CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-025

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OCT - 6 1998

RECEIVED OCT 0 6 1998

NDA#: 21-025

Submission Date:
August 11, 1998

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

Brand Name: Exelon

Sponsor: Novartis

Reviewer: Sayed Al-Habet, Ph.D.

Date of Review: September 30, 1998

Background:

Novartis Pharmaceuticals Corporation has submitted for review the above NDA for Exelon oral solution. We have reviewed the application and found it to be fileable by the Office of Clinical Pharmacology and Biopharmaceutics.

However, the same drug was recently submitted as capsule formulation (NDA # 20-823) but was "Not Approved" by the Agency solely based on the safety issues related to the high risk of death associated with the use of this drug. At the "File/Refuse To File" meeting held on October 1, 1998 for the oral solution, the Division decided to "Refuse To File" this NDA based on the issues addressed in the "Not Approvable" letter issued on July 7th, 1998 for the capsule NDA. A copy of the "Refuse To File" letter issued on October 2, 1998 is attached (Attachment 1).

Recommendation:

This NDA is not fileable as stated in the "Refuse To file " letter issued in October 2, 1998. The oral solution NDA relies extensively on the information submitted in the capsule NDA. Therefore, this NDA will not be reviewed by the Office of Clinical Pharmacology and Biopharmaceutics at this time.

Reviewer /S/ 10/6/98

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 (Barbara Murphy, Central Document Room).

C:\SHFILES\NDAS\21025.WPD

COMPLETED JUL 0 7 1999

JUN 30 1999

RV

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-025

Submission Dates:
August 11, 1998
November 18, 1998

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:	**June 8, 1999**

SYNOPSIS:

EXELON (rivastigmine tartrate, ENA 713) is a reversible acetylcholinesterase inhibitor of carbamate type. It is being proposed for the treatment of Alzheimer's disease. The proposed starting dose of Exelon is 1.5 mg BID titrated to 3 mg BID after two weeks. If tolerated the dose may be titrated up to 4.5 or 6 mg BID. The maximum recommended dose is 6 mg BID (12 mg daily).

The main focus of this NDA is on the evaluation of the bioequivalency between the oral solution and the immediate release (IR) capsule. The detailed data for the IR capsule formulations were submitted in a separate NDA (#20-823) as discussed in the history section below. For convenience, a copy of the review summary of the capsule NDA (#20-823) by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) can be found in Appendix 1.

NDA Brief History:

This drug was submitted to the Agency on April 7, 1997 (NDA# 20-823) as —— 1.5, 3, 4.5, and 6 mg immediate-release, hard gelatin capsules for oral administration and for the same indication. On July 7, 1998 a "Not Approvable" letter was issued. The main reasons for non-approval were due to safety concern and increased risk of death associated with the drug. On

August 11, 1998 the sponsor submitted a new NDA (#21-025) for oral solution and for the same indication. On October 2, 1998, the Agency issued a "Refuse-to-File" letter for oral solution with cross reference to the "Not Approval" letter dated July 7, 1998 for the capsule. On November 18, 1998 the sponsor responded to the Agency's "Refuse-to-File" letter dated October 2, 1998 indicating that the deficiencies in the NDA 20-823 have been addressed by the sponsor.

Bioequivalence Studies For Oral Solution and Capsule:

Three bioequivalence studies were conducted for oral solution and capsules: two pilot studies (#W251, B353) and one pivotal study (#B153). The first pilot study (#W251) was conducted in patients with liver impairment (n=10) and healthy subjects (n=10). The formulation used was an intravenous solution diluted with drinking water to a concentration of 2 mg/5 ml. The dose was 3 mg given as drinking water or as 3 mg IR capsules. The second pilot study (#B353) was similar to the first but at 3 and 6 mg doses given as either drinking water or IR capsule in patients with probable Alzheimer's disease (n=18). It should be noted that both of these studies were previously reviewed by OCPB in NDA# 20-823 (Appendix 1)

Since the formulation used in the two pilot studies (#W251 and B353) was not the final to be marketed formulation, the emphasis of our review was on the pivotal study #B153 using the final to-be-marketed formulation. Our Comments, Summary and Conclusions on this study are as follows (Please see Appendix II for the detailed review, data and study design for study #B153).

1. This was a pivotal study to determine the Bioequivalency of oral Exelon solution (2mg/ml) to Exelon capsules at single doses of 3 and 6 mg in 60 patients with probable Alzheimer's disease (completed: n=27 for 3 mg and n=26 for 6 mg). The selected patients were already on either 3 or 6 mg doses of Exelon during the clinical trials. Treatments were stopped 3 days (i.e., Day -3) prior to the bioequivalance study and restarted on Day 5 after the study was completed. Each patient was titrated back to the original dose of the given clinical trial.

2. The results show that the oral solution is bioequivalent at both doses to the capsule for both the parent and the metabolite, NAP 226-90 (Attachments 1-6). At the 3 mg dose, the 90% CI for the parent $AUC_{0-\infty}$ was 94-109% and for Cmax was 86-106% and for the metabolite was 95-106% for $AUC_{0-\infty}$ and for Cmax was 93-105%. At the 6 mg dose, the 90% CI for the parent $AUC_{0-\infty}$ was 87-100% and for Cmax was 87-110% and for the metabolite was 92-99% for $AUC_{0-\infty}$ and for Cmax was 97-114%.

3. There was no difference in the Tmax for either the parent drug or the metabolite among the four treatments. Overall, the Tmax for the parent drug is about 1 h and for the metabolite is about 1.5 h.

4. It should be noted that this is a highly variable drug. The %CV for Cmax, AUC and CL/F of the parent drug between subjects ranged from 46% to 115% (Attachment 1). For

example, at 3 mg dose solution, the Cmax ranged form 0.73-24 ng/ml and the AUC_{0-t} ranged form 1 to 85 ng.h/ml (Attachment 1). As expected from the assay limitations, the variability was higher at the 3 mg dose than at the 6 mg dose. This was consistent between formulations. Furthermore, it is noted that this variability was lower for the metabolite, NAP 226-90, with a %CV of about 30% (Attachment 4).

5. One important note is that the drug follows non-linear PK. There was a greater than proportional increase in both the Cmax and AUC of the parent compound by doubling the dose from 3 mg to 6 mg (Attachment 1). The Cmax and $AUC_{0-\infty}$ of the parent compound increased by about 3 folds as the dose increased from 3 to 6 mg. By contrast, the metabolite appears to follow a linear PK (Attachment 4). The Cmax and $AUC_{0-\infty}$ were almost doubled as the dose increased from 3 to 6 mg (Cmax from 6 to 11 ng/ml and $AUC_{0-\infty}$ from 36 to 68 ng.h/ml).

