

in the analysis and that required a complete accounting of the sea of patient-time exposure from which they arose.

Importantly, as the firm did not appear to have a "resident" epidemiologist on their staff, Dr. Burkhart and his Safety Unit colleagues offered a number of suggestions for analytic approaches that might prove helpful in the evaluation of the data. In particular, Dr. Burkhart pressed the firm to conduct a more extensive nested case control study that would not only be based on more deaths, but upon a much larger number of controls per risk set. The goal was not simply to evaluate the link between mortality and dose, but to see whether other subject attributes/covariates (e.g., use of concomitant medication, weight loss, concomitant illness, etc.) could explain the signal.

It bears note, in anticipation of latter discussion concerning the firm's views on its choice of poisson regression to pursue the signal detected by Drs. Oliva and Racoosin, that a nested case control offers considerable efficiency over such a model based approach. The advantage lies in the fact that a nested case control only requires that covariate information be collected on a subset (i.e., the case and the random sample of controls matched to the case) of the patients in the population. In contrast, model based approaches used to evaluate the effect of covariates ordinarily require that the status of each patient in the entire data set be known in regard to each covariate examined. Accordingly, although a logistic or poisson model based regression analysis may in theory allow a more complete assessment of "all the clinical experience" gained with a drug, it can only do so if all relevant covariates are known for every patient to be included in the analysis and the collection of this information for a large cohort can prove both costly and time consuming.

Perhaps an even more fundamental limitation of model based analyses is the fact that their results are invariably dependent on the specification<sup>7</sup>

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<sup>7</sup> The firm makes essentially this very point (May 12, 1998 Discussion section, page 72, para 2 last sentence), although clearly with a different intent, when it complains, in respect to a particular partition of the data used by the agency in its analyses, that rate ratios are driven by "how the dose strata are created, rather than an effect of dose, per se." Ironically, the firm may fail to appreciate that this is a major reason that the Dr. Burkhart preferred a risk set based approach to a model

of the terms ~~used~~ in the function predicting the risk (e.g., mortality rate as in the present case) of interest.

In any event, the firm did not follow the Division's preferred approach (nested case control analysis), but elected to conduct analyses on the expanded data sets using "Poisson regression."

### **The Division's subsequent interactions with Novartis**

Throughout February and March, members of the Division's review team had repeated telephone conversations and fax communications with representatives of Novartis in an effort to develop strategies for further analyses of the data available and/or subject to retrieval, that might provide a better understanding (i.e., an explanation ) of the signal.

The firm's initial written response, made on 3/9/98, was found upon inspection to contain errors and inconsistencies that rendered it unsuitable for immediate review (Burkhart, 3/12/98 memorandum). Within days (i.e, 3/16/98), the Division team was again in contact with Novartis in an attempt to clarify the discrepancies and gain additional data to aid the team in its review. As these contacts continued, additional requests and suggestions were made by members of the Division's review team. As a consequence, a relatively large number of analyses of different data sets have by now been carried out.

### **Commentary**

#### **Some acknowledgements about the basis for the Division's concern**

At the very outset, it bears emphasis that the evidence being considered provides a signal of concern, not proof, that exposure to Exelon increases the risk of death among patients who are exposed to it.

It also bears acknowledgement that my understanding of the evidence derives not only from the written review documents generated by

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dependent analysis.

members of ~~the~~ team, but from any number of conversations and meetings held with its members. I am especially indebted to Dr. Burkhart whose expertise in epidemiologic analysis strategies, risk models, and their actual conduct has been invaluable in furthering my understanding of the "signal."

Finally, I want to acknowledge that I am fully mindful that all the analyses conducted, save for those based on the data adduced in the phase 3 RCTs that involved comparisons to a placebo control, were developed with data that 1) were obtained from a variety of heterogenous sources and 2) rely on comparisons among groups (subsets) of patients created, not by randomized assignment to the putative risk factor of interest (i.e., rivastigmine, dose of rivastigmine, dose of rivastigmine/ kilo etc.), but by the analyst conducting the exploratory evaluation. This limitation, importantly, applies both to the analyses done by the Division and the sponsor.

An important corollary to the post hoc nature of these analyses is the fact that any and all estimates of the probability of obtaining the differences in rates seen under the null (i.e., that rivastigmine has no influence on the incidence of mortality) that have been produced are without formal inferential value. This is not an issue in dispute.

Where exploratory analyses are involved, 'p' values have no compelling probative value, no matter how small they may be. Contrawise, large "p" values (i.e., those that are nominally non-significant by traditional standards) have no meaning either, but for a different reason, specifically, lack of statistical power. Even if the comparisons made were between randomized groups, the number of events observed are too few to provide the power necessary to exclude differences in rates that might be important from a public health perspective.

These acknowledgements made, some additional comments on the methods being used seems a necessary prerequisite to a discussion of their findings.

### **Model-based analyses and their limitations**

Both the sponsor and Dr. Burkhart have conducted explorations of the putative linkage between rivastigmine exposure and risk of mortality using a technique known as poisson regression. Poisson regression is widely used in epidemiology when, as I understand it, there is a need to assess the effect of patient attributes/covariates on the rate (i.e., incidence density) of an event where person-time is used in the denominator of the estimate (e.g., counts of persons with the event/1000 PYs). When events are not so rare, and the effect of time at risk is less critical (i.e., censoring is low or presumed to be non-informative), logistic regression would be the analogous analytical strategy used to assess how the frequency of an event[ counts of persons with events/person at risk] was affected by subject attributes/cofactors.

Poisson and logistic regression alike generate a result which represents the ratio of a probability (or ODDs) of an event happening to individuals with a particular set of attributes relative to the risk of that event occurring in a member of some index or control group. Accordingly, the results of such analyses can be highly sensitive to the choice of the control group which, in settings where the control is not naturally defined (e.g., no exposure to the risk factor) or defined by protocol (e.g., randomized assignment to placebo), is entirely in the hands of the analyst.

On a more generic level, the results of poisson regression, like that of any model based method of analysis, can turn on the specification of a particular realization of the model. For example, the decision to include or not include a particular covariate, or the way a covariate is defined, can affect the results obtained with a given data set. This latter aspect of all such models is a major reason why so many frequentist statisticians have so much trouble with analyses that employ data conditioned choices of covariates, especially when the latter are chosen to rescue an otherwise failed or negative experiment.

Accordingly, analyses that require fewer assumptions and bind the analyst by protocol rules are ordinarily preferred when a definitive decision is to be made. In an exploratory mode, however, these limitations must merely be borne in mind because, as noted earlier, the analyses are intended to

explore an ~~issue~~, not to resolve it definitively. Nonetheless, even when explorations are being made, findings that are model independent are generally accorded greater weight than those that depend upon the arbitrary assumptions or specifications of the modeler.

