

Aricept deaths on paper

Patient#	Plausibility	Sudden	Comments
	I	N	Deterioration in clinical course med d/c'd, died >30d after last dose
X	I	N	CVA with hx afib, htn, died 20 after event, can't tell when last dose was given
X	NI	N	Admitted for anemia, hypotension, ?GI bleed, ?sepsis (UTI)
X	I	N	Died from complications of injuries sustained while a passenger in an MVA
X	NI	N	Gangrene of lower extremities, ill-described heart disease
X	NI	N	Dx with pneumonia that was not treated per pt wishes
X	I	N	Death more than 7d after last dose
X	I	N	Off drug for 23d prior to death, dehydration/pneumonia
X	I	N	Metastatic prostate cancer
X	NI	N	CHF/arrest, prior day had fever and diarrhea
X	NI	N	Anterolateral MI, made comfort care
X	NI	N	Cyanosis, dyspnea, lethargy, then death, no autopsy
X	I	N	Death attributed to acute lymphoma
X	NI	N	?CVA not documented, no autopsy
X	I	N	Choked, developed respiratory, heart failure
X	I	N	Off drug 11d, developed dyspnea ?renal failure died 33d after last dose
X	NI	N	Stopped drug for weight loss/anorexia, progressed off drug, died 12d after last dose
X	NI	Y	Sudden death, no autopsy
X	NI	N	Developed pneumonia, decided not to treat
X	NI	Y	Found dead
X	NI	N	Sx are suggestive of MI but no supporting documentation
X	I	N	Admitted for resp fail, MI, renal failure, died in ICU
X	NI	Y	Found unresponsive and failed resuscitative attempts
X	NI	N	Condition deteriorated, developed pneumonia while hospitalized
X	NI	Y	Found dead in bed

Review and Evaluation of Clinical Data

NDA (Serial Number)	20823
Sponsor:	Novartis
Drug:	Exelon®
Proposed Indication:	Alzheimer's disease
Material Submitted:	Response to Agency Letter
Correspondence Date:	3/11/99
Date Received / Agency:	3/11/99
Date Review Completed	4/29/99
Reviewer:	Ranjit B. Mani, M.D.

1. Background

Exelon® (rivastigmine tartrate) is a cholinesterase inhibitor which has been developed by this sponsor for the treatment of Alzheimer's disease under

In the draft labeling originally submitted with this NDA the sponsor proposed that the drug be used, in capsule form, in a dose of 1.5 to 6 mg twice daily, with 1.5 mg twice daily being the starting dose, and with subsequent titration to higher doses to be based upon tolerability.

This NDA was originally submitted on 4/7/97; 19 submissions in connection with the same application were subsequently received, the last on 5/26/98. The Efficacy Review of this NDA was performed by Randy Levin, M.D. The Safety Review of this NDA was carried out primarily by Armando Oliva, M.D., who was assisted by Greg Burkhart, M.D., Judith Racoosin, M.D., and John Feeney, M.D. Dr Burkhart and Dr Racoosin were primarily involved in the assessment of mortality data. Based on these and additional supervisory memoranda, a "not-approvable" letter was issued by Robert Temple, M.D., Office Director, on 7/7/98 on the grounds that the application "fails to provide reports of all tests reasonably applicable to show that the drug will be safe for use under the conditions for use recommended". Please refer to the individual reports, memoranda and "not-approvable" letter for full details.

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The Division's concern that therapeutically effective doses of Exelon® might be associated with a higher mortality rate was based upon the following:

- A several-fold increase in mortality rate (deaths per 1000 patient-years of exposure) among drug-treated patients as compared with those treated with placebo, in Phase 3 randomized, controlled trials; this observation was,

however, based upon a small number of deaths, and the exposure to Exelon® in such trials represented only a small part of the total exposure to that drug in the entire database

- A nested case-control study, performed by the Division's epidemiologists, that used both the randomized controlled trials and their extensions, and which indicated an increasing mortality rate with increasing dose, regardless of whether that was the last prescribed dose, or the last prescribed dose adjusted for body weight at baseline
- A several-fold higher mortality rate for the extension experience of patients randomized to placebo in the preceding randomized controlled trials, as compared with those randomized to Exelon®
- An increasing mortality rate with increasing dose in the extension experience of patients who received Exelon® during the preceding randomized controlled trials

The "not-approvable" letter did however also point out the following:

- In regard to mortality, there was no suggestion of a dose-response in either the randomized controlled trials or in the open-label titration studies
- Many aspects of the methodology used to examine the data were matters of judgment and except when focussed on the randomized controlled trials all analyses were post-hoc and exploratory in nature: these analyses thus had their limitations

The "not-approvable" letter suggested that, as a means of resolving the above concerns, the following might be helpful

- A nested case-control study of all deaths in the Phase 3 experience examining the role of potential patient characteristics that could be associated with an increased risk of death e.g., weight loss, severity of dementia, co-morbid disease and concomitant drug use
- Considering the cause of death, with decisions as to whether the death was drug-related or not being made by reviewers blinded to dose and treatment assignment. Separate analyses could then be carried out on deaths felt to be drug-related and those not felt to be drug-related
- Confining the analyses to deaths occurring within 7 days of drug exposure, unless death resulted from a condition present at 7 days

The "not-approvable" letter did indicate that, based upon review of the NDA, there was more than one adequate and well-controlled study that established that Exelon® was effective for the symptomatic treatment of mild-to-moderately severe dementia of the Alzheimer's type. Therefore, the letter stated, Exelon® could be approved for marketing, if it could be shown that the apparent increase in risk of death from Exelon® was due to factors other than the drug, or if alternative analyses that were persuasive did not show a dose-related risk for death from Exelon® use.

The Division's review team has attempted to explain the apparently increased mortality ~~rate~~ seen with Exelon®. In his NDA Safety Review completed on 3/10/98, Dr Armando Oliva did observe that Exelon® use was associated with weight loss in Phase 3 trials. He then carried out a further analysis, which he summarized in a review completed 5/28/98, to determine if mortality and weight loss in patients receiving Exelon® were linked. From the latter analysis he concluded that those who received Exelon® in a last prescribed dose > 9 mg daily and died, had the greatest percentage weight loss, in comparison with those received the same dose and did not die, and those who received doses ≤ 9 mg daily.

In his review of the efficacy data submitted with this NDA, Dr Randy Levin has concluded that the effective dose of Exelon® for the treatment of mild-to-moderate dementia of the Alzheimer's type may be > 9 mg daily

A "response to not-approvable action" was submitted by the sponsor on 11/11/98 and has been reviewed separately by me on 3/8/99; please see that review for full details. The main points conveyed by the sponsor in that analysis were as follows:

- Based on a nested case-control analysis of all deaths in the Exelon® database, and using all possible controls the relative risk of death was 0.8 for > 9 mg/day vs 1-4 mg/day dose categories, using a model that included specific covariates considered predictive of mortality, and all deaths that occurred within 30 days of last dose
- Analyses based on deaths that occurred within the 7-day cut-off period, as opposed to a 30-day cut-off period, are unrepresentative of time of death in the Exelon® database.
- Analyses based on deaths that were plausibly drug-related are flawed, given the lack of inter-rater reliability in selecting those deaths (the sponsor had 2 raters, _____ evaluate these deaths)

2. Contents of Agency Letter of 2/26/99 and Related Discussions

In internal discussions and at a meeting with the sponsor held on 2/19/99, the Division's staff, principally Dr G. Burkhart, drew attention to the following

- In the Phase 3 Exelon® database, about 55 % of the total exposure to the drug (in person-years) has been in the extensions to the randomized controlled trials; further about 77 % of the total exposure to the 10 -12 mg dose of Exelon® (in person-years) has been in the extensions to the randomized controlled trials. In contrast, only about 12 % of the total exposure to the drug (in person-years) has been in the titration studies, of which 31 % has been at the 10 – 12 mg dose.

- The sponsor's argument that focussing on deaths that occurred within 7 days of last drug use is arbitrary and that deaths that occurred within 30 days of last drug exposure is more appropriate for analysis may not be a valid one: the distribution of the 35 deaths that occurred within 30 days of last drug use during extension studies of metrifonate is as follows:
 - 7 while still taking drug
 - 7 at 1 day
 - 5 at 2-7 days
 - 9 at 7-14 days
 - 3 at 14 -21 days
 - 4 at 18-28 days
- The sponsor's analyses have compared the 10-12 mg dose groups with the < 4 mg dose group; however in the extension to randomized controlled trial experience there are only 134 person-years of exposure at the latter dose
- Using deaths that occurred within 7 days of last exposure to drug in the extensions to the randomized controlled trials, a two-fold increase in mortality rate (per 1000 person-years of exposure) was seen for those receiving 10 -12 mg as the last prescribed dose, versus those receiving lower doses. This adjusted relative rate was about 4-fold higher for those who received Exelon® in the randomized controlled trials, but was not increased for those who received placebo (however there was limited exposure to the 10 – 12 dose in those who received placebo).
- There was no evidence of an early hazard from Exelon® use in the Phase 3 database except possibly in the randomized controlled trials
- The analysis appears to have conformed best to the Agency's request to evaluate the cause of death further by excluding cases thought to be implausibly related to drug. Using this analysis, and considering only those deaths not implausibly related to Exelon that occurred within 7 days of last drug use during the extension studies (n =15), the adjusted (for age, gender, baseline cardiovascular disease, baseline Global Deterioration Scale score, baseline weight and prior exposure in randomized, controlled trials) relative mortality rate for the 10 to 12 mg group versus lower doses was 5. The increased mortality risk appeared to be present only in those who lost weight. 10 of these 15 deaths were sudden deaths, and 8 were deaths at 10 – 12 mg doses.

At the meeting on 2/19/99 the sponsor reiterated its view that the mortality "signal" associated with higher doses of Exelon® was minimized if: deaths that occurred within 30 days of last drug use were considered; if randomized, controlled trials, their extensions and the titration studies were all included in the analysis; and if the 10-12 mg dose of Exelon® was compared with the < 4 mg dose. An additional analysis of the plausibility of a causal relationship between Exelon® use and death, performed by _____, a cardiology consultant to the sponsor, was presented briefly at this meeting.

The differences between the Division's concerns and those of the sponsor, were not resolved at the meeting despite extensive discussion, which also involved several statistical consultants retained by the sponsor.

The Division requested the sponsor to submit additional analyses in an effort to define the mortality risk associated with Exelon® better. In a subsequent formal letter dated 2/26/99, the Division made the following requests in regard to the additional analyses.