   From the available data, it appears that the drug follows Michaelis-Menten kinetics. This suggests that there is a saturation in the metabolic process. Therefore, to avoid toxicity, the drug must be carefully titrated, particularly in patients with renal and liver impairment.

6. In terms of safety, in this particular single dose study (#B153), there were a number of expected adverse events (AEs) related to this particular class of drug. The most common AEs are those related to GI tract and CNS. Some of the AEs data shown in Attachment 7. were re-analyzed and plotted as shown in Attachment 8. It is interesting to note from this plot that the % of patients with AEs is greater at 3 mg dose given as capsule compared to all other treatments. The most significant AEs are those associated with CNS. In addition, a careful examination of the data in Attachments 7 and 8 shows that the % of patients with AEs at the 3 mg dose given as solution appears to be higher than after the 6 mg dose when given as either solution or capsules. Similarly, our re-analysis of the data shown in Attachments 9 and 10 for vital signs shows that the % of patients with diastolic blood pressure was greater after the 3 mg dose given as capsules than after other treatments (Attachment 11).

Conclusions:

1. The oral solution at doses of 3 mg and 6 mg is bioequivalent to the capsule at 3 mg and 6 mg doses, respectively.

2. There is high variability in the data, particularly for the parent drug.

3. The drug follows a non-linear PK with greater than proportional increase in both Cmax and AUC with the increase in dose from 3 to 6 mg. In this case, apparent clearance (i.e., CL/F) decreases with the increase in the dose. This suggests a saturation in the metabolic pathway. Thus, the drug follows a Michaelis-Menten kinetics that requires a careful patient titration to avoid toxicity, particularly in patients with renal and liver impairment. This is particularly important, given the high variability in the PK of the drug.

4. The most common AEs of this drug based on this single dose study are: GI tract disturbances, CNS disorders, and reduction in diastolic blood pressure.

COMMENTS TO LABELLING:

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

RECOMMENDATION:

Based on the information submitted to us, this NDA is ACCEPTABLE to the Office of Clinical Pharmacology and Biopharmaceutics. The oral solution at doses of 3 mg and 6 mg is equivalent to 3 mg and 6 mg IR capsules, respectively.

ClinPharm/Biopharm Briefing on: June 24, 1999.

Reviewed by: /S/ 9/9/

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).

APPEARS THIS WAY
ON ORIGINAL

Mean (±SD) pharmacokinetic parameters of rivastigmine following single oral administration

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

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

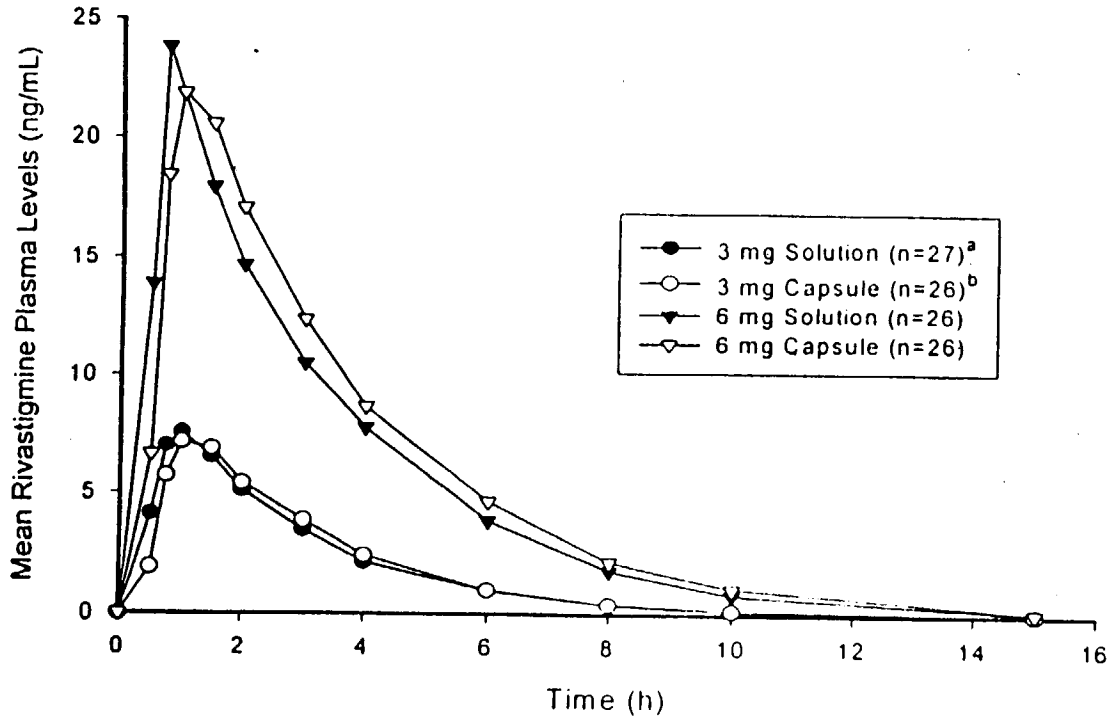
[a] For t_{max}, median values were provided instead of geometric mean and the significance level was obtained from the Wilcoxon signed rank test.

[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

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

Mean (±SD) pharmacokinetic parameters of NAP 226-90 following single oral administration

Parameter	Arithmetic mean±SD Coefficient of variation (CV%) (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 37.0	32.94±9.9 30.1	64.45±19.31 30.0	66.85±20.42 30.5
$AUC_{0-\infty}$ (ng.h/mL)	36.35±14.54 40.0	35.42±11.08 31.3	67.61±19.63 29.0	71.02±20.98 29.5
C_{max} (ng/mL)	6.16±1.76 28.6	6.21±1.57 25.3	10.98±3.37 30.7	10.49±3.47 33.0
t_{max} (h)	1.57±0.62 39.8	1.74±0.75 43.1	1.27±0.51 40.1	1.55±0.58 37.4
$t_{1/2}$ (h)	2.99±0.725 24.3	2.71±0.58 21.3	3.13±0.646 20.6	3.44±0.634 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

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.