### **The data, the analyses, and their interpretation**

My current views on the question of the risk of mortality posed by the use of Exelon derive largely from the work of the Division's safety group that was carried out by or under the direction of Dr. Burkhart. Not surprisingly, therefore, this memorandum is largely derivative of his exposition of the issues.<sup>8</sup>

The tables that follow below provide a succinct summary of the phase 3 clinical experience from which the deaths and patient-time exposure used in the estimation of mortality rates for Exelon derive. In aggregate (across all 3 sources identified below), the phase 3 experience represents some 3629 patient years of use in 3162 individual patients. Fifty six (56) deaths were reported to have occurred (among patients taking, or within 30 days of withdrawal from, rivastigmine) during this patient-time experience (accumulated through the end of June of 1997). The crude estimate of overall mortality among all rivastigmine users is, therefore, 15 deaths per 1000 patient years.

This experience can be subdivided into 2 major sources: 1) that gained in some 2791 Patients who participated in phase 3 randomized controlled trials and 2) that gained in another 559 patients who received rivastigmine in 2 open, so-called, titration studies. A proportion of patients who participated in the randomized controlled phase 3 trials subsequently elected to continue open treatment with Exelon in extension phases to the RCTs. The latter provide the bulk of the patient-time experience with higher (i.e., 10 to 12 mg) doses of rivastigmine

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<sup>8</sup> Dr. Burkhart's March 26, 1998 review of the firm's March 9th submission and his May 28th overview of the mortality findings and experience up to and including the date of June 30, 1997 (as reported in the Novartis submission of May 12, 1998)

**Subjects Entered into RCTs  
(Total n = 2791)**

**Drug:**  
n=1931  
PYs = 805

**PBO:**  
n = 860  
PYs = 396

**6 deaths  
7.5/1000 PY**

**1 death  
2.5/1000 PY**

Dose	Deaths	PY	Rate
1-4	2	377	5.3
5-6	3	125	23.9
7-9	0	145	0
10-12	1	165	6.1

**Subjects Entered into Extension phase to RCTs  
(Total n = 2010)  
(N.B. all patients were re-titrated)**

Dose	Rivastigmine in RCT phase 22 deaths in 1346 PY 16 deaths/ 1000 PY			PBO in RCT phase 13 deaths in 641 PY 20 deaths/ 1000 PY		
	Deaths	PY	Rate	Deaths	PY	Rate
1-4	0	79	0	3	56	53.6
5-6	4	354	11.3	2	222	9.0
7-9	1	194	5.2	2	91	21.9
10-12	17	719	23.6	6	272	22.1

**Rapid Titration Open Trials  
(Total n = 559)**

**14 deaths in 436 PYs  
32 deaths/1000 PY**

<b>Dose</b>	<b>Deaths</b>	<b>PY</b>	<b>Rate</b>
1-3	2	104	19.3
4-6	5	113	44.4
7-9	5	84	59.2
10-12	2	135	14.8

Some numbers entered in the preceding tables may not be identical to those provided in other reports/reviews; these differences are attributable to different methods of patient-time assessment, to differences in dose partitions, and, possibly to minor enumeration/calculation errors. These discrepancies are minor, however, and unlikely to affect anyone's view of the evidence.

Data on mortality and dose in Phase 2 clinical trials are also available<sup>9</sup>, but they provide very little experience (93 PYs) at doses above 6 mg/day and so will not be considered further.

**Some preliminary observations about the data arising from the 3 major data sources**

The overall pooled mortality rate across all sources of rivastigmine exposure collected in the Novartis development program is 15 deaths per 1000 patient-years, a rate that is seemingly consistent with the

<sup>9</sup> See Table 12, page 32 of the firm's May 12, 1998 submission for details

estimates that we have so far been able to obtain for one other anticholinergic drug product<sup>10</sup> for which we have an incidence density estimator of the mortality rate.

In assessing the 3 tables presented above, several points are of interest.

First, that less than 25 % of patient observation time (805/3629) gained with rivastigmine comes from experience gained in the randomized, placebo controlled segments of the phase 3 controlled trials, and of that, less than half is at doses in the higher end of the dosing range from where the stronger evidence documenting Exelon's effectiveness in use comes. Among the 56 deaths, only 6 occurred during Phase 3 controlled trials. In sum, the bulk of the information bearing on the putative risk of higher doses of Exelon is derived from sources for which there is no reliable estimate of the mortality rate in the absence of drug treatment (i.e., no placebo controls).

Second, that in the so called open titration studies (354 and 355), there is no apparent association of the mortality rate and dose, but the overall mortality rate (32 deaths /1000 PYs) is slightly more than double that for the Exelon development program as a whole (15 deaths/1000 PYs) and more than four times that seen in patients randomized to Exelon during the randomized controlled trials ( 7.5 deaths /1000 PYs) In the absence of a comparable no treatment control group, the titration experience can either be taken as reassuring (lack of an apparent dose response) or disconcerting (i.e., rates twice and 4 fold that seen in the overall program and the controlled trials, respectively).

Third, the relationship of dose to mortality rate in the extensions (Studies

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<sup>10</sup> In the still pending \_\_\_\_\_ the mortality rate (based on Dr. Burkhardt's preliminary analysis presented to the team on 6/29/98) among patients randomized to placebo in controlled clinical trials was about 12/1000 PY; among those randomized to the drug, the rate was 10/1000 PY (11/1091 PYs) across all NDA experience. For the approved drug product, Aricept™ (donepezil, aka E2020), the data necessary to construct a patient time analysis are not available, but in Dr. Boehm's survey (6/3/98) of 25 deaths, 13 were on 5 mg, 3 on 10 mg, and 1 was on 20 mg.; the 8 remaining deaths were reported without information bearing on their dose at the time of death.

305 and 353) to the 4, phase 3 randomized controlled trials are dependent upon whether or not the patients were randomized to Exelon or to placebo during their randomized comparison segments. This difference is certainly perplexing, and is again subject to arguable interpretation. It is also noteworthy for other reasons, however.

The firm, in making its case that the signal arising in Dr. Racoosin's nested case control is an artifact, asserts that the patients randomized to placebo in the phase 3 RCTs were for some reason atypical, that is, as a group, they were at a much lower risk of death than the population from which they were recruited (i.e., their observed mortality rate of 2.5 deaths/1000 PY certainly seems consistent with that contention). If so, however, it is difficult to reconcile that assumption with their observed mortality rate of 20 deaths/1000 PYs after being switched to Exelon. Moreover, although it is not a controlled comparison, the dramatic (an 8 fold increment -- from 2.5/1000 to 20/1000 ) in the mortality rate among these previously placebo randomized after being begun on Exelon is, itself, a signal sui generis. (It does, however, also depend upon the low rate in the controlled and blinded segments of these studies).

Also of note is the fact that the apparent lack of a dose response in the placebo patients switched to Exelon during the extension experience is due to 3 deaths occurring among 56 PYs generated by patients at the 1 to 4 mg dose range row. The sensitivity of these analyses to a few patients in a particular sparse cell is well illustrated by this observation, but, admittedly, it applies equally to most of the analyses conducted with these data.

Fourth, although not presented in the summary table of phase 3 experience that appears above, Dr. Burkhart also examined the extension study experience to assess the extent to which the incidence of mortality is affected by the duration of the post-treatment interval in which a death can be deemed attributed to treatment. Tables 5A and 6A<sup>11</sup> (page 12 of his May 28 review) reveals that the dose mortality rate pattern remains basically the same when only deaths that occurred on drug or within 7

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<sup>11</sup> Note: 6A is incorrectly labeled in Dr. Burkhart review as representing drug patients; it actually refers to those on placebo in the RCT.

days of drug discontinuation are considered.