- A formal protocol as to the criteria that _____ intended to utilize in identifying deaths implausibly related to drug in a future analysis
- A discussion of why doses of < 4 mg, as opposed to other dose ranges, were chosen for comparison purposes for the analysis
- A detailed discussion of the strengths and weaknesses of combining data sources by stratification that have different mortality rates
- An analysis of mortality matching by baseline body weight that looks at dosing in mg/kg.
- A discussion of whether patients in the titration studies had more severe underlying disease than those in the randomized controlled trials and their extensions (as the sponsor has contended in the past); a formal comparison of these groups was requested.
- Provide multiple figures (constructed in a manner similar to that in Figure 7.1 on page 40 of the submission of 11/11/98) for cumulative deaths as of each day. A total of 8 figures were to be generated as follows, on the full dataset and the extension data only:

Full Data Set	Extension Data Only
10 & 12, vs. All lower doses	10 & 12, vs. All lower doses
10 & 12, vs. Doses 1 through 4	10 & 12, vs. Doses 1 through 4
deaths by mg	deaths by mg
deaths by baseline weight, mg/kg	deaths by baseline weight, mg/kg

The current submission is a response to the discussions at the meeting on 2/19/99 and to the Agency's subsequent letter of 2/26/99. A detailed review of this submission will be carried out by Dr Greg Burkhart. My review below will be a summary only.

3. Contents of Current Submission

3.1 _____, M.D.

_____ performed an unblinded analysis of the 56 deaths in the Exelon® Phase 3 database

_____ determined that deaths were implausibly related (not related) to study drug, if the death was clearly due to any of the following:

- A "non-pathophysiologic related event" (e.g., a new life-threatening infection)
- Mechanical events (e.g., pulmonary embolism or surgical mishap)

- Neoplasm
- Suicide
- Traumatic accident (e.g., passenger in a motor vehicle accident)
- Ruptured aneurysm

For the remaining deaths a relationship to study drug could not be excluded by Dr Morganroth, and a relationship to drug of "not implausible" (unknown) was assigned. These deaths met the following criteria:

- The death was sudden and unobserved
- The subject was not under the care of a physician for a serious medical event

Based on the above criteria, I judged 14 of the deaths as being "not implausibly" related to study drug, of which 12 deaths occurred within 7 days of the last use of study medication.

The sponsor then performed a nested case-control analysis of these 14 deaths using multiple dose categories based on last prescribed dose. With this analysis, a relative risk of 1.06 (95 % confidence interval=0.1-9.6) for the high dose (> 9 mg per day) compared to the low-dose (1 to < 4 mg/day) category was obtained. This analysis is displayed in the next table:

**Summary of nested case-control analysis for all study groupings based on Dr. J. Morganroth review:
 LPD, deaths that were "not implausible" (n= 14)**

Reference Category (mg/day)	High Dose Category (mg/day)	RR ^a (95% CI)			
		All Phase 3	RCT	EXT	TITR
1- <4	>9	1.06 ^b (0.1-9.6)	ND	ND	0
1-4	>9	2.3 ^b (0.3-19.1)	ND	ND	0
1-<6	≥ 6	5.4 (0.4-28.6)	ND	ND	0.6 (0.06 - 6.7)
1-9	>9	1.7 (0.5-5.4)	only one death (at 6 mg)	3.4 (0.7-16.2)	0
1-10	>10	1.4 (0.5-4.1)	only one death (at 6 mg)	2.2 (0.6-7.9)	0
>0-0.1 mg/kg	>0.1-0.2 mg/kg ^c	0.78 (0.22-2.74)	only one death (at 6 mg)	2.76 (0.33-23.03)	0
>0-0.1 mg/kg	>0.2 mg/kg ^c	2.69 (0.50-14.43)	only one death (at 6 mg)	6.15 (0.55-68.29)	0

^a = high dose vs. reference dose category

^b = NCC analysis done using separate estimates for middle dose categories for RCT, EXT, and TITR

^c = represents last prescribed dose / baseline body weight (0.1-0.2 mg/kg is equivalent to 12 mg in a person who weighs 60-120 kg)); risk was determined after controlling for baseline body weight.

ND = no deaths in reference dose category

A further nested case-control analysis of the 12 deaths that occurred within 7 days of last drug use was then carried out. With this analysis, a relative risk of 0.8 (95 % confidence interval=0.1-8.0) for the high dose (> 9 mg per day) compared to the low-dose (1 to < 4 mg) category was obtained. This analysis is displayed in the next table:

**Summary of nested case-control analysis for all study groupings based on Dr. J. Morganroth review:
 LPD, deaths that were "not implausible" and within 7 days (n=12)**

Reference Category (mg/day)	High Dose Category (mg/day)	RR * (95% CI)			
		All Phase 3	RCT	EXT	TITR
1-<4	>9	0.8 ^b (0.1-8.0)	ND	ND	0
1-4	>9	1.7 ^b (0.2-15.0)	ND	ND	0
1-<6	≥ 6	3.0 (0.3-26.0)	ND	ND	0.6 (0.06 - 6.7)
1-9	>9	1.3 (0.4-4.4)	only one death (at 6 mg)	2.5 (0.5-12.5)	0
1-10	>10	0.9 (0.3-3.1)	only one death (at 6 mg)	1.4 (0.4-5.8)	0
>0-0.1 mg/kg	>0.1-0.2 mg/kg ^c	0.75 (0.21-2.67)	only one death (at 6 mg)	2.62 (0.31-21.90)	0
>0-0.1 mg/kg	>0.2 mg/kg ^c	0.93 (0.09-9.56)	only one death (at 6 mg)	2.06 (0.11-37.39)	0

* = high dose vs. reference dose category

^b = NCC analysis done using separate estimates for middle dose categories for RCT, EXT, and TITR

^c = represents last prescribed dose / baseline body weight (0.1-0.2 mg/kg is equivalent to 12 mg in a person who weighs 60-120 kg)); risk was determined after controlling for baseline body weight.

ND = no deaths in reference dose category

The sponsor emphasizes that analyses so far have shown that the determination of a relationship between Exelon® use and individual deaths is marred by poor inter-rater reliability

3.2 Sponsor's discussion of why doses of < 4 mg were chosen for comparison purposes for the analysis

The sponsor has cited the following reasons for using this category for analysis purposes:

- This is same category that was used for reference in this Division's original nested case-control analysis that suggested an increased mortality risk at higher doses of Exelon®; a similar categorization was therefore used by the sponsor in an effort to dispel this analysis
- This dose range is similar to the lowest dose category (1 to < 3 mg) used for the Integrated Summary of Safety, and includes the lowest dose used in all the different study types: randomized, controlled trials, titration studies and extension studies

- The use of 4 dose categories rather than a simple dichotomization of the dose range allows for determination of the true form of the relationship between Exelon® dose and mortality (the 4 dose categories are 1 to < 4 mg; 4 to 6 mg; > 6 to 9 mg; and > 9 mg)
- A review of the relative risks for all possible dose dichotomizations does not yield any rationale for choosing a particular dose as a cut-off for dichotomization.

3.3 Sponsor's discussion of the strengths and weaknesses of combining data sources (by stratification) that have different mortality rates

The sponsor has cited the following reasons for combining data from these different sources

- Such stratified Cox proportional hazards models are routinely used for the analysis of studies which contain strata where it is known or possible that the hazards are different among the various strata, such as in the titration and extension studies for the Exelon® database.
- No systematic differences were observed between the randomized, controlled trials and titration studies in regard to demographics, severity of disease, dosing strategy, proportion of patients reaching or able to be maintained at the 12 mg/day dose, or mortality rate to justify not pooling the data from these studies
- Differences of patient population and study design between randomized, controlled trials and titration studies should be partly compensated for by the fact that in the nested case-control analyses performed by the sponsor controls were matched for the study of origin

3.4 Sponsor's analysis of mortality matching by baseline body weight looking at dosing in mg/kg

The sponsor has carried out a nested case-control study, matching cases with controls by baseline body weight (in mg) and using the 12 deaths judged by Dr J. _____ as being not implausibly drug-related and occurring within 7 days of last drug administration. The controls were drawn from the same original study as the cases. The sponsor concludes there was no evidence of dose-related mortality from this analysis; nor were the results substantially different from those obtained using models where controls were matched by original study alone. The results are in the following table. The sponsor does acknowledge that when the relationship between dose and mortality in the following table is looked at, the risk appears to increase more sharply for increasing mg/kg categories than for categories based on dose alone. However the sponsor argues that under those circumstances analyses using cumulative dose should provide supportive results, which they have not: the relative risks from such analyses have been less than 1. The sponsor also argues that the use of ratios (such as mg/kg) as independent or dependent variables in regression and generalized linear models could result in spurious correlations.

Mortality risk ratios according to dose categories. Deaths classified as 'not implausible' by Dr. Morganroth and within 7 days of the last administered dose. Conditional logistic regression analysis in a nested case-control study matched by time to failure, study type and origin of the patient.

Dose (mg/kg)	matching controls by baseline weight ^a		matching controls by center ^b			
	cases/controls	odds ratio (95% CI)	cases/controls	odds ratio (95% CI)		
All phase III studies						
> 0 - 0.1 mg/kg	5 / 1276	1.0	5 / 90	1.0	5 / 72	1.0
> 0.1 - 0.2 mg/kg	6 / 1744	0.8 (0.2 - 2.8)	6 / 111	0.9 (0.2 - 3.8)	6 / 99	0.4 (0.1 - 1.9)
> 0.2 mg/kg	1 / 248	0.9 (0.1 - 8.3)	1 / 6	1.6 (0.1 - 26)	1 / 14	0.3 (0.03 - 3.9)
Extension studies						
> 0 - 0.1 mg/kg	1 / 600	1.0	1 / 37	1.0	1 / 17	1.0
> 0.1 - 0.2 mg/kg	6 / 1341	2.8 (0.3 - 24)	6 / 89	2.3 (0.2 - 20)	6 / 78	1.1 (0.1 - 10)
> 0.2 mg/kg	1 / 220	2.8 (0.1 - 45)	1 / 5	4.7 (0.1 - 160)	1 / 12	0.8 (0.04 - 15)
Titration studies						
> 0 - 0.1 mg/kg	3 / 275	1.0	3 / 19	1.0	3 / 27	1.0
> 0.1 - 0.2 mg/kg	0 / 345	0.0 (0.0 -)	0 / 15	0.0 (0.0 -)	0 / 20	0.0 (0.0 -)
> 0.2 mg/kg	0 / 28	0.0 (0.0 -)	0 / 1	0.0 (0.0 -)	0 / 2	0.0 (0.0 -)

^a nested case-control analysis matched by time to failure, study type, origin of the patient and baseline weight defined as baseline weight of the case +/- 1Kg

^b nested case-control analysis matched by time to failure, study type, origin of the patient and treatment center in which the case occurred

3.5 Comparison of baseline and demographic data from main titration study (B355) and pooled data from randomized, controlled trials

The sponsor believes that although these data differed from one randomized, controlled trial to another, the pooled data from the randomized, controlled trials had only minor differences from the main titration study. The latter comparison is illustrated in the following table.