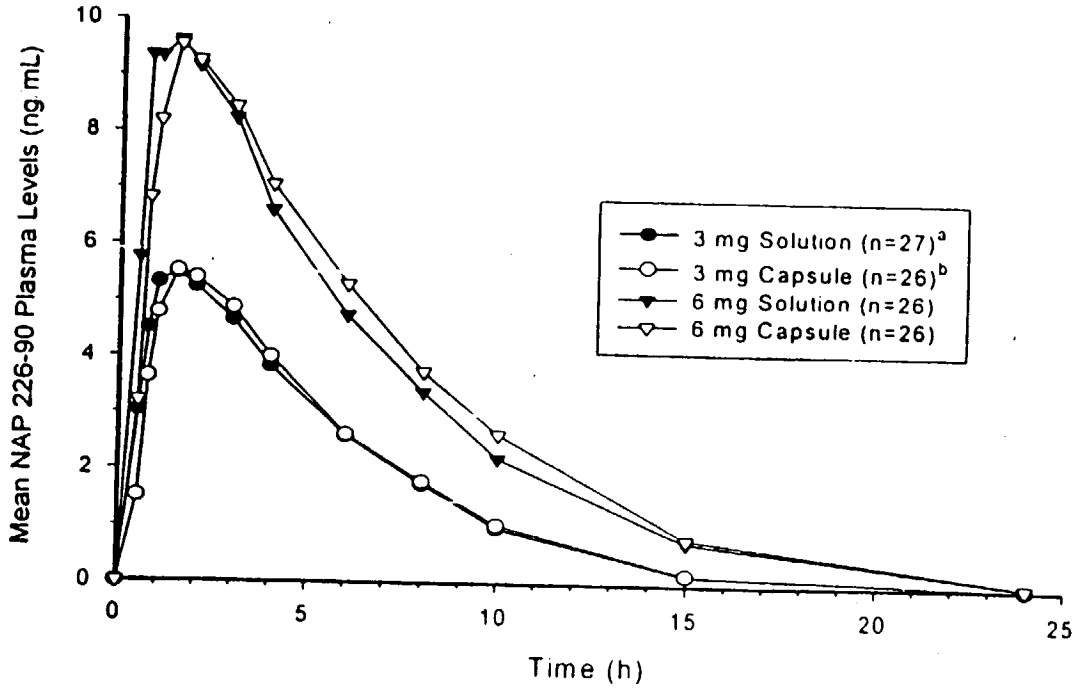
[b] Excluding Patient 1016 who did not have complete pharmacokinetic profile for both periods of the study.

* =statistically significant, $p \leq 0.05$.

Reference: Section 15; Post-text Tables 10.3.4-1.1 10.3.4-1.2 [illegible]

(6)

Mean plasma concentration-time profile of NAP 226-90 following single oral administration of 3 mg and 6 mg dose of solution and capsule



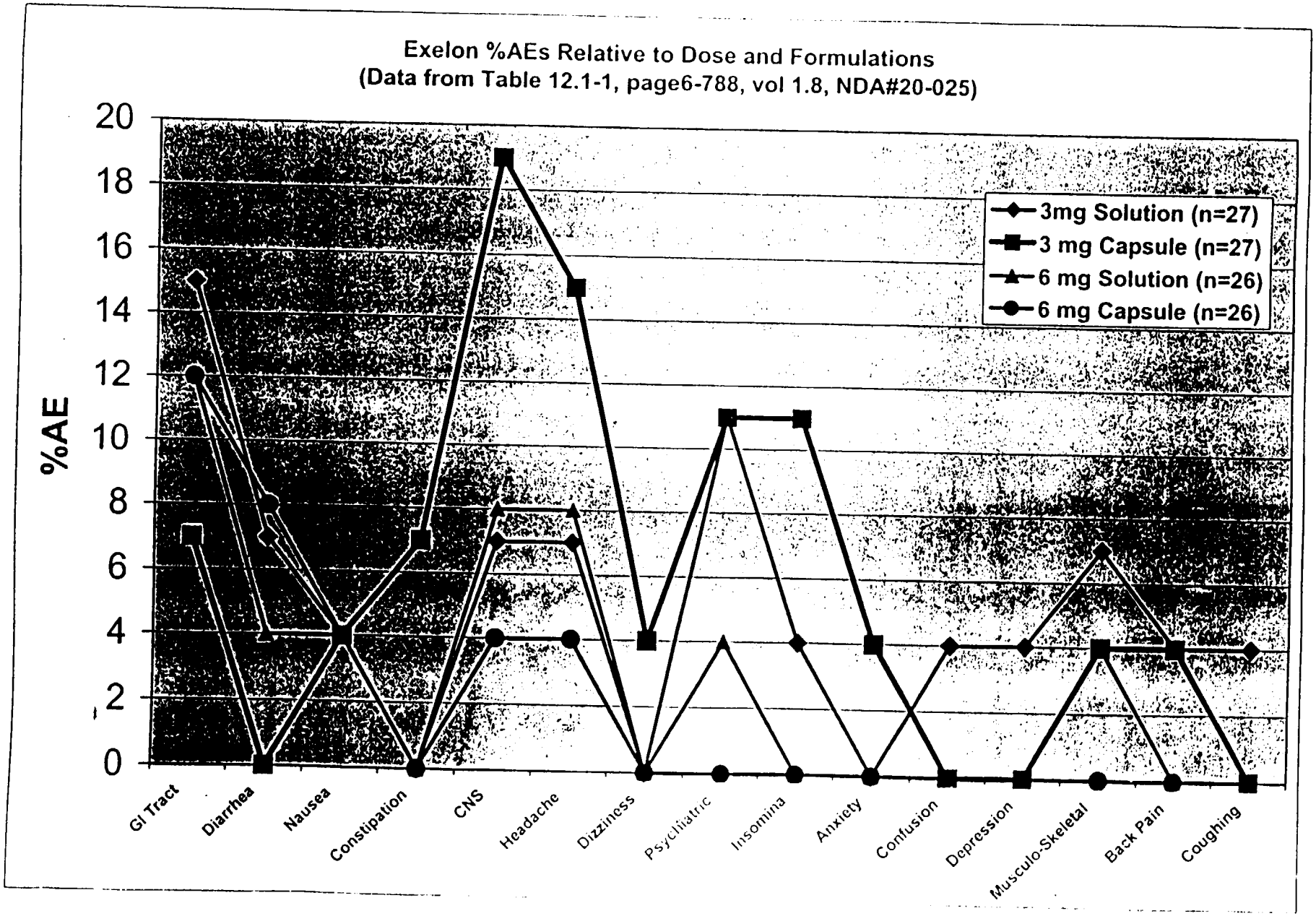
[a] Including patient 1016.

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

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 DISORDERS	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



C:s DAs/21025/AEs

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.