**Poisson regression analyses.**

One way to attempt to make sense of data of this kind is to model it so as to determine whether or not, and if so how, the mortality rate is affected by explanatory factors (e.g., confounders) other than dose.

Some of the limitations of the model based approach have already been discussed. In particular, different models of the same data can produce different results. A further complication is that different statistical tests of a particular model's results may support different conclusions. In multivariate regression, for example, a test of one model containing a term of interest against another identical save for that term (e.g., a likelihood ratio test) may produce a different result than a test of whether or not a particular parameter in a model is zero or not (i.e., a Wald test based on the parameter estimate and its standard error-or equivalent).

Dose Group	Deaths	Patient Years	Rate/1000 Years
placebo	1	396.1	2.5
1 to < 4 mg*	6	456.1	13.1
4 to 6 mg	15	972.7	15.4
> 6 to 9 mg	8	514.0	15.6
> 9 mg	26	1290.3	20.1
<b>TOTAL</b>	<b>56</b>	<b>3629</b>	<b>15.4</b>

The table above represents the phase 3 experience that was in whole or in part modeled by both the sponsor and Dr. Burkhart (Table 19 on page 43 of the sponsor's May 12, 1998 submission; also Table 1 of Dr. Burkhart's May 28, 1998 review, page 10).

**The firm's poisson regression analyses**

In their analyses of this data, the firm analyzed mortality as a function not only of dose, but of age (binary, split at age 75), sex, study, and time since study entry or TSSE (split at 100 days).

The timing of this split of the TSSE at 100 days in their model is important because a major thrust of the firm's argument is that the apparent dose related risk of mortality seen in some of the data is likely to be explained by an increasing hazard of mortality over time. If so, and if dose is confounded with time as it appears to be, then the link between high dose and higher risk of death would, at least in part, be an artifact.

The following table, that presents the results of the sponsor's poisson regression analysis of the extension phases of the RCTs would seem to support their assertion.

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	Dose /mg/d	PYs	deaths	crude rate ratio	adjusted rate ratio
	1-<4	134	3	1	1.0
	4-6	577	6	0.5	0.4
	>6-9	285	3	0.5	0.5
	> 9	991	23	1.1	1.0
Time	≤ 100 days				1.0
	> 100 days				3.5
Age	≤ 75 years				1.0
	> 75 years				2.4

Extracted from Table 17, page 41 of May 12, 1998  
 Novartis Submission for extension phase poisson regression

The relative importance of the 3 deaths in the 1 to < 4 dose range, and the important role of TSSE and age as confounders of the risk seen in this analysis.

Across all phase 3 experience, (see the table below derived from Table 19 in the firm's submission) the suggestion of a dose related increase in mortality is again seen, although it would appear, based on this particular analysis to be unimportant in comparison to the confounding effects of age and TSSE.

	Dose /mg/d	PYs	deaths	crude rate ratio	adjust-ed rate ratio
	1-<4	456	6	1.0	1.0
	4-6	973	15	1.2	1.1
	>6-9	514	8	1.2	1.2
	> 9	1290	26	1.5	1.4
Time	≤ 100 days				1.0
	> 100 days				2.1
Age	≤ 75 years				1.0
	> 75 years				2.3

Extracted from Table 19, page 43 of May 12, 1998  
 Novartis Submission for all Phase 3 experience  
 poisson regression

Although other points made by the firm could be included here, the poisson analysis results just presented are, in essence, the crux of the sponsor's case that the evidence, examined as a whole, provides no indication of a rivastigmine associated increased risk of mortality.

The evidence, however, when examined from a slightly different perspective, reveals that the firm's position cannot be accepted as being as persuasive as the sponsor contends..

### **Dr. Burkhart's poisson regression analyses**

Dr. Burkhart also examined the extension experience, (representing 1987 of the 3629 PYs in the phase 3 experience), using a poisson regression approach.

His initial model linked the Mortality rate to dose (4 levels), and prior exposure to drug in the RTC( binary) and an interaction term (included because on a likelihood ratio test the model including this terms fit the data considerably better than one without it,  $p = 0.10$  for the Likelihood ratio[LR] test). He then modified the model and partitioned the data in an effort to identify what, if any, other factors also affected the overall mortality rate<sup>12</sup>. The table below is reproduced from table 3, page 10 of Dr. Burkhart's 5/28/98 review; it provides an overview the extension experience he modeled.

Dose Group	Deaths	Patient Years	Rate/1000 Years
1 to 4 mg	3	135	22.2
5 to 6 mg	6	577	10.4
7 to 9 mg	3	283	10.5
10-12 mg	23	991	23.2
<b>TOTAL</b>	<b>35</b>	<b>1986</b>	<b>17.6</b>

<sup>12</sup> The results of these analyses are presented in a series of tables on pages 10 through 14 of his May 28 review.

When the data employed to create the table presented above are partitioned according to the treatment assignment of the contributors during the randomized phase 3 trials, a different picture of the evidence emerges; the results are shown in the next two tables, (derived from Tables 5 and 6 on page 11 of Dr. Burkhardt's review).

The first of the two, (from Burkhardt's Table 5), presents the experience of patient who were assigned to drug in the RCT segment.

Dose Group	Deaths	Patient Years	Rate/1000 Years
1 to 4 mg	0	79	0
5 to 6 mg	4	354	11.3
7 to 9 mg	1	194	5.2
10-12 mg	17	719	23.6
<b>TOTAL</b>	<b>22</b>	<b>1356</b>	<b>16.2</b>

The influence of dose group level on morality risk is self-evident.

The second table (from Burkhardt's Table 6), enumerates the experience gained with patients who were assigned to placebo in the DB segments of the controlled trials. In contrast, the second table shows no trend, but it

Dose Group	Deaths	Patient Years	Rate/1000 Years
1 to 4 mg	3	56	53.6
5 to 6 mg	2	222	9.0
7 to 9 mg	2	91	21.9
10-12 mg	6	272	22.1
<b>TOTAL</b>	<b>13</b>	<b>641</b>	<b>20.0</b>

again is worth noting that the experience of the low dose group has a major impact on the table. It is also worth recalling that the overall rate

of mortality (~~29~~/1000 PY) among these patients is some 8 fold greater during their extension experience than during their double blind experience (2.5/1000 PY).

Another important difference between Dr. Burkhart's modeling of the data and the firm's is the approach used to assess whether or not the mortality rate increases systematically with time. This question is of considerable importance in view of the sponsor's contention that rivastigmine dose is confounded with increasing time and that, therefore, the signal of a dose dependent risk is actually due to the confounding of dose and a time dependent increase in the hazard of mortality.

Dr. Burkhart looked at the interval hazard, not as function of a single cut point, but several. The following table, reproduced from Table 8 in Dr. Burkhart's review, page 13, shows that the firm's hypothesized time dependency in the mortality rates (deaths/ 1000 PY) is not consistent with the experience in the extension phase when it is examined more closely. In fact, the rate is, if not stable, falling after 180 days.