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Demography of B355 and pooled RCT, and Baseline Characteristics Potentially Associated with Increased Mortality or Morbidity for which B355 has Numerical Excess over RCT

Variable	Pooled RCT Group			B355 Exelon n = 544
	Exelon n = 1923	Placebo n = 868	Total n = 2791	
Age (yrs)				
Mean	72.9	73.3	73.0	74.1
Age Group (%)				
≤65	19	15	18	16
66-75	40	43	41	36
76-85	38	38	38	42
>85	4	3	3	5
Sex (%)				
Female	59	59	59	62
Race				
Caucas	95	96	95	93
Black	4	3	3	5
Weight (kg)				
Mean	67.3	66.4	67.0	67.1
Duration of Dementia (mos)				
Mean	38.5	39.0	38.7	40.1
Median	36.0	36.0	36.0	36.0
Baseline MMSE				
Mean	19.6	19.6	19.6	19.0
Baseline GDS				
Mean	4.0	4.0	4.0	4.1
≥5 (%)	30	31	31	34
Severity of AD				
Severe (%)	2	2	2	4
Any Current Medical Conditions at Baseline (%)	84	84	84	89
Any Concomitant Medications at Baseline (%)	72	69	71	82

3.6 Sponsor's figures for cumulative deaths as of each day off drug

These have been submitted for all possible combinations including mg/day and mg/kg, and for the extension database alone. No comments have been made by the sponsor

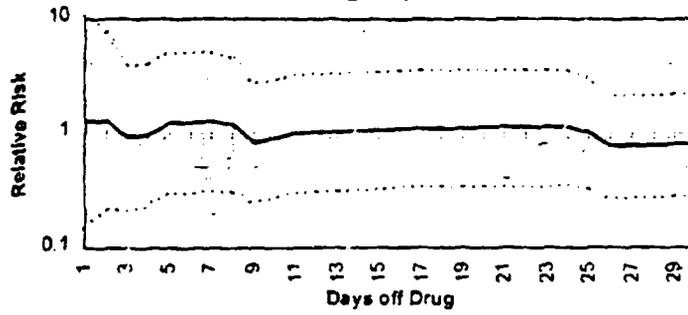
The results for 3 sets of comparisons are presented below:

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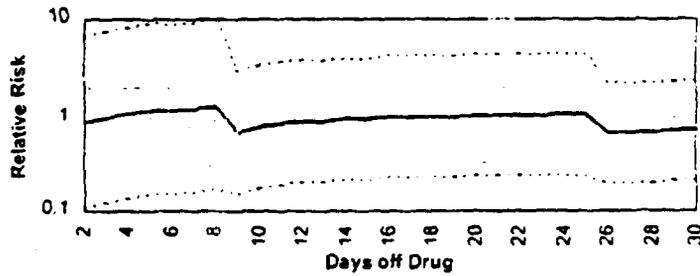
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Days off drug >9 mg vs <4 mg (All Phase 3, EXT, TITR)

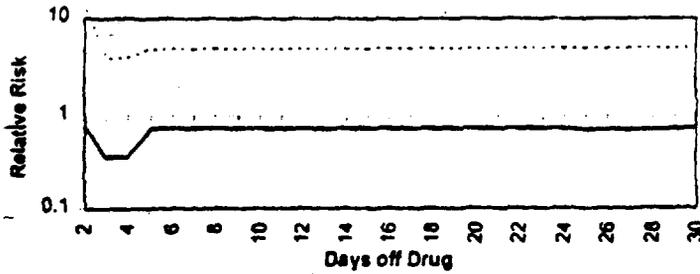
**All Phase III: >9 mg versus <4 mg
Adjusted for Different Study Types in the Middle
Dose groups**



Extension Studies: >9 mg versus <4 mg

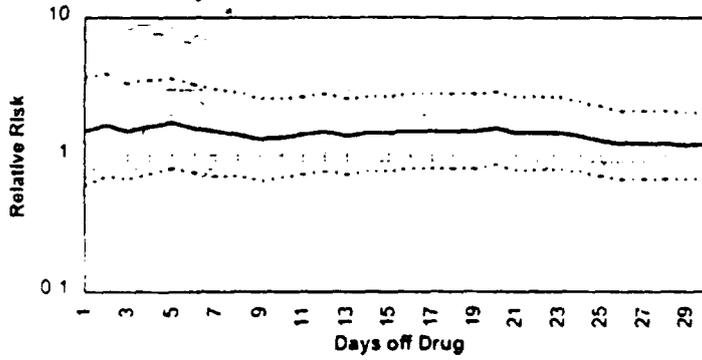


Titration Studies: >9 mg versus <4 mg

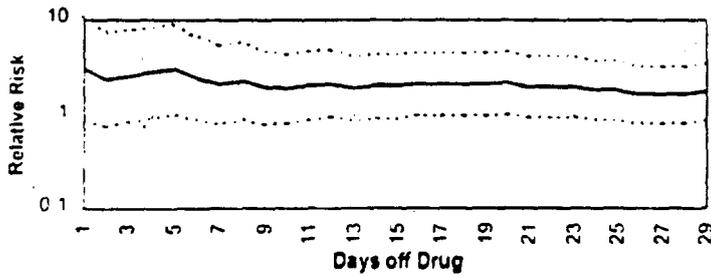


Days off drug > 9 mg vs <=9 mg (All Phase 3, EXT, TITR)

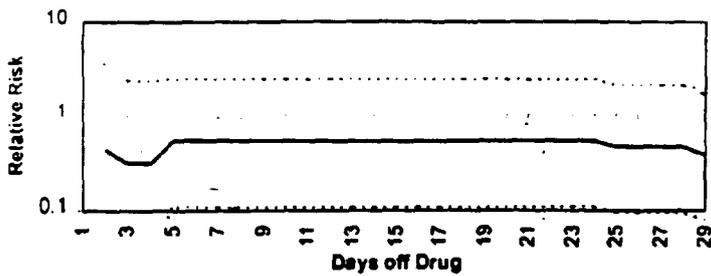
All Phase III: >9 mg versus <=9 mg



Extension Studies: >9 mg versus <=9 mg

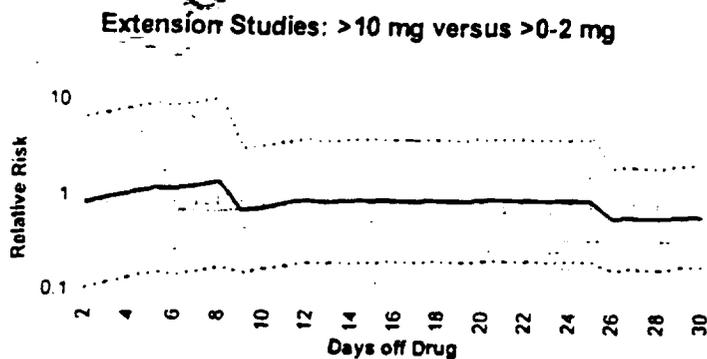


Titration Studies: >9 mg versus <=9 mg



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Days off drug >10 mg vs >0-2 mg (EXT)



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4. Agency Classification of Cause of Death

A group of medical officers working in the Neurology section of this Division were asked to review records pertaining to the 56 deaths that occurred in the Phase 3 database for Exelon®. This group comprised Drs John Feeney, Gerald Boehm and Joel Freiman. The review was completed 3/23/99

These medical officers were asked to identify:

1. Sudden unexplained deaths
2. Deaths in which drug attribution was implausible

The records that were reviewed were provided by Novartis in a submission dated 2/26/99. These records were blinded as to treatment assignment and contained patient narratives, Case Report Forms, hospital records and death certificates when available.

The group of medical officers agreed on the following **DEFINITIONS** prior to performing the review:

Sudden Unexplained Deaths

The following criteria were considered essential to the diagnosis of sudden unexplained death:

- If observed, the death occurred within minutes
- An obvious medical cause of death was not found. If an autopsy was not performed an obvious medical cause of death was also not established based on clinical information
- Accidental deaths such as drownings, motor vehicle accidents (where the patient was the driver) and falls with immediate death were included
- Deaths from gunshot wounds and other violent acts (including death occurring to a passenger in a motor vehicle accident) were not included

Implausible Drug Attribution

Drug attribution was considered implausible in the following situations:

- The death occurred > 7 days after cessation of drug. However, if the precipitating cause of death occurred within 7 days of drug cessation, drug attribution was considered plausible even if death was delayed beyond 7 days of drug cessation
- The death was due to a gunshot wound or other violent act

- The death was due to autopsy-proven coronary artery disease with acute myocardial infarction
- The death was due to stroke in the setting of a cardiac risk factor (atrial fibrillation) or with evidence of peripheral vascular disease
- The death was due to meningitis
- The death was due to subarachnoid hemorrhage
- The death occurred in a patient moribund from cancer

Drug attribution was specifically mentioned as plausible in the following situations:

- The cause of death was unknown or unclear
- The death resulted from suicide
- The death resulted from pneumonia or urosepsis
- The death was classified as a sudden unexplained death
- The death resulted from complications resulting from an accidental fall

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TABULAR CLASSIFICATION OF DEATHS

The following is the tabular classification (of all 56 deaths) presented in the above review. 14 deaths were considered sudden unexplained deaths and 20 deaths were considered implausibly related to drug

Patient ID Number	Assessment of Implausibility	Sudden Unexplained Death	Comments
30309004	Implausible	NO	Died 12 days after last dose following an exacerbation of heart failure
30334018	Not implausible	YES	Found dead in bed; no autopsy
30409003	Not implausible	NO	Died from gastrointestinal bleed not completely investigated owing to underlying malignancy
30411001	Not implausible	NO	Fell, leg fracture, internal fixation, pneumonia, pulmonary embolism, death
30302004	Not implausible	NO	Fell, hip fracture, hip replacement, infected prosthesis, death from sepsis
30304001	Not implausible	NO	Worsening heart failure, ventricular fibrillation, asystole and death
30305010	Not implausible	NO	Recent respiratory infection (?), not well-described
30312016	Not implausible	NO	Fell, hip fracture, died of pulmonary embolism (?)
30329008	Not implausible	YES	Got out of bed, collapsed, became short of breath, lost consciousness and died
30331002	Not implausible	YES	Post hip fracture, died at home but cause of death unclear and sudden
30342006	Not implausible	YES	Died while walking
30403009	Implausible	NO	Died 22 days after last dose of medication possibly of a respiratory infection
30411003	Not implausible	NO	Chest infection
30413010	Implausible	NO	Death associated with malignancy (colon cancer perforation)
30413013	Implausible	NO	Death associated with malignancy (thymoma, hemopericardium)
30417011	Implausible	NO	Myocardial infarction with continuing ischemia leading to death (7 days after last dose)
304425004	Not implausible	YES	Sudden death; no autopsy
30431015	Not implausible	NO	Fell; fractured hip; re-pinned due to misalignment; developed urinary infection, sepsis and death
35103011	Not implausible	NO	Nausea, vomiting and anorexia leading to discontinuation of drug; diagnosed with prostate cancer; 3 days later died
35105003	Not implausible	NO	Left frontal lobe bleed
35215039	Not implausible	YES	Sudden death; heard falling to floor; complete heart block detected; no autopsy
35102071	Not implausible	YES	Loss of consciousness; sudden death; failed resuscitation; no information to support diagnosis of myocardial infarction which is the reported cause of death
35105021	Implausible	NO	Drug stopped due to lack of benefit; died 26 days after discontinuation from study
35106045	Not implausible	NO	Hospitalized for abdominal pain, hematemesis, ileus and possible diverticulitis; died next day
35111049	Not implausible	NO	Fever; slightly increased white blood cell count; possible infection; source unclear. Possible respiratory failure