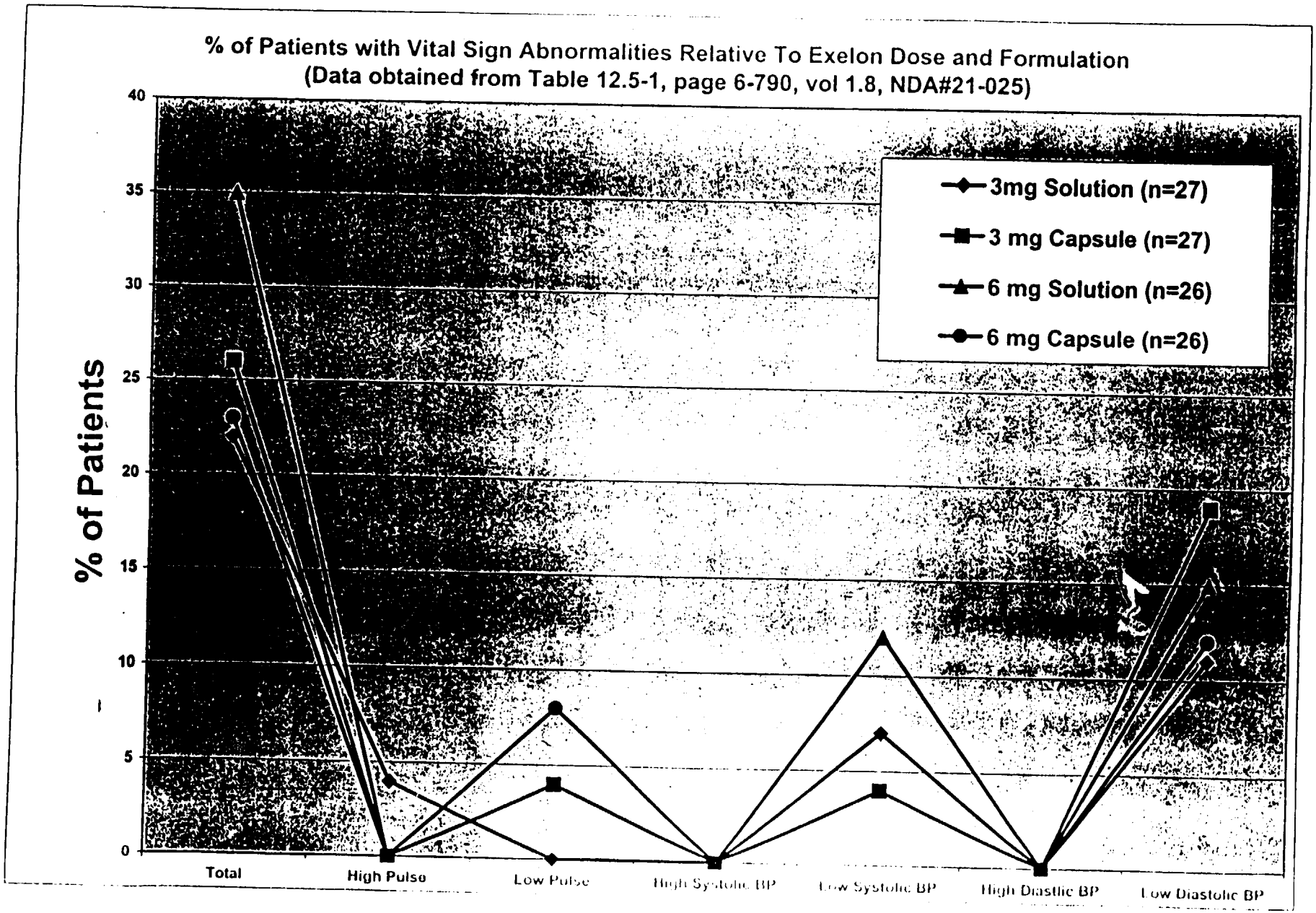
Reference: B153 Clinical Trial Report, Section 15, Post-text Table 12.5-2.

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.


% of Patients with Vital Sign Abnormalities Relative To Exelon Dose and Formulation
(Data obtained from Table 12.5-1, page 6-790, vol 1.8, NDA#21-025)
% of Patients
40
35
30
25
20
15
10
5
0
3mg Solution (n=27)
3 mg Capsule (n=27)
6 mg Solution (n=26)
6 mg Capsule (n=26)
Total
High Pulse
Low Pulse
High Systolic BP
Low Systolic BP
High Diastic BP
Low Diastolic BP

APPENDIX I

(OCPB Review of NDA# 20-823 For IR Capsules)

RECEIVED DEC 1 5 1997 DEC 1 5 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-823

Submission Dates: April 7,1997
July 11, 1997
August 27, 1997
October 29, 1997

Generic Name, Strength(s), and Formulation: **Rivastigmine Tartrate (ENA 713) — 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg (As Free Base), Immediate-Release, Hard-Gelatin Capsules for Oral Administration.**

Brand Name: **EXELON™**

Sponsor: Novartis Pharmaceuticals Co
East Hanover, NJ

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Original NDA

EXELON™ (rivastigmine tartrate, EN A 713) is an acetyl-cholinesterase inhibitor of the carbamate type. It is being proposed for the treatment of mild to moderately severe dementia associated with Alzheimer's disease.

The sponsor is proposing to market EXELON™ as ——. 1.5, 3.0, 4.5, and 6 mg (as free base) immediate-release, hard-gelatin capsules for oral administration.

The proposed starting dose is 1.5 mg b.i.d, with maintenance doses of 3-6 mg b.i.d, and the maximum dose of 6 mg b.i.d.

EXELON™ will be manufactured by Novartis Pharma AG, Basel, Switzerland.

COMMENTS:

(To the Medical Reviewer):

1. The effect of food on the absorption of ENA 713 was evaluated at lower doses (viz., 1 mg and 2.5 mg) in healthy subjects. Food delayed Tmax by 1.5 hours and decreased Cmax and increased AUC by 30 %. Due to nonlinear pharmacokinetics of ENA 713, this effect of food on drug absorption after 1 mg and 2.5 mg doses can not be extrapolated to the highest 6 mg dose. The effect of food may be more pronounced at doses higher than 2.5 mg.

2. The renal impairment study (No.W253) showed that moderately renally impaired patients had higher plasma concentrations of ENA 713 than normals in contrast to severely renally impaired patients who had plasma levels comparable to those in normals. There is no tangible explanation for this discrepancy and therefore, the results of this study are considered inconclusive.

(To be Sent to the Firm):

3. The proposed dissolution methodology and specification for all strengths of rivastigmine tartrate capsules ——— 1.5 mg, 3.0 mg, 4.5 mg, and 6 mg) as outlined below, are acceptable:

Apparatus:	USP Apparatus 2 (Rotating Paddle)
Speed of Rotation:	50 rpm
Medium:	500 mL of water at 37±0.5 °C
Specification:	——— dissolved in 30 minutes

4. The sponsor is requested to incorporate OCPB's pharmacokinetic labeling as outlined in Appendix A.

RECOMMENDATION:

The NDA # 20-823 submitted for EXELON™ capsules has been found to be acceptable provided that the sponsor incorporates OCPB's pharmacokinetic labeling as outlined in Appendix A. Please forward the above Recommendation and Comments 3 and 4 to the firm. Comments 1 and 2 are to the Medical Reviewer.