	0- 60 days	61- 180 days	181-365	>365
Rx in Rct	0	23.8	19.4	13.8
Placebo in RCT	9.5	27.3	23.0	14.9

In sum, Dr. Burkhart's poisson analysis is not anywhere as reassuring as the sponsors. To the contrary, it continues to find signals in the evidence that are not inconsistent with an effect of rivastigmine dose on the mortality rate.

#### **Conclusions about Exelon's use and the risk of mortality.**

Neither I nor member of the review team is persuaded that the evidence available shows definitively that the risk of mortality increases as a function of Exelon dose/exposure. On the other hand, neither I nor any member of the review team is ready to conclude at this point in time that

the evidence ~~excludes~~ that possibility.

### **Options in the face of uncertainty.**

In my personal view, the decision on the Exelon NDA cannot rationally or reasonably be made without considering the potential risks and gains that would accrue from its addition to the armamentarium.

At this point in time, two cholinesterase inhibitors, Cognex and Aricept, are already marketed for the symptomatic management of dementia. There is no evidence to support a belief, let alone a conclusion, that Exelon offers any advantage to either marketed product in regard to effectiveness, although it may well offer an advantage vis a vis convenience of use to Cognex (i.e, its use is not associated with a high incidence of transaminase elevation requiring biweekly LFT monitoring).

In light of these facts, I believe it would be imprudent to recommend the marketing of Exelon on the basis of the evidence in hand. Exelon is a me-too drug product, and for that reason alone, the agency should be reasonably certain prior to allowing its marketing, that it poses no greater net risk than already marketed drug products belonging to the same therapeutic class.

Accordingly, although I have not yet reached a definitive conclusion about the linkage between Exelon dose and risk of death, I cannot recommend that the application be declared approvable at this time.

### **Conclusion**

A not approvable action letter should be issue. The letter should convey that the decision taken was a difficult one and in no way reflects a definitive judgment that Exelon use causes an increased risk of mortality.

The letter should demand, however, that the firm needs to do additional work. Whether or not that will necessitate the conduct of a large clinical trial using a fixed dose parallel approach or not is unclear to me. Another possibility, one that was suggested to the firm earlier, is a large case

control study using existing data but would be based on much larger and more elaborate enumerated risk sets.

I see the latter approach as less likely to be sensitive to arbitrary modeling assumptions, and the firm might like it because it could be done with data already in hand. I am informed that a Cox Proportional Hazards model that uses both baseline and time dependent covariates might represent a reasonable alternative. Again, this is a matter for expert consultation.

A handwritten signature in black ink, appearing to be 'P. Leber', written over a horizontal dashed line.

Paul Leber, M.D.

July 2, 1998

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Leber: Exelon NDA Not approvable Action memorandum

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cc: NDA 20-823

HFD-101

Temple

HFD-120

Katz

Levin

Burkhart

Oliva

Feeney

Racoosin

Boehm

Nighswander

Fitzgerald

Rosloff

HFD-710

Hoberman

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**Review of Clinical Data  
May 12, 1998 Amendment Updating the Mortality Experience  
with Rivastigmine Through June 30, 1997**

**Additional Analyzes Supplementing my May 28, 1998 Review**

**NDA:** 20-823

**Sponsor:** Novartis

**Drug:** Rivastigmine

**Route of Administration:** Oral

**Reviewer:** Greg Burkhardt, M.D., M.S.

**Review Completion Date:** July 7, 1998

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This memorandum provides some additional analyzes that I have conducted on the data submitted in the May 12, 1998 amendment in preparation for a July 6, 1998 meeting with Novartis to discuss the apparent increase in mortality with rivastigmine. Dr. Temple asked me to conduct an additional analysis of deaths in the RCT extensions where we consider only deaths that occurred closer in time to the last prescribed dose than the 30 days that Novartis, Dr. Racoosin and I had previously used to define deaths of interest. At the same time as conducting this analysis, I also computed mortality rates in the RCT extensions for each dose used thereby not performing any categorization of dose.

This memorandum also enumerates the sudden deaths that were identified by Dr. Knudsen, a member of the division's safety team, in his review of 49 of the 56 deaths used in the most recent analysis. Finally, I address Novartis's argument that if the titration period in the RCT extensions is excluded from analysis there is no evidence of risk.

**Mortality rates for deaths within 7 days of last prescribed dose in the RCT extensions**

Using the same dataset that was provided in the May 12 amendment (June 1997 update), I identified deaths that occurred within 7 days of last prescribed use. While 7 days was an arbitrary choice, I did not explore other definitions before settling on this one.

Since Novartis has argued that the interpretation of the mortality by dose group hinges on the dose category definitions (i.e., varies depending on whether 4 mg is in the lower dose, and what dichotomous cut points one uses, etc.), I have also computed the mortality rates for each daily dose used in the RCT extensions, both for deaths within 30 deaths and those within 7 days. Tables 1-4, display these results.

Several interesting features to the data resulting from the changes are apparent. First, when focusing on deaths within 7 days of last prescribed use and eliminating the dose categorization, I think there is greater concern about high dose exposure across all extension experience independent of whether patients had prior exposure in RCTs or not (Table 1). However, the changes also seem to enhance the apparent difference in the mortality patterns when stratifying patients on whether they had prior exposure to drug in the RCT or not (Tables 2 and 3). Finally, note that in patients with prior exposure in the RCTs, the rate ratio for the 10/12 mg dose group compared to all lower dose experience increases from 2.7 to 4.4 when considering deaths within 7 days.

The increase in the rate ratio is somewhat worrisome since it is consistent with risk that is related to current or very recent use of the drug. In a hypothetical scenario where we know that a drug causes events only during current use, focusing on events that occur well after current use will capture events that can not possibly be related to use of the drug, an effect that many have referred to as "a bias towards the null". In such a case, the risk becomes more apparent as we analyze deaths that are closer and closer to the last use of drug. Thus, observing a material increase in the rate ratio (from 2.7 to 4.4 is a 63% increase) is consistent with a drug that has an acute risk although such an increase could still be sampling error as well.

Dr. Leber has suggested repeating this analysis focusing on deaths that occur on drug, those that occur within a week of discontinuation and then from 7-30 days after discontinuation. Such an analysis may be helpful particularly if one is concerned with a hazard upon withdrawal. The "nested" case control study design is particularly well suited to evaluating such a question.

Table 1. Mortality rates by dose for all extension patients separately for deaths within 7 days and then within 30 days of last prescribed use.

Dose	PYRs	<u>Deaths Within 7 Days</u>		<u>Deaths Within 30 Days</u>	
		Counts	Rate	Counts	Rate
2	134	1	7.5	3	22.4
4	221	1	4.5	2	9.0
6	355	1	2.8	4	11.3
8	285	3	10.5	3	10.5
10	231	2	8.7	5	21.7
12	760	12	15.8	18	23.7

Rates are deaths per 1000 person years (PYRs)

Table 2. Mortality rates by dose for extension patients assigned drug in the RCTs separately for deaths within 7 days and then within 30 days of last prescribed use.