351112014	Not implausible	YES	History of abdominal aortic aneurysm; died suddenly; no autopsy
32502038	Not implausible	YES	Found dead in bed
35203002	Not implausible	YES	Died 3 days after hospital discharge, treated for chest congestion, dyspnea and weakness
35203003	Implausible	NO	Diagnosed with pancreatic cancer; palliative treatment
35203023	Not implausible	YES	Found dead in bed
35203025	Not implausible	NO	No history of coronary artery disease; inferior wall myocardial infarction; died 3 days later
35204022	Implausible	NO	Brain lesions probably metastases from a lung primary
35204042	Not implausible	NO	Intraparenchymal cerebral hemorrhage; hypertensive crisis
35206021	Implausible	NO	Septicemia, peridiverticular abscess
35207028	Not implausible	NO	Collapsed; electrocardiogram with inferior ischemic changes consistent with myocardial infarction; later died
35209022	Implausible	NO	Nine days after a myocardial infarction; developed chest pain, loss of consciousness and died
35211009	Implausible	NO	Evidence of metastatic disease with unknown primary
35213004	Not implausible	NO	Developed renal and hepatic insufficiency and died
35213019	Implausible	NO	Metastatic non-small cell lung cancer
35215011	Implausible	NO	Weight loss, general decline with anorexia and weakness
35220009	Implausible	NO	Probable diverticular bleed; post-operative sepsis and death
35222027	Implausible	NO	Exhibited decline; all medications stopped; hospice care initiated; died 8 days after last dose
35502104	Not implausible	YES	Sudden death at dinner table; no autopsy
35507116	Not implausible	YES	Found dead in bathroom; no autopsy
35510117	Not implausible	NO	Suicide; gunshot wound to head
35515108	Not implausible	NO	Syncope; possible aspiration; acute respiratory failure, cardiac arrest and death; no autopsy
35516101	Not implausible	YES	Sudden death; no autopsy
35516104	Implausible	NO	Passenger in a motor vehicle accident
35518102	Not implausible	NO	5 days after last dose died of a stroke
35522103	Implausible	NO	30 days after last dose died, possibly of renal insufficiency; circumstances of death unknown
35524116	Not implausible	NO	Stroke, but unsure of any details; 2 days later died, possibly of a second stroke
35526102	Implausible	NO	Died from aspiration from aspiration and hematemesis following bilateral above-knee amputation for ischemia
35528101	Implausible	NO	Possible underlying pelvic malignancy; had not taken much of the drug; spat out tablets
35528105	Not implausible	NO	Fall, hip fracture, total hip replacement, post-operative infection; died from confirmed pulmonary embolism 27 days after last dose
35528121	Implausible	NO	Metastatic colon cancer diagnosed and drug stopped; died 25 days later
35528126	Not implausible	NO	Possible respiratory infection; few details apart from presence of fever and cough

NOTE: The same team of reviewers has performed an identical analysis of deaths in the NDA (# 20690) for donepezil (Aricept®); this was to facilitate comparison with Exelon®. The review was completed on 4/21/99. Please refer to that review for full details.

5. Summary Review of Mortality Data in Exelon® NDA.

The following summarizes the results of an analysis performed by Greg Burkhart, M.D., which was completed 4/27/99.

In his review Dr Burkhart has described, in detail the methods and results of various analyses, that have been performed so far by the Division and by the sponsor. He has made specific responses to a number of the arguments put forward by the sponsor in its response to the Agency's non-approval letter. He has also highlighted the difficulty analyzing mortality in an elderly population, using largely non-randomized data; in this regard he has cited his own approaches to evaluating the significance of comparisons that are made using such data. Please refer to his review for full details. Key elements of these analyses have already been referred to by me in this review and in my review completed 3/8/99.

Dr Burkhart has, in particular, drawn attention to the following (I have already referred to some of these items earlier in this review):

- Although the pooled experience across the Phase 3 randomized, controlled trials suggested a (statistically weak) association between Exelon® use and increased mortality, this may be a common observation across NDAs. Although 2 out of the 3 deaths (all of which were in metrifonate-treated patients) that occurred within 7 days of last drug use were considered sudden deaths by the FDA team referred to in the previous section, sudden deaths are not rare in this population and are not specific for drug
- When all-cause mortality data across the entire Phase 3 database were pooled
 - The increased mortality for the 10/12 mg daily dose versus lower daily doses and placebo, was 1.6-fold when using the not-implausible deaths listed by the above FDA review group to 3.4-fold when a larger number of not-implausible deaths was used
 - This increased mortality signal was inconsistent across the dataset, being most prominent for the extension studies and least prominent for the titration studies. This signal could be considered moderate or strong only when applying Dr Kane's definition of not-implausible deaths to the extension dataset
 - The increased mortality signal was not associated with evidence of an early hazard, clear dose-response or specific clinical event
- When sudden deaths, as designated by the above FDA special review group across the entire Phase 3 database were pooled and analyzed
 - The increased mortality for the 10/12 mg daily dose versus lower daily doses and placebo, was 2.4-fold, a statistically weaker association than for all-cause mortality
 - This increased mortality signal too became somewhat more prominent (3.5-fold) when the extension study dataset alone were considered
 - The increased sudden death risk for the 10/12 mg dose versus lower daily doses and placebo occurred after long-term use, whereas the increased all-cause mortality risk at

the same dose was in, in part, early during use of the drug. Thus it appeared unlikely that the increased sudden death risk could account for the increased all-cause mortality risk at the 10/12 mg dose

- The magnitude of the risk estimates did not increase when dose was adjusted for body weight, both baseline and change during study

For comparison purposes, analyses were also carried out on the mortality data for donepezil and tacrine, the 2 currently approved cholinesterase inhibitors. The exposure to drug in these NDAs, and especially with donepezil, was much smaller than that with Exelon

- For the donepezil NDA an analysis was carried out using data supplied by the sponsor for that drug and indicated the following
 - For the Phase 2 and 3 randomized controlled trials, the extent of exposure and number of deaths was too limited to arrive at any meaningful conclusions
 - Across the Phase 3 open-label experience, there was no suggestion of a dose-response for all-cause mortality or for sudden deaths
- Data for tacrine were supplied by the sponsor for that drug, and most of the experience for that drug derived from a 30 week randomized, placebo-controlled trial that incorporated multiple dose arms. The data for the latter study suggested that there was an increasing survival advantage with increasing dose. In this study the sponsor ascertained the vital status of all enrolled patients through 30 weeks irrespective of whether they actually took the drug, and it was known that there was a significant dose-dependent patient dropout in this study. Thus the apparent dose-dependent survival advantage may not have actually been as compelling as it seemed from the mortality analysis

Dr Burkhart concludes that there are "weak" associations between Exelon® use and increased mortality in randomized, controlled trials, and between use of higher doses of Exelon® and increased mortality in open-label trials. In using the term "weak" he implies that he believes that it is unlikely that a toxic effect of Exelon® itself is responsible for the increased mortality but that these observations are the result of chance or an unrecognized confounding factor(s)*. However he does feel that the uncertainty is such, at present, that a large randomized study is needed to affirm the safety of Exelon®; his recommendation is based not on the strength of the mortality signal itself but on his estimate that the excess risk may approach 1 per 100 patient-years of exposure. Further, he has outlined the reasons why he believes that only a large randomized, controlled study (larger than the exposure reported in NDAs for drugs intended to treat Alzheimer's disease that have been submitted so far) to provide substantial statistical evidence that a drug was not causing increased mortality in a population of patients with Alzheimer's disease.

*There is at least one pharmacologically-plausible mechanism by which Exelon® may contribute to increased mortality; all anticholinesterase drugs can reduce heart rate and cardiac conduction.

Dr Burkhardt has emphasized in his discussion that the degree of uncertainty that exists with Exelon® also exists with the approved cholinesterase inhibitors, tacrine and donepezil, for which, in fact (as already noted), the extent of exposure at the time NDA approval was granted, was smaller. He does not however feel that that alone is an argument for granting approval for Exelon®.

6. Summary of Key Efficacy Studies for Exelon®

As the extent to which Exelon® is efficacious in the treatment of Alzheimer's disease is pertinent to an assessment of the benefit versus risk equation for this drug, I have summarized the key efficacy studies for this drug in tabular form below.

All studies were randomized, double-blind, placebo-controlled, parallel-arm, and 26 weeks in duration.

6.1 Dosing, and number of patients randomized and completing

STUDY #	DOSE ARMS	Completed/Randomized (%)	Location
B303	Exelon® 1-4 mg/day Exelon® 6-12 mg/day Placebo	209/243 (86) 164/243 (67) 208/239 (87)	Multinational
B304	Exelon® 2-12 mg/day (b.i.d) Exelon® 2-12 mg/day (t.i.d) Placebo	180/229 (79) 174/227 (77) 184/222 (83)	Multinational
B351	Exelon® 3 mg/day Exelon® 6 mg/day Exelon® 9 mg/day Placebo	130/175 (74) 111/176 (63) 91/178 (51) 130/173 (75)	United States
B352	Exelon® 1-4 mg/day Exelon® 6-12 mg/day Placebo	199/233 (85) 149/231 (65) 197/235 (84)	Multinational

6.2 Duration of segments of double-blind phase

STUDY #	DOSE TITRATION PHASE	DOSE MAINTENANCE PHASE
B303	7 weeks	19 weeks
B304	12 weeks (maximum)	14 weeks (minimum)
B351	12 weeks	14 weeks
B352	7 weeks	19 weeks

All studies had a double-blind phase of 26 weeks (total)

6.3 Drug-placebo differences at Week 26 for change from baseline (Observed Cases population)

STUDY #	DOSE ARMS	MEAN ADAS-COG	MEAN CIBIC-PLUS
B303	Exelon® 1-4 mg/day	0.17	-0.14
	Exelon® 6-12 mg/day	2.58*	-0.41*
B304	Exelon® 2-12 mg/day (b.i.d)	2.73*	-0.43*
	Exelon® 2-12 mg/day (t.i.d)	1.40	-0.26
B351	Exelon® 3 mg/day	0.52	0.03
	Exelon® 6 mg/day	1.61*	-0.09
	Exelon® 9 mg/day	1.77*	-0.23
B352	Exelon® 1-4 mg/day	1.87	-0.18
	Exelon® 6-12 mg/day	4.94*	-0.21*

*p < 0.05

6.4 Reviewer's overall impression of efficacy data

- The above data suggest that, in general, the higher doses of Exelon® have an effect size in relation to placebo, comparable to the 2 approved cholinesterase inhibitors, tacrine and donepezil. The only exception to this trend, is the drug-placebo difference for the ADAS-Cog in Study B352; this difference is larger than for the other efficacy studies. The overall efficacy of this drug in the symptomatic treatment of Alzheimer's disease is, at best, modest.
- If the data from all 4 efficacy studies are considered together, it seems likely that the only effective dose of Exelon® may be 10-12 mg daily. Dr Randy Levin appears to have made the same conclusion from his Efficacy Review of the NDA.