Table of Contents

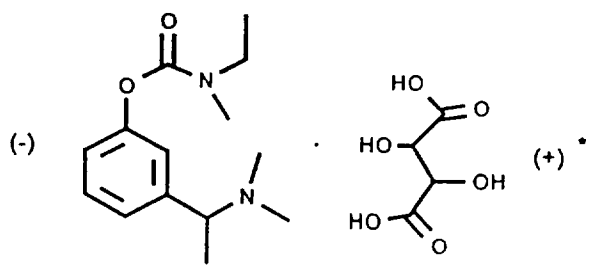
BACKGROUND

EXELON™ (rivastigmine tartrate, ENA 713) is an acetyl-cholinesterase inhibitor of the carbamate type.

PHYSICO-CHEMICAL PROPERTIES:

ENA 713 is a white to off-white, fine crystalline, hygroscopic powder. It is highly soluble in water (>1 g/mL). It has pKa value of 8.8. The partition coefficient in n-octanol/phosphate buffer solution, pH 7 is 3.0.

STRUCTURAL FORMULA:



* The optical rotation of the base is (-); the optical rotation of the (+) hta salt is (+)

CHEMICAL FORMULA:

ENA 713 is chemically known as (S)-N-ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Conversion of the chiral center of the molecule under *in vivo* conditions is unlikely. It has an empirical formula of $C_{14}H_{22}N_2O_2 \bullet C_4H_6O_6$ and a molecular weight of 400 (hydrogen tartrate salt) and 250 (free base).

INDICATION AND USAGE:

EXELON™ is being proposed for the treatment of mild to moderately severe dementia associated with Alzheimer's disease.

HOW IT IS SUPPLIED:

EXELON™ will be supplied as hard-gelatin capsules containing rivastigmine tartrate, equivalent to ——— 1.5, 3.0, 4.5, and 6 mg of rivastigmine base for oral administration.

PROPOSED DOSAGE AND ADMINISTRATION (FIRM'S):

The recommended starting dose of EXELON™ is 1.5 mg BID. After a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and then to 6 mg BID are to be based on tolerability to the current dose. The maximum dose is 6 mg BID (12 mg/day).

MANUFACTURER AND MANUFACTURING SITE:

EXELON™ will be manufactured by Novartis Pharma AG, Basel, Switzerland.

SUMMARY OF BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics (PKs) of ENA 713 were determined in young and elderly volunteers up to single 3 mg and 2.5 mg oral doses, respectively, because of lack of tolerability to the higher doses of the drug. In Alzheimer's patients, PKs of ENA 713 were determined up to 6 mg b.i.d with titration.

ABSORPTION/BIOAVAILABILITY

Absorption: Based on the results from mass balance study in healthy volunteers (n=6, dose=1 mg or 2.5 mg), ENA 713 is rapidly (Tmax =1 hour) and completely (97 % radioactivity recovered in urine) absorbed (Study No. B151).

Absolute Bioavailability: Mean±SD absolute bioavailability of ENA 713 is 35.5±13 % following single 3 mg oral and 1 mg intravenous doses to 12 healthy subjects (Study No. W361).

Relative Bioavailability: Mean±SD relative bioavailability (F_{rel}) of ENA 713 from capsule compared to an oral solution in nine Alzheimer's patients is 125±49 % after a single 3 mg dose and 104±21 % after a single 6 mg dose. However, dropping one patient with a F_{rel} value of 242 % brings the mean to 109±23 % following the 3 mg dose (Studies No. B353). Relative bioavailability was also determined after a single 3 mg dose in 10 healthy volunteers (Study No. W251) and averaged 105±14 %.

BIOEQUIVALENCE

No bioequivalence studies were required to be conducted since the final to-be-marketed capsules (—— 1.5, 3.0, 4.5, and 6 mg) were identical in composition to those used in the clinical trials.

FOOD EFFECT

In a single-dose, 4-way crossover study (Study No. W101) involving two separate doses, 1.0 mg and 2.5 mg given under fed and fasting conditions (n=24 healthy subjects), food was found to decrease the rate of absorption of END 713. Food delayed mean time to Cmax (Tmax) by 1.5 hours, lowered mean Cmax by 30 % and increased mean area under

plasma concentration/time curve ($AUC_{0-\infty}$) by 30 %. The effect of food has not been studied following the highest recommended dose (i.e. 6 mg), however, in clinical trials patients were instructed to take the drug with food if tolerability (especially nausea, vomiting, and diarrhea) was a problem.

DISTRIBUTION

In Vivo: ENA 713 is widely distributed throughout the body with a mean apparent volume of distribution of 5.1±2.8 L/kg (416 L) in 10 healthy subjects following a single 3 mg oral dose (Study No. W251). ENA 713 penetrates the blood brain barrier reaching CSF peak concentrations in 1-4 hours. Mean AUC_{0-12hr} ratio of CSF/plasma averaged 40±0.5 % following 1-6 mg b.i.d. doses in patients (Study No. W252).

In Vitro: ENA 713 is about 40 % bound to human plasma proteins at concentrations ranging from 1-400 ng/mL which covers the therapeutic concentration range of the drug. ENA 713 distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

METABOLISM

An *in vitro* study (Study No. 303-302) of ENA 713 with human liver, small intestine, and plasma revealed that ENA 713 is extensively metabolized in liver (1.15 μmol/kg), small intestine (0.26 μmol/kg), and to lesser extent in plasma (0.006 μmol/kg). The major pathway of biotransformation is the direct cholinesterase-mediated decarbamylation of ENA 713 to the phenolic metabolite, ZNS 114-666 (See Figure 1). Results also indicate that saturable first-pass metabolism exists with ZNS 114-666 formation being 80 % and 60 % at 10 μM and 50 μM incubations, respectively. ZNS 114-666 is subsequently conjugated with sulfate or, to lesser extent, N-demethylated followed by conjugation with sulfate. Cytochrome P450 system plays a minimal role in the metabolism of ENA 713. The exposure to ZNS 114-666 (as measured by AUC) is about 7-fold higher than that to parent drug (Study No. B151). However, the pharmacological activity of ZNS 114-666 is unknown.

ELIMINATION

Mass-Balance: Following single 1 mg and 2.5 mg oral doses of ^{14}C-ENA 713 to healthy male volunteers (n=6/dose), excretion appears to be exclusively via the renal pathway. Total radioactivity recovered is 97 % in urine and 0.4 % in feces over 120 hours. No parent drug is detected in urine, indicating that ENA 713 is completely metabolized before being excreted. At both dose levels, the sulfate metabolite is the major component excreted in urine and represents about 40 % of a dose. ZNS 114-666 represents 1 % of dose following the 1 mg dose and 7% of dose following the 2.5 mg dose (Study No. B151).

