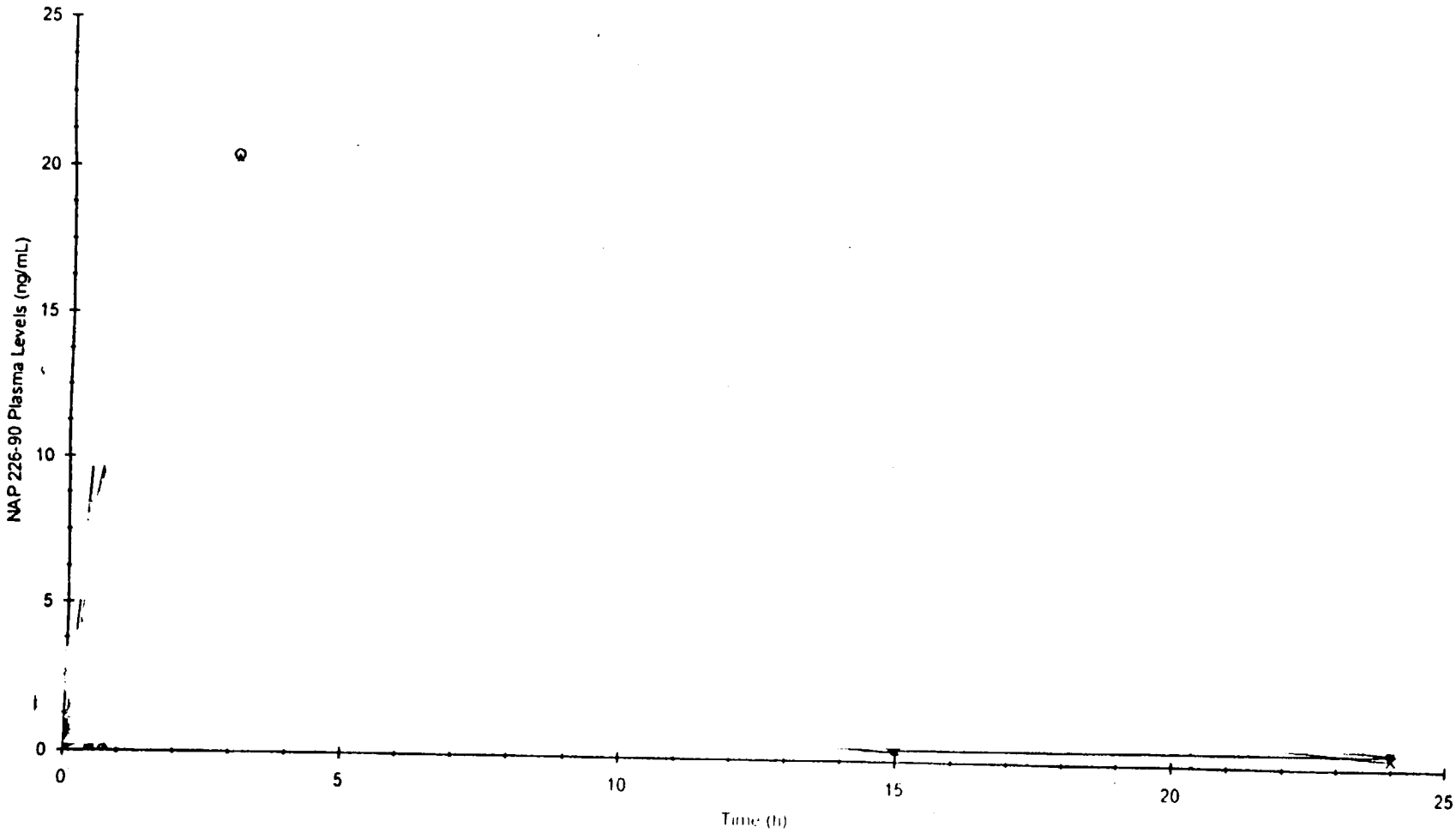



Note: Excluding patient 1016 who had no measurable plasma levels of rivastigmine and NAP 226-90