7. Comments

- There do appear to be separate associations, albeit not strong ones, but nevertheless of concern, between the use of Exelon® in doses of 10-12 mg daily, and an increased all-cause mortality risk in open-label studies, and between Exelon® use and mortality risk in randomized, placebo-controlled trials. There are no specific clinical phenomena that can clearly explain this risk. As Dr Burkhardt has recommended, a large randomized trial comparing several doses of Exelon® with several doses of donepezil may be the only way of resolving this concern
- The 10-12 mg daily dose of Exelon® may also be the only dose range that has true efficacy
- Exelon® does not appear to have any advantage as regards efficacy in comparison to tacrine or donepezil, or in regard to safety in comparison with donepezil. It is unlikely therefore that Exelon® will, if approved for marketing, represent a significant improvement to the very modest armamentarium already available for the symptomatic treatment of Alzheimer's disease.
- Given the above considerations it is hard to recommend that Exelon® be approved prior to the above-described associations between Exelon® use and increased mortality being resolved.

8. Recommendations

- At the present time, my preference is to recommend that Exelon® not be approved for marketing for the symptomatic treatment of Alzheimer's disease, unless concerns about an increased mortality risk with Exelon® can be appeased; a large randomized trial comparing several doses of Exelon® with several doses of donepezil, as suggested by Dr Burkhart, may be one way of resolving these concerns.
- Should the drug being approved for marketing based on the data available at present, and regardless of the above concerns, the following should, at a minimum, be required of the sponsor
 - That the above concerns regarding the mortality experience for this drug be explained clearly in the package insert
 - That approval be made conditional on a commitment by the sponsor to perform a randomized study of the kind recommended by Dr Burkhart.

~~ISI~~
Ranjit B. Mani, M.D.
Medical Reviewer

R. Levin, M.D. ~~ISI~~ 199
(see my memo)

rbm 4/29/99
cc:
HFD-120
NDA 20823
electronic copy-Levin
Nighswander

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: May 3, 1999
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-823, Exelon
To: file

Introduction:

Exelon (rivastigmine tartrate) is an acetylcholinesterase inhibitor for the symptomatic treatment of mild to moderate Alzheimer's disease.

The original NDA was submitted on April 7, 1997. During the initial review, we found evidence for an increase risk for mortality in the patients on higher doses of the drug. The original due date was extended to allow for the review of additional data on mortality. After review of the data, we concluded that there was evidence of increased mortality as a function of Exelon dose/exposure. In a non approval letter sent July 7th, we asked that the sponsor provide additional analyses to address this concern.

On November 11, 1998, the sponsor provided a complete response to the non approval letter. The response only addressed the issue of increased mortality. This response was reviewed by Dr. Burkhart and Dr. Mani.

In this memo, I discuss the issue of the increase risk for mortality and summarize the conclusions from the original NDA. See my previous memo for additional details.

Chemistry

According to Dr. Rzeszotarski, the reviewing chemist, there are no chemistry issues precluding approval except for the description of Exelon as "New Exelon" on the professional Sample carton label. The phrase "RX only" should also be on the label. The sponsor was informed of this problem on February 1, 1999.

Nonclinical toxicology

No new nonclinical toxicology information has been provided. According to Drs. Rosloff and Fitzgerald, the pharmtox reviewers, there are no nonclinical pharmtox issues precluding approval. See the attached labeling for recommendations for wording of the appropriate sections. There are no other outstanding issues.

Human pharmacology

According to Drs. Safaa Ibrahim and Sahajwalla, the human pharmacology reviewers, there are no issues precluding approval. See the attached labeling for recommendations for wording for the appropriate sections. There are no outstanding issues.

Clinical efficacy

No new efficacy data has been presented by the sponsor since the non approval letter. Dr. Hoberman and I reviewed the efficacy data and concluded that the sponsor had provided sufficient evidence in more than one adequate and well controlled study that the drug was effective as a symptomatic treatment for Alzheimer's disease.

The sponsor provided 5 adequate and well controlled evaluating efficacy. For a symptomatic treatment of Alzheimer's disease, a study is considered positive for efficacy when a statistically significant difference in both a measure of cognitive performance (e.g., ADAS-cog) and a clinical assessment of change (e.g., CIBIC plus) is demonstrated.

Two of the five studies were not positive. The studies evaluating fixed doses up to 9 mg/day failed to show a statistically significant difference for the CIBIC plus. For the ADAS-cog, the differences for the 6 and 9 mg/day groups were statistically different from placebo. The remaining three studies had some positive findings. In two studies, a dose range of 6 to 12 mg/day were evaluated. In both studies, this group was statistically different from placebo for both outcome measures. In these two studies, a dose range of 1 to 4 mg/day was also evaluated. The comparison between 1 to 4 mg/day and placebo was positive in one study but not the other. In one study, a range of 2 to 12 mg/day was evaluated. This group was statistically different from placebo on both outcome measures. In one study a tid dosing regimen was evaluated (in the other studies, the dosing regimen was bid). The comparison of the tid dosing regimen with placebo was not positive.

Because of the conflict in the findings of the dose range studies and the fixed dose study for doses of 3, 6 and 9 mg/day, I did a separate analysis comparing patients receiving 12 mg/day and those receiving less than 12 mg/day. In two of three studies, the positive findings were seen only in the patients receiving the higher doses of the drug. In all cases, the numbers and direction were in favor of the patients receiving the higher doses.

This finding suggests a dose related benefit of the drug with consistent evidence for efficacy at the highest dose of 12 mg/day (6 mg bid). The evidence for efficacy at doses of 2 to 9 mg/day is not consistent across studies.

Clinical safety

In response to the non approval letter, the sponsor sent in additional analysis and information on deaths in the NDA database.

Dr. Burkhart summarized his review of the sponsor's response in a memo dated April 27, 1999. He also analyzed the mortality data seen in the Aricept and Cognex trials.

The database for Aricept was smaller than the Exelon database. For example, there was around 1200 patient years in the Exelon controlled trials compared to 700 for Aricept including study 304 completed after the NDA was approved. In the Aricept controlled trials, the mortality rates were higher in the placebo group compared to the drug groups. For example, in study 304, approximately 825 patients were randomized equally to placebo, 5 or 10 mg/day (about 275 per group). The study was 30 weeks. Including the dropout rate of 20 to 25% across the groups, there was slightly over 100 patient years experience in each dose group. There were 4 deaths in total that were not implausible as being drug related. Two patients on placebo died. One patient in the 5 mg/day group and one patient in the 10 mg/day group died. In the Aricept open label experience, there was little difference between the high and low dose groups. In the tacrine studies, the death rates were also lower in the drug groups compared to the placebo group.

This differs from the Exelon controlled trials, where the mortality rates were higher in the treated patients and in the open label extension studies for the controlled trials, the mortality rates were higher in patients treated with doses > 9 mg/day compared to those with lower doses.

After completing additional analyses, including a blinded assessment of the deaths, Dr. Burkhart concluded that the findings represent a signal that Exelon could have a life threatening risk. The signal comes from a "weak" association between Exelon and mortality in the randomized trials and a "weak" association between the highest dose of Exelon and mortality in the open experience. This difference is based on a relatively small number of deaths and did not reach statistical significance. Dr. Burkhart defines a "weak" as being "more likely attributable to chance or confounding factors rather than to a direct toxic effect of the drug". Because the signal suggests the possibility of a life threatening event approaching 1 in 100 person years, Dr. Burkhart felt that an additional study be conducted to better determine the safety of Exelon. This study would compare the mortality risk in patients randomized to high and low doses of Aricept or Exelon.

Conclusions

The sponsor has provided sufficient data to provide regulatory evidence for efficacy for the treatment of mild to moderate Alzheimer's disease. In fixed dose studies, patients on

doses of 3, 6, and 9 mg/day failed to be distinguished from patients on placebo on the standard dual outcome measurements. Only the studies using doses above 9 mg/day had positive findings for both outcome measures. The use of dose ranges in these studies rather than fixed doses make it difficult to determine the dose at which the drug is effective. The only consistent evidence for efficacy is for the dose of 12 mg/day. The evidence for efficacy of doses of 9 mg/day or less is inconsistent across clinical trials.

While there were no comparison studies performed, the treatment effect for Exelon appears to be similar to Cognex and Aricept and appears to be confined to a modest symptomatic effect. In the Exelon trials, an activities of daily living test rated by the caregiver was collected. This was a secondary outcome measure and was only consistently associated with a nominal p value of < 0.05 in a single study and only in the high dose group. For Aricept, an activities of daily living test was assessed in study 304. In this study, the Interview for Deterioration in Daily Living Activities (IDDD) for complex activities and basic self care were secondary outcome measures. The treatment difference for the IDDD complex activities was associated with a nominal p value < 0.05 for the high dose group.

Overall, there is no evidence to suggest that efficacy of any of these drugs are different from one another.

Aside from the issues of an increase mortality, the adverse events seen with Exelon were similar to those seen with Aricept. The overall safety profile is no better and possibly worse than Aricept with a higher incidence of nausea, vomiting, anorexia and weight loss seen in the Exelon trials.

Safety data from the long term extension studies of the efficacy trials show a 1.6 to 3.4 fold increase in the risk of death in patients receiving the high dose (10 to 12 mg/day) of Exelon compared to those receiving low doses. This finding could be related to a toxic effect of the drug, a confounding event, or just a chance occurrence. It is not clearly related to a toxic effect of the drug. No specific mechanism of action or cause related to use with Exelon was found in the analysis of the data. At the same time, no confounding event was found and its difficult to conclude that the finding is only a chance occurrence with this limited experience.