Clearance and Half-life: Mean oral clearance is 3.5±1.4 L/min following 1 mg b.i.d dosing (n=3 patients) and 1.8±0.6 L/min following 6 mg b.i.d dosing (n=3 patients) (Study No. W252). ENA 713 is rapidly eliminated with a mean elimination half-life ($t_{1/2}$) of 1.6±0.1 hours at 6 mg b.i.d in patients (n=3). The half-life ($t_{1/2}$) remained relatively constant across doses and ranged from 1-2.5 hours (Study No. W252).

DOSE-PROPORTIONALITY

In patients with Alzheimer's disease (n=3/dose), ENA 713 exhibits linear kinetics over the dosing range of 1mg to 3 mg b.i.d. At higher doses of 3-6 mg b.i.d, ENA 713 tends to display nonlinear kinetics; doubling the dose from 3 to 6 mg b.i.d resulted in 4-fold increase in $AUC_{0\text{-}12hr}$ (Study No. W252).

Population PK analysis (Studies No. B351 and B352) revealed that ENA 713 displays nonlinear kinetics over the doses of 1.5 mg to 6 mg b.i.d. In medium size (70 kg, 175 cm), nonsmoking male patients with severe Alzheimer's disease, AUC and Cmax increased 10-fold as dose increased 4-fold (1.5 mg to 6 mg).

Nonlinearity is more pronounced in young volunteers (n=24), elderly volunteers (n=24), hepatically impaired patients (n=10), and renally impaired patients (n=16) compared to patients with Alzheimer's disease. In young and elderly volunteers, AUC_{0-} increased 5-fold when dose increased from 1 mg to 2.5 mg (Study No. W101). In hepatically and renally impaired patients, AUC_{0-} increased 9-fold as dose increased from 1 mg to 3 mg (Studies No. W251 and W253, respectively). This nonlinearity may be attributed to saturable esterase metabolism in liver and small intestine.

MULTIPLE-DOSE

ENA 713 has a short half-life ($t_{1/2}$ ~ 2 hours) and its steady state plasma levels are expected to reach within 1 day of dosing. Accumulation of the drug is not expected upon b.i.d dosing.

SPECIAL POPULATIONS

AGE: Following a single 2.5 mg oral dose to elderly volunteers (> 60 years of age, n= 24) and younger volunteers (n=24), mean oral clearance of ENA 713 was 7 L/min and 10 L/min, respectively (Study No. W101). Elderly subjects have a 30 % lower clearance than younger subjects. No dosage adjustment is necessary in elderly patients, since the dose of the drug is individually titrated to tolerability, and further, safety and efficacy studies have been conducted in elderly population. In addition, population PK analysis (Studies No. B351 and B352) showed that age has no effect on the oral clearance of ENA 713 (n=625 patients, age =50-92 years).

GENDER AND RACE: No formal PK study has been conducted to examine the effect of gender or race on the pharmacokinetics of ENA 713. However, population PK analysis indicated that gender (n=277 males and 348 females) and race (n=575 Caucasians, 34 Blacks, 4 Orientals, 12 Others) has no effect on the oral clearance of ENA 713.

NICOTINE USE: Population PK analysis showed that nicotine use increases the oral clearance of ENA 713 by 23 % (n=75 Smokers and 549 Nonsmokers).

HEPATIC DISEASE: Following a single 3 mg dose (Study No. W251), mean oral clearance of ENA 713 is 60 % lower in hepatically impaired patients (n=10, biopsy-proven liver cirrhosis) than in healthy subjects (n=10); 1.2 L/min vs 3.1 L/min. Variability (cv) in clearance was high (cv=50-70 %). The half-life of ENA 713 was similar in hepatically impaired patients and healthy volunteers. Accumulation upon twice a day dosing is not expected in hepatically impaired patients. Dosage adjustment is not necessary in hepatically impaired patients as the dose of the drug is individually titrated to tolerability.

RENAL DISEASE: Following a single 3 mg dose (Study No. W253), mean oral clearance of ENA 713 is 64 % lower in moderately impaired renal patients (n=8, GFR=10 - 50 mL/min*) than in healthy subjects (n=10, GFR≥60 mL/min); CL/F=1.7 L/min (cv=

45 %) and 4.8 L/min (cv=80 %), respectively. In severely impaired renal patients (n=8, GFR < 10 mL/min), oral clearance values were within the normal values. Two subjects in severe group (#4 and #8) with GFR values of 0.0 mL/min were found to have very low clearance values, 0.77 L/min and 0.96 L/min, respectively; which is about 80 % lower than in normal subjects (4.8 L/min). Mean oral clearance in the severe group is about 35 % higher than in the healthy group, CL/F = 6.5 L/min (cv=89%) and 4.8 L/min (cv=80 %), respectively. [*GFR was determined by ^{99m}TC-DTPA]

In this study, it is noted that two subjects (#5 and #6) with GFR values of 11.7 and 11.5 mL/min were included in the severe group, which according to the definition in the protocol should be considered and analyzed in the moderate group. At the reviewer's request (October 3, 1997), the sponsor reanalyzed the data after removing these two subjects from the severe group and placing them in the moderate group. Similar results were obtained, that is:

Mean oral clearance of ENA 713 is 54 % lower in moderately impaired renal patients (n=12, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR ≥ 60 mL/min); CL/F = 2.2 L/min (cv= 64 %) and 4.8 L/min (cv=80 %), respectively. Mean oral clearance in the severely impaired renal patients (n=8, GFR < 10 mL/min) is 6.9 L/min (cv=90%), which about 43 % higher than in healthy subjects (n=10, GFR ≥ 60 mL/min); CL/F = 6.9 L/min (cv=90 %) and 4.8 L/min (cv=80 %), respectively.

The moderate renal group had a decreased clearance and an increased Cmax while the severe group had virtually no change. At the reviewer request (Submission dated October 28, 1997), the sponsor provided an explanation, suggesting large intersubject variability and relatively small number of patients studied may be responsible for this discrepancy. The study results are inconclusive due to this discrepancy.

No obvious correlations were observed between GFR and any of the PK parameters of the drug. Dosage adjustment may not be necessary in renally impaired patients as the dose of ENA 713 is individually titrated to tolerability.

ALZHEIMER'S DISEASE: A cross-study comparison (Studies No. B353 and W251) showed that patients with Alzheimer's disease clear ENA 713 slower than healthy subjects. Following a single 3 mg dose, mean CL/F is 2.2±1.0 L/min in patients (n=9) and 3.1± 1.9 L/min in healthy subjects (n=10) (about 30 % lower). Mean Half-life is 2.1± 1.1 hours in patients and 1.6±0.7 hours in healthy subjects (about 30 % longer in patients). Mean apparent volume of distribution is comparable; 382±205 L and 416±

257 L in patients and healthy subjects, respectively. Dose-nonlinearity is less pronounced in patients than in healthy subjects (see DOSE PROPORTIONALITY).