**Post-Text Figure 10.3.2-9.** **Individual plasma concentration-time profiles of NAP 226-90 following a single 6 mg oral dose of solution (n=26)**



**Post-Text Figure 10.3.2-10. Individual plasma concentration-time profiles of NAP 226-90 following a single 6 mg oral dose of capsule (n=26)**



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Confidential,
Commercial Information

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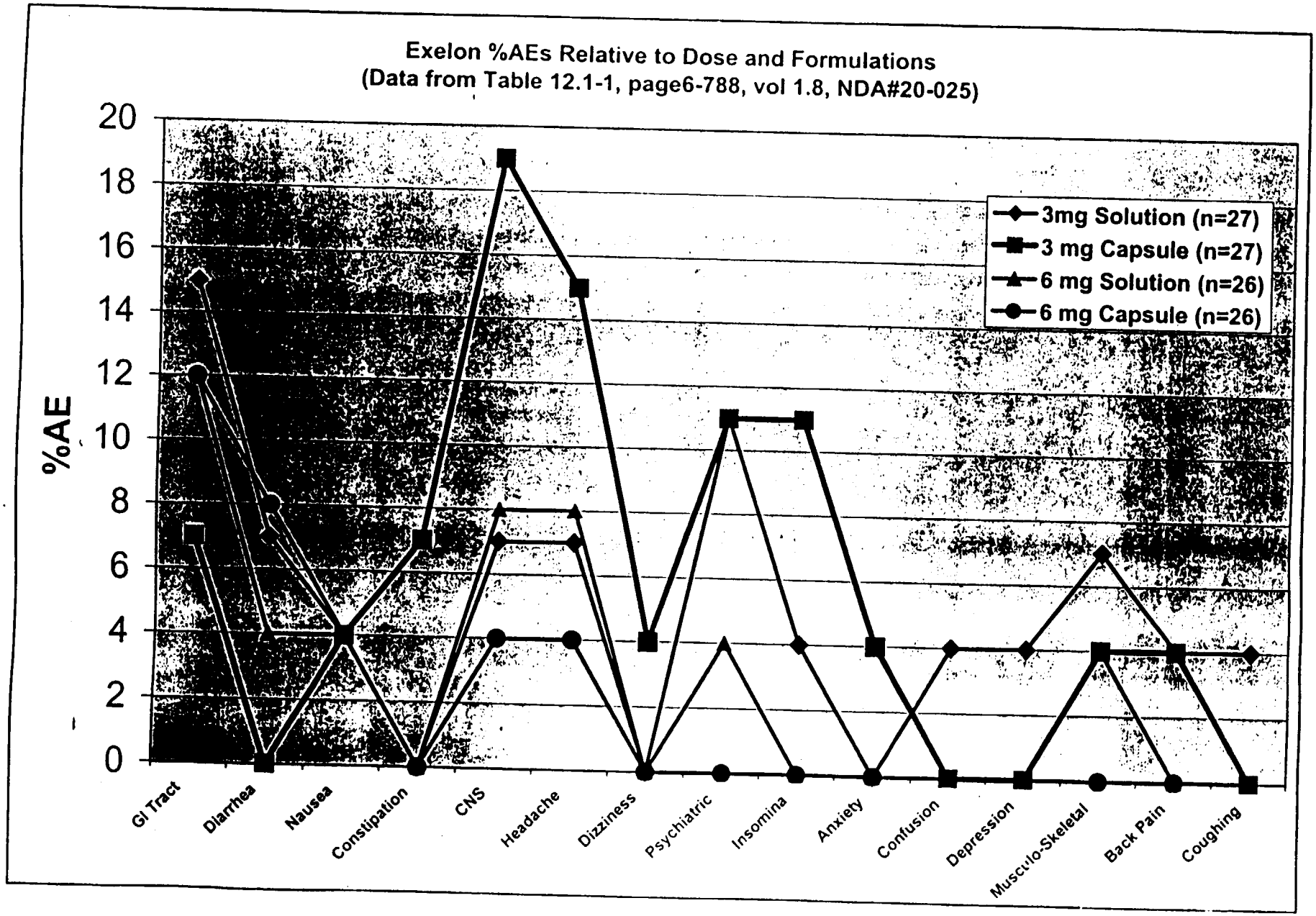