Any time we take a drug, we are taking a risk for an adverse event. The greater the benefit, the greater the justifiable risk. The greater the safety risk, the greater the benefit needed to justify taking the drug. Without an answer to the cause of the increase mortality rate seen with high dose Exelon, the benefit of the Exelon would be weighed against the risk of death. Exelon provides only a very modest symptomatic benefit. There is no evidence that it offers a benefit over Aricept, a currently available treatment. Exelon theoretical mechanism of action is the same as Aricept. In addition, Exelon's safety profile offers no apparent benefit over Aricept.

I would suggest that we do not have sufficient information to conclude that Exelon is safe for use and would recommend that Exelon not be approved until an additional study

shows the risk for mortality to be the same or better than Aricept (see Dr. Burkhardt's memo for a description of this study) or show significant benefit of Exelon over Aricept.

An alternative decision would be that the strength of the signal for an increased risk for mortality is not sufficient to prevent approval. If this is the case, I would still recommend conducting the safety study recommended by Dr. Burkhardt. The sponsor should also describe the signal of increased mortality in labeling.

A compromise between approval with commitment to complete the safety study in phase 4 and non approval until the study is completed is to initiate the study prior to approval and conduct an interim analysis looking for an early risk. If there an increase risk was not seen, the drug could be approved with a commitment from the sponsor to complete enrollment within 1 year of approval.

I have provided draft labeling based on the Aricept labeling. I have asked the sponsor to describe all of the adequate and well controlled studies and have included a brief discussion of the fatality issue. In the dosing section, I noted that the efficacy information at doses < 12 mg/day is not consistent and recommended discontinuation of the drug for patients who were unable to tolerate doses of 12 mg/day. The professional-sample carton label will need to be changed to eliminate the word "new" to describe Exelon. The Exelon support program will need to be discussed so that the sponsor's representation of the drug is fair and balanced and the adverse event reports will be handled properly. The question and answer brochure will also need to be revised to eliminate false and misleading statements and provide a fair and balanced representation of the drug.


Randy Levin, M.D.
Neurology Team Leader

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DATE: ~~May~~ 3, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I/HFD-100

&

File, NDA 20-823

SUBJECT: Recommendation For Action on NDA 20-823, for the use of Exelon (Rivastigmine Tartrate) in Patients with Alzheimer's Disease

NDA 20-823, for the use of Exelon (Rivastigmine tartrate), a cholinesterase inhibitor, in patients with Alzheimer's Disease, was submitted by Novartis on 4/7/97. The application contained the results of 5 controlled trials, in addition to safety data from a variety of sources. The sponsor was issued a Not Approvable letter on 7/7/98, because, although substantial evidence of effectiveness had been demonstrated, there emerged a signal of increased mortality at higher doses that the Agency had concluded required additional clarification before approval could be granted. This signal arose from the controlled trials, as well as from the larger, uncontrolled experience.

With regard to effectiveness, the controlled trials utilized various titration and fixed dose placebo controlled parallel group designs. As has been noted in previous reviews, the most consistent evidence of effectiveness was demonstrated at the higher doses tested, namely 10-12 mg/day.

An increase in mortality compared to placebo was noted in the controlled trials, although this difference was not statistically significant. Nonetheless, this difference motivated a search of the remaining data to further evaluate the signal in the remainder of the NDA database. Because the additional data in the NDA consisted of uncontrolled experience, this further evaluation entailed the use of numerous epidemiologically styled approaches, in which attempts were made to compare mortality at the high doses (10/12 mg/day) to that with the low doses. These attempts included the use of case control methods (in which risk sets for each death reported at that time were constructed), as well as comparisons of mortality rates between the high and low dose groups. While the limitations of these approaches were well understood at the time, the findings in these analyses, coupled with the differences seen in the controlled trials, gave rise to concerns that precluded the approval of the product without additional investigation. Specifically, there appeared a signal of increased mortality at the high doses in the extensions to the RCTs (which had the majority of the high dose experience) but not in the studies which used a more rapid titration scheme (the so-called titration studies).

In the 7/7/98 Not Approvable letter, the sponsor was asked to perform additional analyses of the mortality data. Specifically, Novartis was asked re-evaluate the deaths, in a blinded fashion, to determine which of the deaths were implausibly related to treatment, and then to perform additional analyses on the remaining deaths, including more extensive case control studies. In addition, they were to perform these analyses including only those deaths which had occurred within 7 days of discontinuation of the treatment, or for which the event that led to death had occurred within 7 days of discontinuing treatment (most of the original analyses had included deaths that had occurred within 30 days of discontinuing treatment). The choice of 7 days was, of course, arbitrary, but was chosen because it was felt that the period of greatest risk for a drug related adverse event was during the period closest to drug discontinuation. Of particular interest to the Agency were requested analyses that attempted to adjust for various patient characteristics, with the thought that confounders could be identified that would explain the excess mortality in the high dose groups.

On 11/18/98, the sponsor responded to the Not Approvable letter. This submission has been reviewed in detail by Dr. Greg Burkhart, Safety Team Leader, in a review dated 4/27/99, and by Dr. Randy Levin, Neurology Team Leader, in a review dated 5/3/99. Dr. Burkhart has concluded that there persists what he refers to as a weak signal (meaning that it is not likely to be related to the treatment), arising from both the controlled trials and uncontrolled experience, and recommends that additional data be gathered to further clarify this signal. Dr. Levin concludes that the application should not be approved at this time, but he also suggests that there are several different approaches that could reasonably be taken at this time, including approval. My own view is that the application should not be approved until additional data is obtained, and that the preferred action is to issue a second Not Approvable letter on or before the current PDUFA due date of 5/12/99. I will explain the basis for my decision in this memo.

As has been described in detail by Dr. Burkhart and others, the signal of increased mortality first arose in the controlled trials; using the most recent controlled trial data, the relative rate of mortality of drug compared to placebo is 2.7 (6/1923 pt-years on drug vs 1/868 pt-years on placebo for deaths within 30 days of the last dose) from the pooled Phase 3 controlled trials. This difference is not statistically significant, and there does not appear to be any specific cause of these deaths. There were 3 drug and 0 placebo deaths that occurred within 7 days of the last dose, with 2/3 drug deaths being classified as "sudden unexplained" deaths.

Multiple additional analyses have been performed by both the Agency and the sponsor. Obviously, before any analysis can be performed, a clear rule for deciding which deaths to include must be agreed upon. As described earlier, in the Not Approvable letter, the Agency asked the sponsor to determine which deaths could be considered not plausibly related to treatment, and then perform the analyses on the remaining deaths. Also, the analyses were to focus on deaths that occurred (or in which the initiating event occurred) within 7 days of the last dose.

The sponsor asked _____ to evaluate the deaths. Of the total 35 deaths that occurred in the extensions to the RCTs, _____ concluded that 16 were not implausibly related to treatment. On the other hand _____ concluded that all deaths were implausibly related to treatment. As Dr. Burkhart notes, it appeared as if Dr. _____ sought to determine which deaths were affirmatively related to treatment, which was not the task set to the sponsor in the NA letter.

Because any analysis performed of course will depend upon the deaths included, and because the sponsor provided such disparate enumerations of the events of interest, the Division constituted its own panel, consisting of medical reviewers Drs. Boehm, Feeney, and Freiman. This panel examined the relevant data on the cases (deaths) in a blinded fashion, and determined whether or not they were implausibly related to treatment. Of the 35 deaths in the RCT extension studies, this panel concluded that 21 were not implausibly related to treatment (interestingly, this panel used as one of the criteria for determining implausibility the fact that the death—or initiating event—occurred more than 7 days after the last dose).

Further, the sea of experience from which these deaths arose was a critical factor in the analyses. Specifically, several uncontrolled data sources existed: the extensions to the RCTs, and the “titration” studies. In these latter studies, patients were more rapidly titrated to a given dose, physicians were presumably given a freer rein to determine the patient’s final dose (compared to the extension trials), and patients also appeared, on average, to be somewhat different (considerably greater incidence, for example, of concomitant CV medications, etc.) than those in the extension trials.

Finally, the choice of the group to which mortality rates in the 10/12 mg dose groups were to be compared also was critical. For example, the sponsor argued that the appropriate comparator group should be the experience at doses below 4 mg/day. Alternate choices were, for example, all doses below 10 mg/day, including placebo.

Ultimately, analyses were performed on multiple data sets. In particular, the sponsor chose to emphasize the deaths that had occurred within 30 days of the last dose, pooling the experience from the extension and titration studies, and using as the comparator group the experience at doses less than 4 mg/day. In addition, the sponsor felt that the widely discrepant results of the “implausibility” classification performed by their 2 experts supported the view that this designation was inappropriate.

Dr. Burkhart, on the other hand, chose to emphasize the analyses (performed separately) using the deaths identified by _____ and the FDA review panel. In addition, he utilized, in his analyses, the deaths that occurred within 7 days of the last dose. Further, he argues that the titration data and extension data should not be pooled, but examined separately as well. Finally, he argues that the appropriate comparator group is that consisting of the experience at doses lower than 10 mg/day, including placebo.

I find Dr. Burkhart’s explanations for his choices compelling.

First, it is clear that, when seeking to identify adverse events related to a treatment, it is reasonable to examine those events that occur in a reasonable (usually close, but perhaps related to half life, etc.) temporal relationship to the last dose of treatment given (this is importantly to be distinguished from the question of the attribution of events to treatment seen at a considerable duration after the initiation of treatment, but while treatment is being continued, a point to which I will return later). As Dr. Burkhart noted, events seen at considerable durations after discontinuation of treatment are more likely to not be related to treatment, and the inclusion of these events in analyses is likely to obscure any differences between treatment and control (a bias towards the null, as he describes it).

While it is true that 7 days is an arbitrary time point, examination of the data suggests that the number of deaths does decrease with increasing time after discontinuation, and, further, 7 days was the period described prospectively by the Agency in the NA letter.

Next, the Agency asked the sponsor to classify deaths as not implausibly related to treatment for a valid reason. It is extremely difficult to affirmatively ascribe a cause of death based on the sort of clinical data collected in trials like those performed in this NDA. Because we can rarely have confidence that this can be done, the Agency asked that only those deaths which are clearly not (that is, implausibly) related to treatment be excluded from the mortality analyses; all other deaths could, by definition, possibly be related to treatment. It is of course true that reasonable people could disagree about which deaths are implausibly related to treatment, as well as which deaths were considered sudden; indeed, this was the case with those identified by _____ and the FDA panel. However, it is clear that _____ did not evaluate the deaths with an eye toward excluding only those that were implausibly related to treatment. On the contrary, he appeared to attempt to identify only those deaths which were clearly related to treatment. For this reason, it is reasonable to reject his assessment. Because there is no reason to reject the deaths identified by _____ or the FDA panel, separate analyses were performed on both sets.