Dose	PYRs	<u>Deaths Within 7 Days</u>		<u>Deaths Within 30 Days</u>	
		Counts	Rate	Counts	Rate
2	78	0	0.0	0	0.0
4	132	0	0.0	0	0.0
6	222	1	4.5	4	18.0
8	194	1	5.2	1	5.2
10	168	2	11.9	4	23.9
12	552	9	16.3	13	23.6

Rates are deaths per 1000 person years (PYRs)

Table 3. Mortality rates by dose for extension patients assigned placebo in the RCTs separately for deaths within 7 days and then within 30 days of last prescribed use.

Dose	PYRs	<u>Deaths Within 7 Days</u>		<u>Deaths Within 30 Days</u>	
		Counts	Rate	Counts	Rate
2	56	1	17.9	3	53.6
4	89	1	11.2	2	22.4
5	133	0	0.0	0	0.0
8	91	2	21.9	2	21.9
10	63	0	0.0	1	15.9
12	208	3	14.4	5	24.0

Rates are deaths per 1000 person years (PYRs)

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Table 4. Adjusted Rate Ratios for 10-12 mg Compared to Lower Doses

	Adjusted RR	95% CI
<u>All Extension Patients</u>		
Deaths within 30 days	1.8	0.9,3.6
Deaths within 7 days	2.2	0.9,5.8
<u>Extension Patients with Drug in RCT</u>		
Deaths within 30 days	2.7	1.01,7.5
Deaths within 7 days	4.4	0.96,19.9
<u>Extension Patients with Placebo in RCT</u>		
Deaths within 30 days	1.0	0.3,3.0
Deaths within 7 days	0.9	0.2,4.1

Adjusted for age, sex and time since study entry

**Additional review of deaths to identify those that appear to be “sudden” in nature**

I asked Dr. Knudsen from the division’s safety team to review the 56 deaths used in the most recent analysis to determine which were “sudden” in nature. For this review, I asked Dr. Knudsen to define “sudden” as a death occurring in a patient who appeared to be physiologically stable within 24 hours of death in his opinion. Given the limited number of sudden deaths and paucity of clinical details, he did not try to determine which, if any of the sudden deaths, were also “unexplained”.

Dr. Knudsen was able to review the clinical materials for 49 of the 56 deaths with 7 deaths missing CRFs and/or narrative summaries. In his opinion, he found 13 of the 49 deaths to be possibly “sudden” in nature. The 13 PIDs were 30309004 30312016, 30329008, 30331002, 30342006, 35105021, 35112014, 35203002, 35211009, 35502104, 35516101, 35522103 and 35526102.

Of the 13 deaths classified by Dr. Knudsen as “sudden”, 4 (30331002, 35112014, 35203002, 30312016) occurred in RCT extension patients who had prior exposure in the RCT. The last prescribed doses of these 4 were 12, 10, 12, and 10, and 3 of the 4 occurred within 7 days of the last prescribed dose. There were 4 other possible sudden deaths in extension patients who had placebo in the RCT (30329008, 30342006, 35105021, and 35211009). Their last prescribed doses before deaths were 8, 12, 2 and 2 mg, with 2 of the 4 within 7 days of the last prescribed dose.

In my view the numbers are too small to draw any conclusion other than that the distribution of the sudden deaths by dose is consistent with the extent of use at each dose for the two groups of patients. In short, we do not have a “clinical cause” for the apparent excess in deaths in patients who had prior exposure to drug in the RCTs. The only clinical

finding remains Dr. Oliva's observation that the high dose deaths had more weight loss than other deaths at lower doses or surviving patients who had high dose exposure.

**Does exclusion of the titration period eliminate the signal as claimed by Novartis?**

On page 50 of Novartis's May 12, 1998 submission, they report findings after "excluding the titration period" from the extension experience and interpret these as showing no evidence of a signal. They also presented this analysis at the July 6, 1998 meeting.

I somewhat addressed this question in my May 28 review in Tables 9,10 and 11 which show mortality rates, case counts and person-time stratified by time since study entry which was classified as the first 60 days, days 61-180, days 181-365 and days 365+. It is clear when looking at Tables 9-11 that my concern about the 10 and 12 mg dose group remains irrespective of the experience in the first 60 days of experience. This is particularly true for days 61-180 and for patients with prior exposure.

The Novartis analysis is based upon a fundamental epidemiological error in the methods of making observations in time. In effect, they "start the clock" for time-at-risk after they know where a patient ends up with respect to dose. In other words, they are arguing that patients who reach higher doses were never at risk at lower doses, and therefore this time at lower doses in such patients should be excluded from the analysis. Of course, the mortality rate in the low dose group has to increase since the numerator remains the same (they couldn't reach higher doses because they died) but the denominator gets smaller because time has been excluded.

Of course, the clock for determining "time at risk" should always be prospectively defined - not after one knows that patients survived the titration period. The fact that I am alive today does not mean I wasn't at risk to die yesterday. This is not to say that I don't think one should examine rates conditional on time since starting the study. In fact, I do exactly that in Tables 9-11. However, such a conditional analysis has to use the same time periods for each patient that are not determined by a patient's tolerated dose.

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## Conclusion

The apparent increase in mortality at 10/12 mg in patients with prior exposure in the RCTs remains unexplained. When examining the deaths within 7 days of last prescribed use, the relative increase in mortality becomes larger and, in my opinion, makes the signal more compelling. However, the apparent increase in mortality in patients with prior exposure could still be due to confounding by some unstudied factor such as disease severity. Thus, I still think that proceeding with a nested case-control study of all extension deaths may be informative, and perhaps, exonerating. If it is not, a large randomized study will probably be necessary to clarify the issue.

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Greg Burkhart, M.D., M.S.  
Safety Team Leader  
Neuropharmacological Drug Products

HFD-120/Leber/Racoosin/Oliva/Levin/Burkhart

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SEP 3 1998

**Review of Clinical Data  
August 26, 1998 Submission Describing Plan to Address Issues  
Raised in the FDA NA Letter**

**NDA:** 20-823  
**Sponsor:** Novartis  
**Drug:** Rivastigmine  
**Route of Administration:** Oral  
**Reviewer:** Greg Burkhart, M.D., M.S.  
**Review Completion Date:** September 3, 1998

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On 7/7/98 the FDA issued a NA letter after completing review of the rivastigmine NDA and its amendments. The letter described the findings from the sponsor's and division's analyses that showed mortality to be increased with the higher doses of rivastigmine with no obvious explanation for the increase. The letter suggested that the sponsor conduct a case control study to evaluate potential explanatory factors.

On 8/26/98, Novartis submitted a plan to address the issues raised in the letter and clarified some aspects of their plan in a 8/31/98 teleconference.

The sponsor plans to conduct a case control study of the 56 deaths that were observed within the June 30, 1997 database as the NA letter suggested. This database was the basis for the most recent mortality analysis, the findings of which were summarized in the NA letter of 7/7/98.

