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## 7. Sponsor's Arguments In Favor Of Proposed Titration Rates

As noted earlier the sponsor has proposed the following dosing regime for Exelon® in the draft package insert. As the subject is a complex one, it is being reviewed in this section, rather than as part of the draft label.

*"The recommended starting dose of Exelon® is 1.5 mg twice a day. If*

*the maximum dose is 6 mg b.i.d. (3 mg per day)*

The sponsor states that the above schedule is the manner in which the drug is prescribed in the 60 countries in which it is marketed.

A comparison of the regime proposed by the sponsor, and that recommended by the Agency in earlier draft labeling accompanying the approvable letter, is as indicated in the following table:

	Sponsor's Proposal	Original Agency Recommendation
Initial Dose	1.5 mg b.i.d	1.0 mg b.i.d
Minimum Interval Between Dose Increases	2 weeks	1 week
Dose Increase Over Each Interval	3 mg per day	0.5 to 1 mg per day
Maximum Dose	6 mg b.i.d	6 mg b.i.d

The sponsor's arguments in favor of the proposed titration rate are presented as follows:

### 7.1 Titration Rates In Phase III Program Except B 356 Study

3 different titration rates were used in the Phase III studies as indicated by the following table

Study Type	Titration Rate	Minimum Time To Reach 6 Mg Daily	Minimum Time to Reach 12 Mg Daily
Randomized controlled trials	0.5-1.0 mg/week	4 weeks*	9 weeks
Extension Studies**	2.0 mg/week	2 weeks	5 weeks
Titration Studies***	3.0 mg/week	1 week	3 weeks

\*6-12 mg per day groups from B 303 and B 352, as well as the b.i.d group from B 304, but excluding B 351

\*\*B 305 and B 353

\*\*\*B 354 and B 355 (B 354 was a small study that enrolled only 15 patients)

In regard to the above titration schedules, the sponsor has drawn attention to the following:

- In the randomized controlled trials
  - The titration schedule stipulated that all patients had to attain at least the minimum dose

within the assigned dose group by a fixed period of time. Failure to attain this dose resulted in the patient being discontinued from the study. In addition patients were not permitted to maintain a dose level below the pre-specified minimum dose of the randomized dose range for more than 2 weeks. The sponsor has stated that the randomized controlled trials were designed along the lines of a maximum tolerated dose study

- To ensure compliance with this regime these trials required about 19 visits over a 26-week period of time
- In the open-label extension and titration studies
  - Although patients were encouraged to reach the highest doses they could tolerate there were no penalties for deviating from the titration rates proposed in these trials
  - Visit frequencies were much lower with patients requiring only 7 visits over a 26-week period

### 7.2 Comparative Analysis Of Titration Rates Used In Phase III Program Except B 356 Study

The sponsor has then presented an analysis of the 3 titration rates from the Integrated Summary of Safety submitted with the original NDA. At the time of the analysis only interim data (Weeks 1 through 14) were available for the B 355 study and only about 103 patients who received placebo in the preceding randomized controlled trials had data collected from the extension studies B 305 and B 353.

The table below shows the proportion of patients in each titration schedule who were able to reach the 6 mg/day and 12 mg/day dose at the earliest timepoint within the respective groups of studies. The sponsor points out that 80 % of patients in B 355 had their dose increased from 3 to 6 mg after just one week, whereas patients in the randomized controlled trials needed 7 weeks and 7 steps to achieve this dose. Note that the table below does not include data from the efficacy Study B 351 where patients began treatment with 1 mg/day or 1.5 mg/day and were titrated to each of their doses of 3 mg, 6 mg and 9 mg over 12 weeks (this rate of titration was slower than in the other randomized controlled trials)

**Patients Who Reached A Prescribed Dose Of 6 Or 12 mg/day At the Earliest Time-point Designate by the Protocol**

	1.0-1.5* mg/week (N=592)	2.0† mg/week (N=103)	3.0‡ mg/week (N= 559)
<b>Prescribed Dose</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>6 mg/day</b>	<b>430 (73)</b>	<b>67 (65)</b>	<b>448 (80)</b>
<b>12 mg/day</b>	<b>196 (33)</b>	<b>24 (23)</b>	<b>175 (31)</b>

\*Phase III Controlled studies - B303 and B352 (6-12 mg/day randomized dose group) and B304 interim (> 12 mg/day dose range)

† Phase III Uncontrolled Extension studies - B305 and B353 interim (only for patients previously assigned to placebo)