The question of pooling the extension and titration data is a difficult one. However, as Dr. Burkhart has determined, there is statistical evidence that the estimates of risk in the titration and extension datasets are sufficiently disparate that it is inappropriate to pool these data (indeed, the risk estimate in the titration studies is in the opposite direction from that in the extension studies). However, again as noted by Dr. Burkhart, additional credence is lent to the decision not to pool the data from these 2 sources if it can be demonstrated that the patients in these 2 study types were fundamentally different. (In earlier submissions, the sponsor had, in fact, suggested that the titration patients were sicker than those in the extension trials, as an explanation for the finding that the overall mortality in the titration studies is about twice that seen in the extension studies, and this rate-20/1000 pt-yrs-is greater than that seen in other NDAs in comparable populations.) In an attempt to further investigate this issue, Dr. Burkhart found, for example, a substantially higher rate of use of 2 CV medications in the titration patients (79%) compared to that in the extension studies (4.9%). Also, 11.6% of the titration patients used no CV medications, compared to 62.6% in the extensions. These findings suggest that these patients might have been different in important ways.

Critically, the extensions represent about 75% of the experience at the high dose. This further argues for the appropriate consideration of this experience (compared to the controlled trials as well as the titration studies) being distinct from these other data sources.

For these reasons, it seems reasonable to consider these data sources separately. This does not mean that the titration data should not be considered. On the contrary, it should certainly be considered, but it should be considered separately from the extension data. How these 2 databases should be considered in the overall decision process is not entirely clear, but I will address this later in the memo.

Finally, the choice of the appropriate comparator group is also a difficult one, but as Dr. Burkhart notes, there is very little experience at less than 4 mg/day (the sponsor's choice), making this a relatively poor choice, given the instability of any mortality estimates that may arise in this group. In addition, it is entirely appropriate to compare the 10/12 mg group to the other dose groups (including placebo) because these are the only doses at which effectiveness was consistently established.

Given these considerations, we can turn to the analyses performed by Dr. Burkhart.

The following rates and rate ratios for _____ and FDA deaths within 7 days of discontinuation are reported below. The rates are given as deaths/patient-years, with the rate/1000 pt-yrs in parentheses (taken from Dr. Burkhart's Table 6):

	_____	FDA
RCT Extensions		
<10 mg	2/996 (2.0)	6/996 (6.0)
10/12 mg	17/991 (17.2)	15/991 (15.1)
RR (95%CI)	8.5 (2.0, 37.0)	2.5 (0.97, 6.5)
Titration		
<10 mg	6/301 (19.9)	8/301 (26.6)
10/12 mg	1/135 (7.4)	1/135 (7.4)
RR (95%CI)	0.4 (0.04, 3.1)	0.3 (0.0, 2.2)
All Studies		
Placebo	0/396 (0)	1/396 (0.3)
<10 mg	10/1943 (5.1)	18/1943 (9.3)
10/12 mg	19/1290 (14.7)	17/1290 (13.2)
RR (95%CI)	3.4 (1.6, 7.4)	1.6 (0.8, 3.1)

Nested case control analyses performed by the sponsor on the _____-identified deaths within 7 days in the extension trials yielded a relative mortality of between 3.9-5.0 (the latter adjusted for age, sex, baseline CV disease, GDS, baseline weight, and prior

exposure to drug in the RCTs) for high dose vs all other doses. The 95% CI's for both estimates range from slightly above 1 to between 14-18. As Dr. Burkhardt notes, the relative mortality increases with the re-classification of a single death (see his review, page 10-11). A nested case control analysis was not performed using the FDA classified deaths.

It should be noted that all rate ratios performed using 30 day deaths are lower than those cited above.

The following chart, adapted from Dr. Burkhardt's Tables 7, 8, and 9, represent information on sudden unexplained deaths (SUD), based on determinations made by the FDA review team. Ratios represent the number of SUD over the experience in patient years, with the rate, per 1000 patient years, given in parentheses:

	Overall	Between Days			
		0-60	61-180	181-365	365+
< 10 mg	2/996 (2.0)	0/237 (0)	0/260 (0)	2/315 (6.3)	0/184 (0)
10/12 mg	7/991 (7.1)	0/81 (0)	1/302 (3.3)	1/367 (2.7)	5/240 (20.8)

In an attempt to compare the mortality experience in this NDA with that in the 2 approved treatments for Alzheimer's Disease (donepezil and tacrine), Dr. Burkhardt examined relevant data from the NDAs of these 2 latter treatments.

For donepezil, the FDA review team performed an analysis analogous to that they performed for rivastigmine. The rate ratios for deaths within 30 days and 7 days in Study 303, which compared 10 mg to 5 mg, were 1.5 (0.5, 4.8) and 1.0 (0.3, 3.3), respectively. In this study, there were 163 patient years of exposure at 5 mg and 1109 at 10 mg. Note that the rate ratio decreases when moving from 30 day to 7 day deaths, unlike that seen with rivastigmine.

Mortality rates in all open phase 3 trials with donepezil hovered around 1 when comparing the 10 mg experience (1421 patient-years) with lower doses (about 400 patient-years) when all deaths and FDA classified deaths (including sudden unexpected deaths) are included.

No signal arises from the tacrine data, which was mostly derived from a single 30 week study (indeed, the rate ratios are below 1 when comparing 80, 120, and 160 mg individually to placebo).

Discussion

This data set has been subjected to extensive analyses, and there is no one analysis that can be considered "correct". The majority of the analyses have been performed on non-randomized data, and they are subject to all of the criticisms that normally apply in this

setting. Importantly, the use of p-values for inferential purposes in this setting is problematic at best, and probably inappropriate for the most part. Beyond the lack of randomization, a great number of sub-groups have been examined, a point the sponsor makes to cast doubt on the Agency's findings. It is true, but it should also be pointed out that comparing the high dose group to all other doses is, as Dr. Burkhart notes, a "natural" comparison, given that it is this high dose group in which the only consistent evidence of effectiveness is found, and that the entire enterprise is founded on the assumption that finding a dose response for mortality would be suggestive (though not proof, for all the reasons that these analyses are not definitive) of an adverse drug effect.

When the data are examined in toto, in my view they are suggestive of a signal of increased mortality, though, as noted above, these findings can in no way be considered to definitively establish that 10/12 mg/day of rivastigmine is associated with increased mortality compared to lower doses. Indeed, there is much in the data that mitigate the finding of an increased risk.

First, the original signal from the controlled trials is associated with a p-value of about 0.3, a value that would ordinarily not be considered significant, or close to significant, suggesting that this finding is certainly consistent with chance, if the true state of nature is that there is no dose related increase in mortality. This raises the question of whether or not this can fairly be considered even a signal.

Next, as has been noted by the sponsor, multiple contrasts have been performed, and numerous subgroups have been examined. Indeed, the various contrasts made (for example, the choice of examining deaths within 7 days instead of those within 30 days of the last dose, the choice of all lower doses, including placebo, as the appropriate comparator, etc.) can all be considered arbitrary and retrospective. Even given this, none of the rate ratios I have described have reached even nominal significance, **without** any corrections (even if it was possible, which I do not believe it is, to determine what an appropriate correction would be). Further, and importantly, the data examined are not randomized, so the chance that the findings we have seen are related to an as yet undetermined confounder are great. For example, it is possible that patients receiving the higher doses were sicker, in ways that we cannot at this time identify, than the patients who received lower doses, and were therefore at greater risk of dying (of course, the non-random nature of the data also make any p-values calculated not useful from an inferential perspective in any event).

In addition, the finding of increased mortality in the high dose patients would be more credible if a single, or predominant, cause could be determined, but none seems obvious. Many of the deaths appear to be related to causes common in an elderly population, with no common etiology that appears obviously related to a drug effect. Also, the sudden deaths appear late after treatment initiation, removed in time from the other deaths, which appear earlier and appear related to these more common causes. Had the sudden deaths appeared earlier, and overlapped the other deaths, that would have been more compelling evidence of a drug effect (sudden deaths are generally considered more likely drug related than other causes that appear commonly in this population, because it is possible

to imagine a mechanism-arrhythmias-that could explain them; also, the later during treatment a specific event occurs, especially sudden death, the less likely it is ordinarily attributed to drug.

Further, the data from the titration studies not only do not support a dose related increase in mortality, but suggest the opposite, and there is no obvious reason that this data should not be considered in the overall judgment, or even given less weight than the extension data.

All of the above are true. Nonetheless, certain findings have consistently been made in this data set. A numerical, non-significant increase in mortality was noted in the controlled trials, motivating, reasonably in my view, the review team to examine the rest of the database to further understand and characterize this finding, if possible. Various methodologies have been applied, including nested case control studies and person-year analyses. The datasets examined were admittedly arbitrary, but reasonably constructed, (although it should be pointed out that the use of all deaths except those that were not plausibly related to treatment that occurred within 7 days of the last dose was prospectively described in the NA letter), and all analyses based on these constructions yielded rate ratios greater than 1, varying from over 2 to over 8, using both case control and person-year (Poisson regression) methodology when the extension data are evaluated separately from the titration data. Even when the titration data are included an increase in mortality is still seen, albeit lower than that seen in the extensions alone.

The lack of an obvious cause of death (as well as the occurrence of sudden deaths late in treatment) certainly can be considered to suggest that the finding (weak though it is) does not "make sense", further weakening it. However, I am loathe to rely on a lack of understanding of an event to help dismiss its occurrence. Drugs can cause death in ways that we may not understand (certainly we cannot ascribe an obvious cause of any sort to most of these deaths), and while it is perfectly reasonable to search for a common cause in the face of the weak signal seen here, in an attempt to "strengthen" the signal, the absence of one should not, in my view, cause the signal to be dismissed. In any event, cholinergic drugs are known to have cardiac effects (rivastigmine causes bradycardia, for example), and it is possible that these, or other, mechanisms are at work but that we simply cannot easily detect them. Further, it is likely that, even if drugs did cause late deaths, or increase the incidence of deaths due to "common" causes (e.g., MI, pneumonia, etc.) through unknown mechanisms, this would be extremely difficult to know, and equally difficult to detect, given the sorts of studies ordinarily performed.

Importantly, it appears that there is little that is fundamentally different from the findings available at the time that the Not Approvable letter was sent. That is, the finding in the controlled trials is unchanged, and the analyses we asked the sponsor to conduct have been performed, and have not erased the signal, even though that signal is acknowledged to be weak (of course, the sponsor prefers to rely on analyses that further weaken the signal, but, as I have discussed earlier, they have not provided compelling arguments that would allow me to conclude that their analyses are preferable to those requested by the Agency). In particular, the letter held out the possibility that certain patient

have performed at this time. For example, if an appropriate increase in mortality of rivastigmine ~~over~~ donepezil could be excluded in an adequately designed and powered comparative, randomized trial, I might have a very different view of the approvability of the rivastigmine NDA, even in the absence of a concurrent placebo group.