In short, the methods will allow the sponsor to conduct a person-time based case control analysis that will closely approximate a cox survival analysis. Controls will be matched to cases by time-at-risk, country of origin (US vs non-US), study number (both extension and original RCT if applicable). Time-at-risk will be defined from the point of first exposure. All available controls will be included in the analysis. The sponsor verified that rivastigmine dose would be determined for each risk set using the time of death for the index death. Thus, they are analyzing complete risk sets and treating dose as time dependent which will closely approximate a cox analysis

In addition to including all 56 deaths, the sponsor will also separately evaluate selected subgroups of deaths based upon either cause or plausibility. Cause and plausibility will be determined from blinded review of the deaths (blinded to dose). Deaths within 7 days or within 30 days of last dose will also be separately analyzed.

The analyses will also consider past medical history, baseline medication use and baseline body weight. Since the plan did not specifically mention evaluation the effects of either changes/additions of medications or changes in body weight that occurred during treatment with rivastigmine, we discussed these issues in detail in the TC.

Apparently, the June 30, 1997 database does not contain complete data from the CRFs for all patients. The sponsor thinks there will be a sizable subgroup with complete data which could allow for an analysis of the effects of new concomitant medications and changes in weight in this subset. Of course, the absence of the information in the full dataset means that we wouldn't know which patients had stopped taken medications that were prescribed at baseline. I encouraged the sponsor to either collect the additional data for the full cohort or at least to analyze the subset of patients with complete data.

Overall, the plan to evaluate the mortality signal in the rivastigmine NDA is methodologically sound and should allow for a more thorough investigation of the mortality signal. Its value would be enhanced if the sponsor can collect the additional data on changes in medications and body weight during treatment with rivastigmine.

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9/3/58  
Greg Burkhart, M.D., M.S.  
Safety Team Leader  
Neuropharmacological Drug Products

HFD-120/Leber/Racoosin/Oliva/Levin/Burkhart

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM OF TELEPHONE CONVERSATION  
NDA 20-823**

**Drug:** Exelon™ (rivastigmine tartrate) Capsules  
**Sponsor:** Novartis Pharmaceuticals Corp.  
**Date:** August 31, 1998  
**Conversation Between:** Agency: Greg Burkhart, M.D.  
Randy Levin, M.D.  
Robbin Nighswander, M.S. Firm: Ravi Anand, M.D.  
Jeff Veech, M.S.  
Larry Hauptman, Ph.D.  
Robert Kowalski, Pharm.D.

**Telephone #:** (973) 781-6869

RE: NDA 20-823 Exelon and the firm's "Complete Response Proposed Action Plan" dated August 26, 1998. The purpose of this phone call was to clarify aspects of the proposed plan.

Dr. Burkhart began by stating that the proposed plan was, for the most part, very clear and appeared to address many of the Division's concerns; however, several areas need clarification.

Dr Burkhart noted that since they are using all information collected and all possible controls, that the analysis is really more in the style of a Cox Regression rather than a nested case control except they plan to use conditional logistic regression instead of Cox. The firm agreed.

Time/Risk Sets: The firm explained that time on drug would be calculated from first exposure to drug irregardless of when the event occurred (DB phase or in extension). Furthermore, a patient's dose would defined as that dose in use at the time of the event for the indexing death.

Body Weight: The firm explained that only baseline body weight will be examined as a covariate because 1) body weight data is incomplete at later time-points and 2) body weights that do exist at later dates may differ by as much as several months from death-date. Dr. Burkhart suggested that body weight be evaluated to the extent possible (i.e., last recorded weight & days to observation).

Concomitant Medications: The firm clarified that only baseline concomitant medications will looked at as a covariant since similar database problems exist for this data as exist in the body weight database. Dr. Burkhart suggested that information from a smaller subset may be helpful using those patients for whom data is available.

Dose: The firm clarified that the dose used for any patient in a risk set would be that patient's dose at the time it is matched to the death.

Dose Categorization: In response to a question from the firm regarding our preference for dose categorization, Dr. Burkhart noted that since they had included handling dose as a continuous variable, we had no preference. However, in response to further questions from the firm, Dr. Levin noted that handling the 4 mg dose in the lowest category was preferable to handling the 4 mg dose in the 2nd category. Finally, we explained that the proposal for 2,4,6,8, ... etc. [point (C)(2)(d) in the proposal] was also acceptable.

Death Categorization (Plausible/Implausible): The firm explained that "implausible" meant that the death was clearly not related to drug.

  
Robbin Nighswander  
Regulatory Management Officer

cc:  
Orig NDA  
HFD-120  
HFD-120/Leber  
    /Levin/Oliva  
    /Burkhart/Racoosin  
    /Nighswander

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**APPEARS THIS WAY  
ON ORIGINAL**

## Review and Evaluation of Clinical Data

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<b>NDA (Serial Number)</b>	<b>20823</b>
<b>Sponsor:</b>	<b>Novartis</b>
<b>Drug:</b>	<b>Exelon</b>
<b>Proposed Indication:</b>	<b>Alzheimer's disease</b>
<b>Material Submitted:</b>	<b>Response to not-approvable action</b>
<b>Correspondence Date:</b>	<b>11/11/98</b>
<b>Date Received / Agency:</b>	<b>11/11/98</b>
<b>Date Review Completed</b>	<b>3/8/99</b>
<b>Reviewer:</b>	<b>Ranjit B. Mani, M.D.</b>

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### 1. Background

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

The "not-approvable" action was based upon an unresolved concern that Exelon®, in doses that have been shown to be effective in treating Alzheimer's disease, may have been responsible for an increased risk of mortality. The action letter stated that while the available evidence did not clearly show that the risk of death increased as a function of the dose or duration of exposure to Exelon®, that possibility needed further examination.

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 detailed review of this submission is being performed by Dr Greg Burkhardt. My review will be a summary only.

## **2. List of Phase 2 and 3 Studies**

### **2.1 Phase 2 Studies**

#### **Controlled Studies** (all randomized, double-blind, placebo-controlled)

B103, B104, B105, B106, OR1

#### **Uncontrolled Studies**

##### ***Open-label Extension***

B103-E-06, B104-E-01, B104-E-02

##### ***Compassionate Use***

B901, B902

##### ***Tolerability***

AD/EP-11, VD/EP-11

### **2.2 Phase 3 Studies**

#### **Controlled Studies** (all randomized, double-blind, placebo-controlled)

B303, B304, B351, B352

#### **Uncontrolled Studies**

##### ***Open-label Extension***

B305, B353

##### ***Titration***

B354, B355

### 3. Contents of Submission

This submission comprises 2 reports:

1. A "Complete Response Mortality Analysis"
2. An "Epidemiology Report"

### 4. Sponsor's Analysis of Mortality Data

#### 4.1 Complete Response Mortality Analysis

I have summarized the main results of this analysis, as presented by the sponsor, below.