‡ Phase III Uncontrolled Titration Studies - B354 and B355 interim

The sponsor adds that:

- While only 31 % of patients participating in B 355 reached the 12 mg dose, there are no specific data available as to why patients did not adhere to the prescribed titration rate. However the difference was not apparently because of tolerability as there were "no substantive differences" between the 3 mg/week rate of increase, and the 1 to 1.5 mg/week rate of increase in regard to adverse events and discontinuations.
- The incidences of the most common types of adverse events through the first 12 weeks of the respective studies were "comparable" between the 3 titration rates
- The Kaplan-Meier cumulative probability analyses revealed that there was virtually no difference in the probability of a dose-related adverse event occurring in the 3 titration paradigms at the end of 12 weeks
- Adverse events occurred earlier with faster titration rates but this was to be expected since patients titrated under these paradigms achieved higher doses earlier and the intolerance observed with Exelon® was dependent on dose
- In the titration studies the same proportion of patients were able to achieve doses within the effective dose range of 6-12 mg, only at a much faster rate.

Although the sponsor believes that the 3.0 mg/week titration schedule is as well tolerated as the 1-1.5 mg/week schedule, the interval between dose increases was lengthened to every 2 weeks to further improve tolerability and for convenience so that patients would not have to return to their doctors weekly for dose increases.

The sponsor performed a further analysis to determine the proportion of patients who attained the 12 mg dose at the earliest timepoint possible in the "pivotal" and titration studies. A window of +/- 3 days was applied to the timepoint; patients who were prescribed 12 mg during the window were counted as having achieved 12 mg at the earliest possible time. For the "pivotal" efficacy studies, the fastest a person could achieve a dose of 12 mg daily would have been by Week 9.

**Patients Reaching Maximum Dose of 12 mg During 26 Weeks of Study Participation**

	N	Reaching 12 mg/day by Earliest Point in Titration
B303 (6-12 mg)	242	88 (36)
B352 (6-12 mg)	229	68 (30)
B304 (BID)	227	60 (26)
B355	544	169 (31)

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following: adverse event dropout rate, adverse event incidence, proportion of patients with a maximum dose of 12 mg daily and proportion of patients adhering to the protocol-defined titration rate. The results are presented below in tables copied from the submission.

**Overall Discontinuation Rates and Adverse Drop-Out Rates by Study After 26 Weeks in Phase III studies and US Phase IIIb Study B356**

	Dose Increases	N	Overall D/C	ADO
B351 - 9 mg	0.5 - 1.0 mg/ wk	178	87 (49)	60 (34)
B352 - 6-12 mg	0.5 - 1.0 mg/ wk	231	82 (35)	67 (29)
B303 - 6-12 mg	0.5 - 1.0 mg/ wk	243	79 (33)	55 (23)
B304 - BID	0.5 - 1.0 mg/ wk	227	54 (24)	41 (18)
B355	3.0 mg/ wk	544	175 (32)	108 (20)

**Common Adverse Events by Study: Percent of Patients Experiencing an Adverse Event Over 26-Weeks of Treatment**

	Dose Increases	N	Nausea	Vomiting	Diarrhea	Anorexia	Abdominal Pain	Dizziness	Headache
B351 - 9 mg	0.5 - 1.0/ wk	177	64 (36)	40 (23)	32 (18)	23 (13)	24 (14)	38 (21)	15 (8)
B352 - 6-12 mg	0.5 - 1.0/ wk	231	125 (54)	75 (33)	57 (25)	53 (23)	27 (12)	64 (28)	45 (20)
B303 - 6-12 mg	0.5 - 1.0/wk	243	121 (50)	82 (34)	40 (17)	34 (14)	29 (12)	48 (20)	45 (19)
B304 - BID	0.5 - 1.0/wk	227	123 (54)	88 (39)	40 (18)	47 (21)	34 (15)	42 (18)	40 (18)
B355	3.0/wk	544	314 (58)	181 (33)	99 (18)	77 (14)	77 (14)	128 (24)	90 (17)

**Patients Reaching Maximum Dose of 12 mg During 26 Weeks of Study Participation**

	N	Reaching 12 mg/day at Earliest Point in Titration	Reach 12 mg
B303 (6-12 mg)	242	88 (36)	155 (64)
B352 (6-12 mg)	229	68 (30)	130 (57)
B304 (BID)	227	60 (26)	118 (52)
B355	544	169 (31)	260 (48)

The sponsor has concluded from the above that

- The overall discontinuation rate and the adverse event dropout rates were comparable across studies in which a weekly rate of increase was used; these rates decreased when the 2-week and 4-week titration paradigms were employed
- The most common adverse events with the different titration schemes are essentially the same. In addition there were no substantial differences in the incidence rates for the most common adverse events. Adverse events appeared to be related more to the dose of Exelon® than the manner in which it was titrated

**Reviewer's Note:**

For the above tables, patients who reached high doses in the randomized controlled trials B 303, B 351 and B 352, have been compared with patients titrated to the entire range of final doses (3 to 12 mg) in the extension studies.