Population PK analysis showed that oral clearance values in patients with moderate (n=335) and severe (n=14) Alzheimer's disease decreased by 13 % and 30 %, respectively, compared to the basic mean population clearance estimate value (i.e. with no covariates). Mean (SE) population clearance estimate value is 0.51 (0.09) L/min.

OTHER DISEASES:

Population PK analysis with a data base of 625 patients indicated that arthritis (n=186), diabetes mellitus (n=36), dyspepsia (n=46), hypertension (n=201), neoplasms (n=2) have no effect on the oral clearance of ENA 713.

DRUG INTERACTIONS

In Vitro Interaction Studies (Study No. 303-343): *In vitro* enzymatic studies revealed that:

(a) ENA 713 had no inhibitory effect on substrates of cytochrome P450 for the major isoenzymes such as CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. ENA 713 is therefore unlikely to influence the metabolism of the majority of drugs which are metabolized by cytochrome P450 system.

(b) Potentially coadministered drugs, such as haloperidol, fluoxetine, thioridazine, amitriptyline, nortriptyline, and diazepam, as well as the enantiomers of the phenyl metabolite of ENA 713, ZNS 114-666, have no effect on ENA 713 decarbamylation, the major pathway of drug biotransformation.

(c) Drugs that inhibit butyrylcholinesterase, such as thioridazine, amitriptyline, and nortriptyline, have no effect on ENA 713 decarbamylation in human liver.

In Vivo Interaction Studies:

Digoxin: Coadministration of ENA 713 (3 mg single dose) with digoxin (1 mg loading dose and 0.25 mg QD) did not alter the steady-state pharmacokinetics of digoxin in 12 healthy subjects (Study No. W361). The combination of ENA 713+digoxin was not different from placebo+digoxin in the pharmacodynamic variables (viz., heart rate, PR intervals, systolic and diastolic pressure, and pulse rate). Digoxin also did not alter the

pharmacokinetics of ENA 713.

Warfarin: Concomitant administration of ENA 713 (3 mg single dose) with warfarin (30 mg single dose) did not alter the pharmacokinetics of racemic warfarin or its enantiomers in 12 healthy subjects (Study No. W362). Coadministration of ENA 713 did not alter the prothrombin complex activity of warfarin. Mean change from baseline in the prothrombin complex activity of warfarin was 38.5±9.8 % after warfarin+ENA 713 administration and 41.25±9.6 % after warfarin alone administration. Warfarin also did not alter the pharmacokinetics of ENA 713.

Diazepam: A single 3 mg dose of ENA 713 administered in combination with 2 mg diazepam did not have any effect on the pharmacokinetics of either diazepam or its metabolite, nordiazepam in 12 healthy subjects (Study No. W363). Diazepam also did not alter the pharmacokinetics of ENA 713.

Fluoxetine: Administration of a single 3 mg dose of ENA 713 did not alter the pharmacokinetics of either fluoxetine or its metabolite, norfluoxetine (40 mg single-dose fluoxetine) in 12 healthy subjects (Study No. W365). Fluoxetine also did not alter the pharmacokinetics of ENA 713.

In addition, population PK analysis with a data base of 625 patients showed that the pharmacokinetics of ENA 713 were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), non-steroidal anti-inflammatory drugs (n=79), estrogens (n=70), analgesics (n=177), antianginals (n=35), benzodiazepines (n=2), and antihistamines (n=15).

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONSHIP

Study No. W252:

ENA 713 inhibits the **AChE** and **BChE** activities in **CSF** over the dosing range of 1-6 mg b.i.d (n=3 patients/dose). Inhibition was observed within 1 hour and was maintained over the 12-hour dosing interval. Mean maximum inhibition ranged from 20 % at 1 mg b.i.d to 60 % at 6 mg b.i.d (n=3 patients/dose). Inhibition of **BChE** activity in **plasma** is lower than that in **CSF**; mean maximum decrease in BChE activity ranged from 7 % at 1 mg b.i.d to 35 % at 6 mg b.i.d (n=3 patients/dose).

$AUC_{0\text{-}12hr}$ of **AChE** activity in **CSF** is linearly correlated with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **plasma** ($p < 0.0001$, n=3) and with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **CSF** ($p < 0.0001$, n=3). $AUC_{0\text{-}12hr}$ of **BChE** activity in **plasma** is linearly correlated with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **plasma** (p=0.0018, n=3) and with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **CSF** (p=0.027, n=3).

Cmax of **AChE** activity in **CSF** is linearly correlated with Cmax of ZNS 114-666 in **plasma** (p=0.0104, n=3). **Cmax of BChE activity in plasma is linearly correlated with** Cmax of ZNS 114-666 in **plasma** (p=0.0078, n=3).

Studies No. B351 and B352:

Linear regression analysis (n=625) of relationships between efficacy measures (viz., ADAS, CIBIC, and PDS) and exposure at Weeks 12, 18, and 26 showed that a significant relationship exists between ADAS at Week 12 and dose-normalized $AUC_{0\text{-}12h}$ and Cmax of ZNS 114-666 ($p > 0.05$). However, significant relationship was not shown when the $AUC_{0\text{-}12h}$ and Cmax were not dose-normalized; which is a more relevant analysis. No significant relationships between efficacy measures and exposure to drug or its metabolite was found at Weeks 18 and 26.

Logistic regression analysis (n=625) showed that a significant relationship between ZNS 114-666 exposure and the incidence of gastrointestinal adverse events ($p > 0.05$). During the titration phase, the incidence of anorexia and diarrhea were significantly and directly related to ZNS 114-666 $AUC_{0\text{-}12h}$ and Cmax, while nausea and vomiting were directly related Cmax of ZNS 114-666. During the maintenance phase, anorexia, diarrhea, and nausea did not change, while vomiting was directly related to $AUC_{0\text{-}12h}$ and Cmax of ZNS 114-666. Clinically notable weight loss of more than 7 % after Day 84 was associated with the $AUC_{0\text{-}12h}$ and Cmax of ZNS 114-666 during the maintenance phase but not during the titration phase. The significant PK/PD relationship with ZNS 114-666 indicates that this metabolite may be a better surrogate for the exposure of the parent drug.

FORMULATION

The sponsor is proposing to market --

IN VITRO DISSOLUTION

ENA 713 is a highly soluble drug. Its permeability is not known. Dissolution of the drug substance is independent of pH over the physiological pH range of 1-7. Water was selected as a dissolution medium for ENA 713 capsules. Dissolution testing was performed using the USP Apparatus 2 (rotating paddle) at a speed of 50 rpm in 500 mL of water at 37± 0.5 °C. Dissolution data (mean, % RSD, and range) were submitted for the to-be-marketed as well as stability capsules.