The issues raised in this NDA have an important impact on the evaluation of safety for many drugs, especially for those being developed in the elderly. Specifically, current applications that do not examine mortality as a primary endpoint do not ordinarily provide the sort of evidence necessary to rule out important increases in mortality (Dr. Burkhart talks about detecting an excess risk of 1/100 pt-yrs, for example), especially if the deaths do not appear to be related to an obvious drug related cause. It might be appropriate to reconsider the standards currently applied in these settings (in terms of numbers of patients required to be exposed prior to approval, as well the designs of trials that could address these questions) so that we might have a good idea about the potential of these drugs to increase mortality compared to an appropriate control prior to approval. This seems especially important in the case of treatments with minimal symptomatic effects.

**APPEARS THIS WAY
ON ORIGINAL**

RECOMMENDATIONS

For the reasons stated above, I recommend that the attached Not Approvable letter be sent to the sponsor, and that we work toward scheduling a meeting of the PCNS Advisory Committee.

I realize, however, that the decision on this NDA is a difficult one, and turns on a personal judgment about the nature of the signal and whether additional data is necessary. For this reason, we are also preparing a draft Approvable letter and draft labeling, and we are forwarding these as well for your consideration.

//
/S/

Russell Katz, M.D.

Cc:

NDA 20-823

HFD-120

HFD-120/Katz/Levin/Mani/Burkhart/Nighswander/Rosloff/Fitzgerald

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: May 13, 1999
FROM: Director, Office of Drug Evaluation I
SUBJECT: Exelon (rivastigmine), NDA 20-823
TO: Dr. Katz

This application poses a difficult problem. It is clear that Exelon is effective and equally clear that an advantage over the marketed drug Aricept has not been demonstrated. Neither Aricept nor Exelon has a large effect, and it would be difficult to conclude that either could be marketed in the face of a significant risk. Exelon shows some evidence of dose-response for effectiveness, and, at least in many patients, requires a dose of at least 12 mg/day (6 mg bid) to be effective.

The data include a "signal" of increased mortality but the signal at the effective dose is weak and probably does not reflect an effect of Exelon. It arises principally from an examination of deaths in open-label uncontrolled extension studies and specifically, a comparison of mortality in patients receiving 10-12 mg/d of Exelon with patients receiving lower doses. Among the weaknesses of the data, all well-recognized by you, and Drs. Levin and Burkhart, are:

1. There is no plausible pharmacologic mechanism for lethality, except, perhaps, cholinomimetic effects, nor is there any pattern to the deaths, except that there are some late (after one year of exposure) sudden deaths.
2. The signal itself, for the whole database, does not attain nominal statistical significance and, as we would tell anyone dealing with data like this, nominal significance in such cases requires considerable adjustment. Given a starting nominal p-value > 0.05, outcomes of this kind can be expected often. What can we do to avoid over-reacting to spurious findings? The answer, I think, is that the plausibility of the finding needs to be considered clinically and pharmacologically as well as statistically. Specifically, the deaths themselves need a close look. This may seem obvious (Don't we always look at findings for sensibility?) but I'm describing a

fundamentally different approach to data that arise in a hypothesis-testing setting and data that do not. We are, appropriately, skeptical about attempts post hoc to adjust, subset, and in general “explain” unwelcome results in an RCT (even though, of course, these results can be chance occurrences, population, unique events, etc.). We have, in other words, a strong “prior” in favor of believing results from planned studies and analyses without modification. We know that an intelligent person can explain away most results, at least those not very extreme. In contrast data arising not from RCT’s but from non-randomized sources lack the basis for such believability and deserve aggressive “testing” for consistency, plausibility, etc. Strong, clear findings will survive this, weaker findings may not.

3. The deaths that drive much of the weak signal for Exelon are sudden death, within seven days of Exelon discontinuation that occur late (after 365 days) in treatment. This is a relatively implausible outcome for, say, a cardiac standstill-inducing or pro-arrhythmic drug; these generally affect vulnerable people early (not necessarily exclusively early; CAST showed both early and late effects for type 1C antiarrhythmics).
4. The reasons for excluding the titration studies, which do not support increased risk, from the pooled analysis, are, I think, circular, the principle one being that the risk estimates for the titration and extension studies are different. That says, in effect, if a non-significant increased risk is seen in one group of studies, a non-significant decreased risk in another group is not a “rebuttal” because it shows a different result. I thought looking at both sources was the point. I therefore consider the pooled results a major analysis (perhaps the major). The overall analysis, using FDA assessed possibly drug-related deaths, shows a RR of 1.6 (0.8-3.1), NS, and a very small RR for an epidemiology finding.
5. The SUD analysis (Katz, page 6) is of particular interest. For the entire period of 365 days (as I add them), there are 2/812 (<10mg) vs 2/750 (10-12mg) deaths, or close to dead even. All the difference comes from 5/240 vs 0/184 deaths after one year. As noted above, late SUD’s seem a little odd but late SUD without accompanying early SUD’s makes very little sense and seems very unpersuasive.
6. The blind review of deaths (March 23, 1991) is also of interest. Although one cannot know for certain what Exelon does or doesn’t do, many of the deaths seem pretty implausible to me. I can’t tell what effect dropping them would have (I don’t know the doses), but one might grade some of these deaths as, say nearly implausible. One reason for implausibility, in my view, is a serious finding unaccompanied by milder forms of the same thing. For example:

- a. Falls leading to hip fracture and a bad outcome (infection, etc.) could be a real consequence of a drug with orthostatic effects, but if this is so, one should see clear drug-related orthostatic or dizziness (and I don't see evidence of this) symptoms and plenty of non-fatal falls. I am therefore doubtful about five deaths that were consequences of falls:

30411011
30302004
30312016
30431015
35528105

- b. One should not have only fatal intracranial and other bleeds, AMI's, infections. There should be milder non-fatal versions of events (all of which are common in this population), perhaps often enough to show up in the controlled trials. I am therefore doubtful about these deaths:

30409003 – GI bleed
30305010 – Respiratory infection
30411003 – Chest infection
35103001 – Died with prostate Ca
35105003 – L frontal bleed
35106045 – GI bleed
35111049 – Infection, respiratory failure
35203025 – AMI
35204042 – Intraparenchymal bleed, hypertensive crisis
35207028 – AMI
35213004 – Renal/hepatic insufficiency
35510117 – Suicide
35518102 – CVA five days after last dose
35524116 – CVA
35528126 - ? respiratory infection

Obviously, I've found most of the deaths very improbable _____ as drug related deaths. In a different content they might be (e.g., suicides for a drug that causes depression; fall related deaths for a drug causing falls) but there's no pattern, no milder forms (at least not that I've noticed; this could need more exploration). The SUD's can always be considered plausible, but as noted, the pattern is very odd.

7. The various databases do not show a consistent pattern. The initial "signal" considering all deaths within 30 days, showed:

	<u>Deaths</u>	<u>PY's</u>	<u>Rate/1000 PY's</u>
Plbo	1	396	2.5
1-4	2	377	5.3
>4-6	3	125	23.9
>6-9	0	145	0
>9	1	165	6.1
<u>≤9</u>	6	1043	5.8
>9	1	165	6.1

The ≤ 9 vs >9 comparison is as close to the ≤ 10 vs 10-12 comparison in the extension data as we can get for the RCT's. There is, obviously, no finding [I would do the seven-day calculation but can't find the figures] so that the extension studies cannot be said to confirm a finding or signal in the RCT's. [The RCT signal was drug vs placebo, which the extension studies could not test]

The "titration studies," as has been described, show decreased deaths at the higher doses, also obviously not consistent with the extension "signal." There is nothing I've seen about the titration patients to suggest they are a relevantly (being sicker does not seem relevant) distinct subgroup or that findings in that group (decreased risk with dose) are not as plausible as opposite findings in a different group. The one possibly pertinent difference is that, without late extensions (beyond one year), these studies could not replicate the SUD-beyond-one-year finding, which is, I think, the only "finding" there is. As noted, the possibility that the group was "sicker" is not a good explanation for resistance to sudden death.

Nothing in the open databases forces one to divide the data into the <10 and 10-12 groups (except that we believe effectiveness is in the 10-12 mg range) and, of course, the data cuts for comparison are critical.

Given the weak signal and small number of events, one would certainly not expect confirmation in all data sets. On the other hand, a weak signal in one data set without similar trends in other data sets is a still weaker signal.

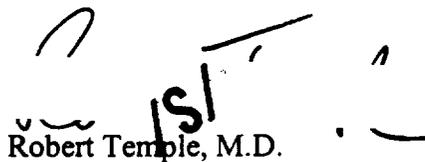
Conclusion:

The weakness of the signal of excess mortality is appreciated by all primary, secondary and tertiary reviewers, but most have recommended non-approval at this time, albeit with the acknowledgement that the case is very close. I differ only slightly with respect to my evaluation of the signal, but I believe approvability is appropriate. My reasons for not believing there is a meaningful finding can be found in sections 1-7 above. Most important is the complete failure of the three data sets to show similar findings, the random pattern of causes of death, together with the implausibility of the late sudden

death finding (see Burkhart April 27, 1999, page 22), the lack of nominal statistical significance together with need for a major adjustment (three study data sets, various dose cut points, seven day vs 30 day, and other inclusion/exclusion decisions).

Despite my skepticism, I believe the substantial number of unanalyzed deaths deserves evaluation prior to a final decision on approval (but because I expect the analysis to show nothing, approvability seems appropriate). Any residual doubt after this analysis should probably lead to presentation at PCNSAC. I do not believe the nature of the action letter will affect any discussion before the committee. I would also like to present this case at Rounds or elsewhere; we've had several similar cases and these experiences deserve sharing and discussion.

I am, more generally, concerned about the idea that even a very weak signal (NS and small relative effect, described by Dr. Burkhart, page 21, as weak on both of his strength measures and one "unlikely" to be related to drug exposure arising from non-randomized data, should be a basis for non-approval or even requesting more data prior to approval, which is the same thing as non-approval); after all, non-approval is what a strong adverse finding would lead to, rebuttable, of course, by further data. A strong and weak finding thus seem to lead to the same outcome. Given the certain that spurious chance findings will occur in the course of our examinations, we need to give some attention to how we will judge these observational approaches. This may also represent an opportunity to consider whether the controlled trial data bases for drugs with expected wide use should be larger, not so much because we've had any actual surprising findings (I don't consider sertindole surprising), but because expectations for assurance about risk may be greater.


Robert Temple, M.D.

- cc: Dr. Behrman
- Dr. Lumpkin
- Dr. O'Neill
- Dr. Bilstad

**APPEARS THIS WAY
ON ORIGINAL**