- The analyses below were performed on the Exelon® extended database for Phase 3 studies alone. The cut-off date for this database was 6/30/97; the database consisted of 3162 patients exposed to the drug for 3629 patient-years. In this database there were 56 deaths that occurred within 30 days of last exposure to Exelon®. These 56 deaths were distributed as follows:

Type of trial	Number of deaths	Exposure
Randomized, controlled trials	7 (6 drug; 1 placebo)	1207 patient-years (811 drug; 396 placebo)
Extension studies	35	1986 patient-years
Titration studies	14	436 patient-years

- The sponsor has performed a nested case-control analysis of all the above deaths, using a much larger number of controls than were used in the analyses performed by this Division (a total of 3033 patients were used in the analysis); in the analysis reported in the current submission the sponsor has used all possible controls, matched for the study of origin; in addition the method for observation time case-control matching has been changed. From this analysis the sponsor has concluded that 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. The specific covariates used included age, severity of illness, low baseline weight, presence of cardiac risk factors and male gender; each of these covariates was associated with an increased mortality risk. Analyses evaluating the effects of Exelon® dose and the five covariates, both alone and in combination, demonstrated that Exelon® dose did not create any additional risk. The final results of the nested case-control analysis involving comparison of higher dose groups to the (reference) 1-<4 mg dose group is outlined below.

**Relative Risks and 95% Confidence Intervals from Results Based on Pairwise Models**

Model	Dose Category (mg/day)	All Phase 3	RCT	EXT	TITR
1	Placebo	0.4 (0.0-28.7)	0.4 (0.0-28.7)	NA	NA
reference category	1 - <4	1.0	1.0	1.0	1.0
2	4 - 6	1.5 (0.5-4.6)	∞	0.4 (0.1-1.5)	2.0 (0.4-11.1)
3	>6 - 9	1.0 (0.3-3.4)	0	0.3 (0.1-1.4)	3.0 (0.6-15.3)
4	>9	0.8 (0.3-2.1)	∞	0.7 (0.2-2.4)	0.7 (0.1-4.9)

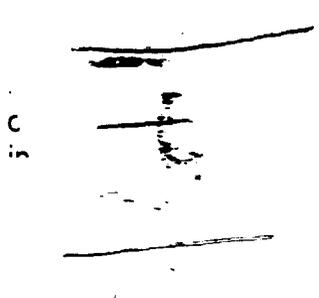
- The sponsor points out that in the titration studies, in which the dose increments were identical to those proposed in labeling, the relative risk of mortality for the > 9 mg category was < 1.0 in relation to the lowest dose category, suggesting the absence of any increased risk for patients treated with the higher doses of Exelon®
- When mortality rates for patients treated with > 9 mg/day in the extension studies were analyzed according to whether they received Exelon® or placebo in the previous randomized controlled trials, the rates for the 2 groups (23.6 versus 22.1 per 1000 patient-years, respectively) were similar. These differences are displayed in the table below. These mortality data

**Distribution of deaths, exposure and mortality rate in EXT by individual dose\* by original treatment in RCT**

Dose (mg /day)	Total	Placebo			Exelon		
	Mortality Rate (deaths/1000 Patient yrs.)	Deaths (n)	Exposure (Patient yrs.)	Mortality Rate (deaths/1000 Patient yrs.)	Deaths (n)	Exposure (Patient yrs.)	Mortality Rate (deaths/1000 Patient yrs.)
2	22.4	3	56	53.6	0	78	0
4	9.0	2	90	22.2	0	132	0
6	11.2	0	133	0	4	223	17.9
8	10.5	2	91	22.0	1	194	5.2
10	21.7	1	63	15.9	4	168	23.8
12	23.7	5	209	23.9	13	552	23.6
≤ 9	12.0	7	370	18.9	5	627	8.0
> 9	23.2	6	272	22.1	17	720	23.6
Total	17.6	13	642	20.3	22	1346	16.3

\* Deaths are categorized by last prescribed dose and exposure is by prescribed dose. Mortality rates pertain to deaths that occurred within 30 days of drug exposure.

- The same 2 physicians were also asked to select, again in a blinded manner, cases where death occurred within 7 days of the last dose of study

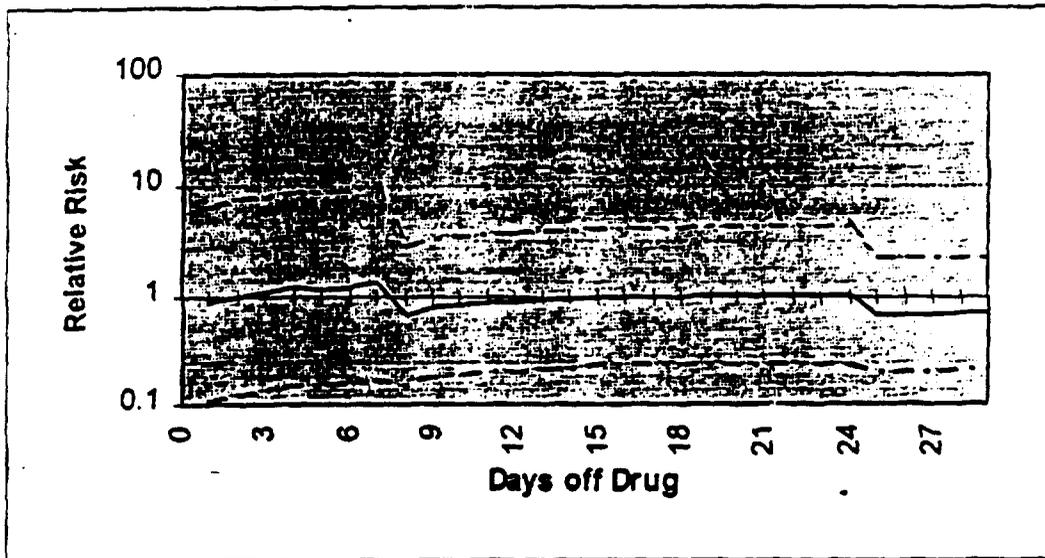


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- The sponsor considers analyses based on deaths that were plausibly drug-related to be flawed, given the lack of inter-rater reliability in selecting those deaths.
- The sponsor also considers analyses based on deaths that occurred within the 7-day cut-off period to be unrepresentative of the Exelon® database; exclusion of deaths outside this cut-off period would result in the exclusion of approximately 40 % of all deaths in the database; moreover the sponsor considers the relative risk of mortality (for the > 9 mg dose group versus the 1-<4 mg dose group) during the extension studies to remain fairly constant throughout the 30-day period after the last dose of study drug during the extension studies, as indicated by the above figure

Relative risk (>9 mg/day vs 1-<4 mg/day) for mortality (95% CI) vs. days off study drug for EXT studies



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#### 4.2 Epidemiology Report

This report is a discussion of the nested case-control analysis of all the deaths in the Exelon® database referred to in Section 4.1. The conclusions are already described in Section 4.1.

In this report the sponsor concludes that the most striking predictor of the mortality rate was time since entry into the initial randomized trial; mortality rates increased more than 4-fold during a period of about 12 months following entry into the randomized trial, and then "flattened out". The sponsor believes that this sharp increase in the one year following entry was related to the "screening effect of recruitment" i.e., individuals who are considered near death are not recruited into clinical trials and as a result short-term mortality rates immediately following recruitment are very low. Further the sponsor states that time since initial entry into the Exelon® study program is correlated with dose of Exelon® and with weight loss, because dose levels tend to increase with time and weight loss develops over time. Thus time represents a factor that could confound the effect of Exelon® dose and dose per body weight; the sponsor appears to suggest that any the apparent relationship between Exelon® dose and mortality as well as weight loss and mortality may be explained at least partly by the confounding effect of time, and this confounding effect cannot be entirely controlled for fully because of the effect of subject screening.