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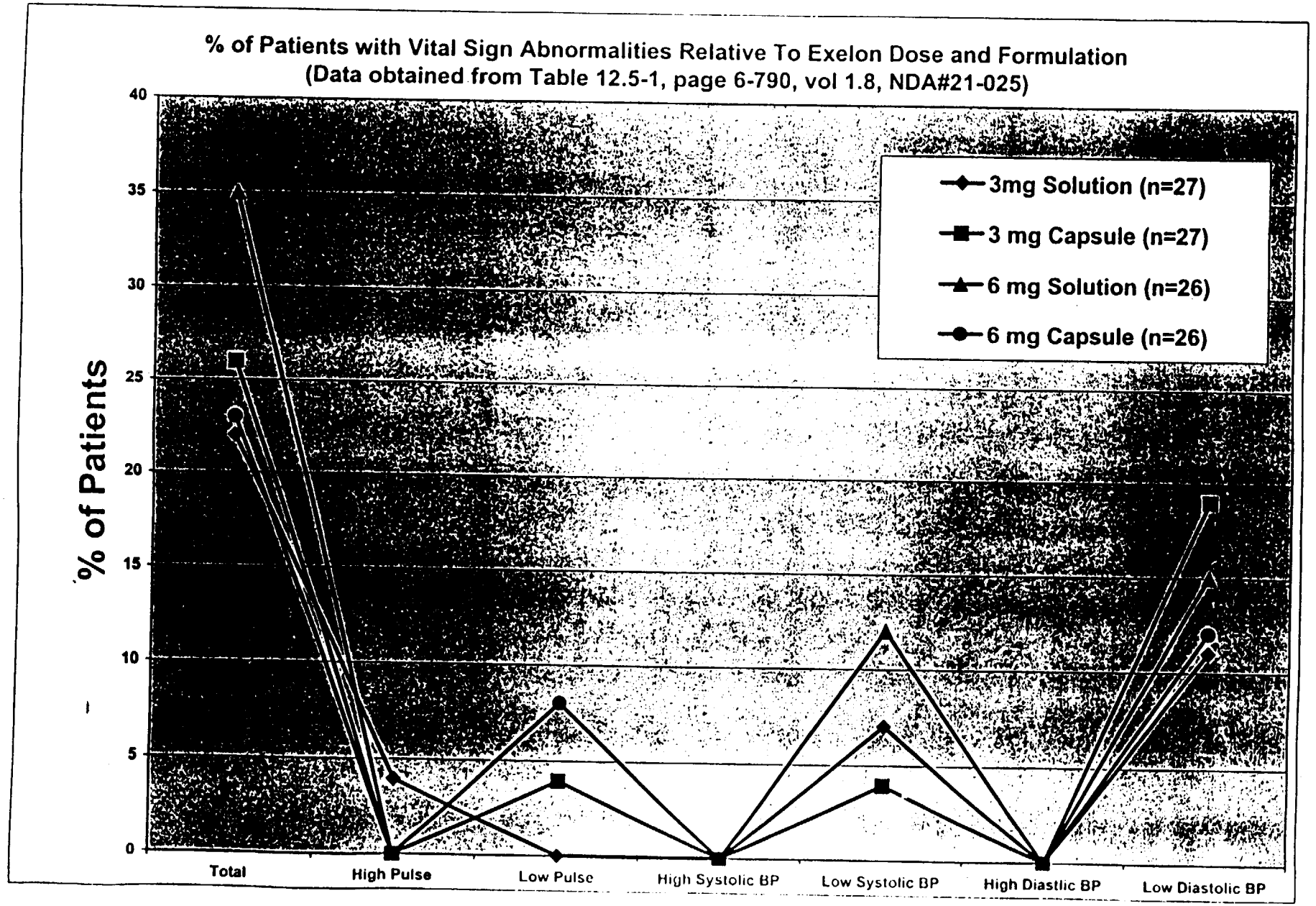