Dissolution of rivastigmine tartrate in water was fast; mean % dissolved was more than —— in 30 minutes (See also **APPENDIX III**). However, some individual capsules, especially those of stability batches showed dissolution rate as low as ——— in 30 minutes. The sponsor proposes a specification of —— dissolved in 30 minutes.

The Agency agrees on the firm's dissolution methodology and specification for <u>all</u> strengths of rivastigmine tartrate capsules (——, 1.5 mg, 3.0 mg, 4.5 mg, and 6 mg) as outlined below:

<u>Apparatus:</u>	USP Apparatus 2 (Rotating Paddle)
<u>Speed of Rotation:</u>	50 rpm
<u>Medium:</u>	500 mL of water at 37±0.5 °C
<u>Specification:</u>	— dissolved in 30 minutes

ANALYTICAL METHODOLOGY

In the studies submitted, the sponsor utilized a ——— method to measure plasma concentrations of ENA 713. The method is adequately validated. Details of the method are shown in **APPENDIX IV**.

/S/ 1997

Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on: November 26, 1997 (Attendees: Drs.: Malinowski, Chen, Lazor, Mehta, Baweja, Miller, Sahajwalla, Ibrahim, Tammara, Levin, Fitzgerald, Rosloff)

RD/FT initialed by C. Sahajwalla, Ph.D /S/ 12/15/97

cc: NDA # 20-823 (Orig.), HFD-120, HFD-860 (Ibrahim, Sahajwalla, Malinowski), HFD-19 (FOI), and Drug files (Barbara Murphy, CDR).

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 4

❖❖❖

Draft Labeling
(not releasable

APPENDIX II

(Review of Study #B153, BE of Oral Solution and IR Capsule)

Study # B153 (BE, single doses of 3 and 6 mg, oral solution vs capsules in patients with AD)

Study Design:

See attachments 2,3 and 5-8)

Results

See attachments 9-40

Reviewer's Comments:

1. This was a pivotal study to determine the bioequivalence of oral Exelon solution (2mg/ml) to Exelon capsules at single doses of 3 and 6 mg in 60 patients with probable Alzheimer's disease (n=27 for 3 mg and n=26 for 6 mg). The selected patients were already on either 3 or 6 mg doses of Exelon during the clinical trials. Treatments were stopped 3 days (i.e., Day -3) prior to the bioequivalance study and restarted on Day 5 after the study was completed. Each patient was titrated back to the original dose of the given clinical trial.

2. The results show that the oral solution is bioequivalent at both doses to the capsule for both the parent and the metabolite, NAP 226-90 (**Attachments 15,16,24,25**). At the 3 mg dose, the 90% CI for the parent $AUC_{0-\infty}$ was 94-109% and for Cmax was 86-106% and for the metabolite was 95-106% for $AUC_{0-\infty}$ and for Cmax was 93-105%. At the 6 mg dose, the 90% CI for the parent $AUC_{0-\infty}$ was 87-100% and for Cmax was 87-110% and for the metabolite was 92-99% for $AUC_{0-\infty}$ and for Cmax was 97-114%. The individual relative bioavailability data are shown in **Attachments 34-38.**

3. There was no difference in the Tmax for either the parent drug or the metabolite among the four treatments. Overall, the Tmax for the parent drug is about 1 h and for the metabolite is about 1.5 h.

4. It should be noted that this is a highly variable drug. The %CV for Cmax, AUC and CL/F of the parent drug between subjects ranged from 46% to 115% (Attachment 11). For example, at 3 mg dose solution, the Cmax ranged form 0.73-24 ng/ml and the AUC_{0-t} ranged form 1 to 85 ng.h/ml (Attachment 11). As expected from the assay limitations, the variability was higher at the 3 mg dose than the 6 mg dose. This was consistent between formulations. Furthermore, it is noted that this variability was lower for the metabolite, NAP 226-90, with a %CV of about 30% (Attachment 12). The individual plots are shown in Attachments 26-29 for the parent compound and in Attachment 30-33 for the metabolites. In addition, the individual data for the PK parameters for the parent compound and the metabolites are shown in Attachments 34-38 for both doses.

5. One important note is that the drug follows non-linear PK. There was a greater than proportional increase in both the Cmax and AUC of the parent compound by doubling the

dose from 3 mg to 6 mg (Attachment 11). The Cmax and $AUC_{0-\infty}$ of the parent compound increased by about 3 folds as the dose increased from 3 to 6 mg (Attachment 11). By contrast, the metabolites appear to follow a linear PK (Attachment 12). The Cmax and $AUC_{0-\infty}$ were almost doubled as the dose increased from 3 to 6 mg (Cmax from 6 to 11 ng/ml and $AUC_{0-\infty}$ from 36 to 68 ng.h/ml).

From the available data, it appears that the drug follows Michaelis-Menten kinetics. This suggests that there is a saturation in the metabolic process. Therefore, to avoid toxicity, the drug must be carefully titrated, particularly in patients with renal and liver impairment.

6. In terms of safety, in this particular single dose study, there were a number of expected adverse events (AEs) related to this particular class of drug. The most common AEs are those related to GI tract and CNS. Some of the AEs data shown in Attachment 18 were re-analyzed and plotted as shown in Attachment 39. It is interesting to note from this plot that the % of patients with AEs appears to be greater at 3 mg dose given as capsule compared to all other treatments. The most significant AEs are those associated with CNS. In addition, a careful examination of the data in Attachments 18 and 39 shows that the % of patients with AEs at the 3 mg dose given as solution appears to be higher than after the 6 mg dose when given as either solution or capsules. Similarly, our analysis of the data for vital signs (Attachments 20 and 21) shows that the % of patients with low diastolic blood pressure was greater after the 3 mg dose given as capsules than after other treatments (Attachment 40).

Conclusions:

1. The two formulations are bioequivalent.

2. There is high variability in the data, particularly for the parent drug.

3. The drug follows a non-linear PK with greater than proportional increase in both Cmax and AUC with the increase in dose from 3 to 6 mg. In this case, apparent clearance (i.e., CL/F) decreases with the increase in the dose. This suggests a saturation in the metabolic pathway. Thus, the drug follows Michaelis-Menten kinetics that requires careful patient titration to avoid toxicity, particularly in patients with renal and liver impairment. This is particularly important, given the high variability in the PK of the drug.

4. The most common AEs of this drug based on this single dose study are: GI tract disturbances, CNS disorders, and reduction in diastolic blood pressure.

THE FOLLOWING PAGES,
ALTHOUGH RENUMBERED SEQUENTIALLY,
ARE REFERENCED BY THE
REVIEWER FROM THE SPONSOR'S
STUDY REPORT.

(THERE ARE NO PAGES MISSING)