### 5. Dr Greg Burkhardt's Analysis of Mortality Data

In internal discussions and in a face-to-face meeting with the sponsor (2/19/99), Dr Burkhardt has drawn attention to the issues that are summarized below:

- 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
- \_\_\_\_\_ 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.
- Dr Burkhart concluded that the sponsor had not shown that the drug was safe for its intended use. He recommended that if the drug was "significantly" beneficial, it could be approved with a description of the mortality data in the labeling and a subsequent Phase 4 study to evaluate the mortality risk further. If the drug was however of no meaningful value, a randomized controlled trial would be needed before approval

## 6. Divisional Meeting with Sponsor on February 19, 1999

At a meeting held on this date, at which Dr R. Temple was present, the mortality in the Exelon® database was again discussed at length. Please see the minutes for full details. 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, \_\_\_\_\_

The differences between Dr Burkhart's conclusions (with which the Division concurred), 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 \_\_\_\_\_

- 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 at the end of Section 4.1 above) 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

## 7. Comments

- Based on the analyses performed by this Division, the concern remains that mortality increases, particularly for sudden death, at higher doses of Exelon®, and especially at those doses that are the most effective. Thus, it cannot be stated that the sponsor has conclusively shown that Exelon® is safe for its intended use.
- The efficacy of Exelon® in the symptomatic treatment of mild-to-moderate Alzheimer's disease does not appear superior, when compared with that of approved symptomatic remedies for the treatment of Alzheimer's disease.

## 8. Conclusions and Recommendations

Unless further analyses can assuage the Division's concerns about mortality associated with Exelon® use, this drug should not be approved for marketing

Ranjit B. Mani, MD, HFD-120 Medical Review  
NDA 20823, Exelon, Novartis

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8/99

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

R. Levin, M.D. ~~ISI~~

4/29/99

(see my memo)

rbm 3/8/99 -

cc:

HFD-120

NDA 20823

electronic copy-Levin

Nighswander

**APPEARS THIS WAY  
ON ORIGINAL**

## Memorandum

**Date:** ~~March~~ 23, 1999  
**To:** Russ Katz, M.D.  
Acting Director, Division of Neuropharmacological  
Drug Products  
**Through:** Greg Burkhart, M.D. / **ISI**  
Safety Team Leader  
**From:** Gerry Boehm, M.D.  
John Feeney, M.D.  
Joel Freiman, M.D.

**Subject:** Classification of Deaths in NDA 20-823

We were asked to review the records available for 56 deaths. We were asked to 1) identify the sudden unexplained deaths and 2) identify the deaths in which drug-attribution was implausible.

The records we reviewed were provided by Novartis in a February 26, 1999 submission (7 volumes). The records were blinded as to treatment assignment. They contained patient narratives, serious adverse event case report forms, hospital records, and death certificates where available.

Before reviewing the cases, the three of us met and agreed on the following definitions.

### **Sudden Unexplained Deaths**

We considered the following criteria essential to our diagnosis of sudden unexplained death (SUD).

1. If observed, the death occurred within minutes.
2. 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.
3. Accidental deaths such as drownings, motor vehicle accidents (where the patient was the driver), and falls with immediate death were included.
4. Deaths from gunshot wounds and other violent acts (passenger in a motor vehicle accident) were not included.

## Implausible Drug-Attribution

Drug attribution was considered implausible in the following situations.

1. 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.
2. The death was due to a gunshot wound or other violent act.
3. The death was due to autopsy-proven CAD with acute MI.
4. The death was due to autopsy-proven pulmonary embolism.
5. The death was due to stroke in the setting of a cardiac risk factor (atrial fibrillation) or with evidence of peripheral vascular disease.
6. The death was due to meningitis.
7. The death was due to subarachnoid hemorrhage.
8. The death occurred in a patient moribund from cancer.

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

1. The cause of death was unknown or unclear.
2. Death resulted from suicide.
3. Death resulted from pneumonia or urosepsis.
4. The death was classified as a SUD.
5. The death resulted from complications caused by an accidental fall.

**Results:** The attached table reflects the results of our review. Twenty deaths were considered implausible. Fourteen deaths were considered SUDs. A brief rationale for the classification of each case is also included in the table.

~~ISI~~  
Gerry Boehm, M.D.

~~ISI~~  
John Feeney, M.D. /

Joel Freiman, M.D.  
~~ISI~~

Spreadsheet for the exelon blinded review of deaths

Patient number	Assessment of implausibility	SUD	Comments
30309004	implausible	NO	Died 12 days after last dose following a CHF exacerbation
30334018	Not implausible	YES	Found dead in bed, no autopsy
30409003	Not Implausible	NO	Died from GI bleed that was not completely worked up due to underlying malignancy
30411001	Not Implausible	NO	Fell, leg fx, pin inserted, developed pneumonia, PE, died
30302004	Not Implausible	NO	Fell, hip fx, hip replacement, infected prosthesis, died from sepsis
30304001	Not implausible	NO	developed worsening CHF, then vfib, asystole, death
30305010	Not implausible	NO	Recent ?respiratory infection not well described
30312016	Not implausible	NO	Fell, fx hip, died from ?PE
30329008	Not implausible	YES	Got out of bed, collapsed, became SOB, LOC, death
30331002	Not implausible	YES	Post hip fx, died at home but cause of death unclear, sudden
30342006	Not implausible	YES	Died while walking
30411003	Not implausible	NO	Chest infection
30412001	implausible	NO	Death associated with malignancy (thymoma, thymoparaneoplasia)
30412001	implausible	NO	MI with continuing ischemia leading to death 7 days after last dose
304425004	Not implausible	YES	Sudden death, no autopsy
30431015	Not implausible	NO	Fell, fx hip, pinned, re-pinned due to misalignment, developed UTI, sepsis, death
35103011	Not implausible	NO	Nausea, vomiting, anorexia -d/c'd drug, next day dx with prostate CA, died 3d later
35105003	Not implausible	NO	Left frontal lobe bleed
35215039	Not implausible	YES	Sudden death, heard falling to floor EMS called CHB no autopsy
35102071	Not implausible	YES	LOC sudden death failed resuscitation, no info to support MI (reported cause)
35106045	Not implausible	NO	hospitalized for abd pain, hematemesis, ileus, ?diverticulitis and died next day
35111049	Not implausible	NO	?infection, neg CXR, neg urine ?blood, +fever, sl inc WBC, ?resp failure
351112014	Not implausible	YES	Hx of AAA, died suddenly, but no autopsy
32502038	Not implausible	YES	Found dead in bed
35203002	Not implausible	YES	Died 3 days after hosp discharge, treated for chest congestion, dyspnea, weakness
35203002	implausible	NO	Diagnosed with pancreatic cancer, palliative tx
35203023	Not implausible	YES	Found dead in bed
35203025	Not implausible	NO	No hx CAD, inferior wall MI, died 3 days later

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