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# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-025

Submission Dates:
July 26, 1999

| | |
|---|---|
| Generic Name: | **Rivastigmine Tartrate Oral Solution (ENA 713)** |
| Brand Name: | **EXELON®** |
| Strength(s): | **2 mg/ml** |
| Formulation: | **Solution** |
| Sponsor: | **Novartis** |
| Type of Submission: | **NDA (NME)** |
| Reviewer: | **Sayed Al-Habet, Ph.D.** |
| Date of Review: | **August 11, 1999** |

**Recommendation:**

The contents of the attached letter were noted in the original review dated June 30, 1999. Therefore, no further action is necessary.

Reviewed by: /S/

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

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

cc: NDA # 21-025 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), HFD-19 (FOI), and Drug files (Biopharm File, CDR).

Attachment 1

Robert W. Kowalski, PharmD
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel (973) 781-6869
Fax (973) 781-6325
Internet: robert.kowalsk.
@pharma.novartis.com

NOVARTIS

**ORIG AMENDMENT**

DUPLICATE

N (BP)

July 26, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 27 1999

RECEIVED HFD-120

Russell Katz, MD
Acting Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

**NDA No. 21-025**

**EXELON® (rivastigmine tartrate)**
**Oral Solution**

**GENERAL CORRESPONDENCE**

Dear Dr. Katz,

Please refer to my conversation with Dr. Sayed Al-Habet of HFD-860 in June 1999. Dr. Al-Habet telephoned to clarify whether the names "ZNS 114-666" and "NAP 226-90" for the primary metabolite of rivastigmine were synonymous. I confirmed in my telephone conversation with Dr. Al-Habet that these two terms are identical. I explained that there was a change in nomenclature during the development of Exelon and that is why both terms can be found in various documents supporting the Application. ZNS 114-666 is used in older "legacy" documents, and NAP 226-90 is now used consistently in all "new" documents.

While this is documented in several "Notes to Reviewer" in the original application for Exelon Capsules (NDA 20-823), which serves as a cross-reference for the present Application, Dr. Al-Habet asked that I document this clarification via General Correspondence to the present NDA for the oral solution.

If you have any comments or questions with regard to this submission, please contact the undersigned at (973) 781-6869.

Sincerely,

Robert W. Kowalski, Pharm.D.
Associate Director,
Drug Regulatory Affairs

Submitted in Duplicate

cc (via fax): Dr. Sayed Al-Habet (HFD-860)

FEB 3 2000

**NDA#: 21-025**

Submission Date:
October 22, 1999

**Compound:** Rivastagmine Tartrate Oral Solution (2 mg/ml)

**Brand Name:** Exelon

Indication: Alzheimer's disease

**Sponsor:** Novartis

**Reviewer:** Sayed Al-Habet, Ph.D.

**Date of Review:** February 3, 2000

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## Background:

Novartis Pharmaceuticals Corporation has submitted for review a response to the approvable letter dated September 8, 1999. This NDA was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) on June 30, 1999.

**Comment to the Clinical Division:**

In the Comments to Labeling section of OCPB review dated June 30, 1999 the following statement was made:

"*The bioavailability of oral solution relative to capsule is 100% at the 3 mg dose, and is 90% at the 6 mg dose*"

The Clinical Division is requested to ensure that the above statement is incorporated in the updated version of the labeling for Exelon solution.

**Reviewer**

/S/

---

Sayed Al-Habet, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by Ray Baweja, Ph.D. -- /S/

cc: NDA # 21-025, HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), Drug file (Biopharm File, Central Document Room).

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