**7.4 Reviewer's Comments About Proposed Titration Scheme**

- It remains clear that for the titration regime proposed by the sponsor
  - There was a high incidence of nausea (52 %) and vomiting (33 %); the incidence of vomiting, may be prohibitively high
  - Despite these figures, 73.1 % of patients enrolled in this regime in Study B 356 were able to remain at a dose of  $\geq 6$  mg at Week 26 of the study, and 39.3 % were at 12 mg at that timepoint. Only 13.1 % of patients in this titration arm dropped out of the study on account of adverse events
  - The incidence of nausea and vomiting for the 4-week titration regime in Study B 356 was only slightly lower.
- It is also clear that the titration regime proposed by the sponsor is more convenient to use and will result in patients reaching the 6-12 mg dose range more quickly than the regime proposed by the Agency.

- For patients titrated to specific high-dose arms in 2 out of 4 efficacy studies the incidence of nausea and vomiting was as high as in the 2-week titration arm in B 356 (all doses). It is important to note that the 6-12 mg dose range is what is currently believed to be effective.

Study and Dose Group	Dose Increases	N	Nausea (%)	Vomiting (%)
B 352 6-12 mg	0.5-1.0 mg/week	231	54	33
B 303 6-12 mg	0.5-1.0 mg/week	243	50	34

- Even for Exelon®-treated patients in the entire Phase III placebo-controlled trials group, the majority of whom were titrated using the regime earlier recommended by the Division in draft labeling, the incidence of nausea and vomiting, 34.1 % and 21.1 %, respectively was higher than what might be considered entirely acceptable.
- There is therefore no titration regime that has been studied which could be considered optimal as regards the incidence of nausea and vomiting. Vomiting is an adverse event of potentially serious consequence in elderly, frail patients; it can lead to fluid depletion and its sequelae, aspiration and the Mallory-Weiss syndrome. The incidence of vomiting with Exelon®, particularly in the titration studies is even less acceptable when considered in the context of the drug's very modest efficacy
- However, as the sponsor too concedes, the titration regime used for the randomized controlled trials was a rigid one with patients having to reach at least the minimum dose of their assigned dose group within a pre-specified period of time; and patients not being permitted to maintain a dose level below the pre-specified minimum dose of the randomized dose range for more than 2 weeks. The titration regime used for the B 356 study was more flexible with dose increases being made only if the current dose was well-tolerated, with the intervals between dose increases being lengthened if needed, with no requirement to reach a specific dose within a specific period of time and with dose decreases being permitted at any time and for any duration.
- A more flexible version of the dosing regime used in the randomized controlled trials may therefore be somewhat better tolerated, if the drug is approved for marketing, as outlined below:  
*"The recommended starting dose of Exelon® is 1.0 mg twice daily. Depending on how well the drug is tolerated, further increases of 0.5 to 1.0 mg per day may be made at intervals of not less than a week. The maximum dose of Exelon® is 6 mg b.i.d."*  
There is, admittedly no firm evidence that this proposed regime will be well-tolerated.

## 8. Other Specific Labeling Issues

### 8.1 Mortality

In addition to a discussion of the titration rate the sponsor has, in this submission, discussed a number of additional items pertinent to labeling. These are summarized below

### 8.2 Effective Dose

#### 8.2.1 Background

The sponsor has concluded that for all Phase III randomized controlled trials, including INT-03, the mortality rate for Exelon® had not exceeded that for placebo as in the following table

	Exelon® (n = 1982)	Placebo (n = 929)
Number of Deaths (within 30-day window)	6	3
Mortality Rate	0.30 %	0.32 %
Total Exposure	829.5 patient-years	417.0 patient-years
Number of Deaths per 100 Years of Exposure	0.72	0.72

This item has been discussed elsewhere in this review. It does not, now, appear necessary for a description of mortality findings to be included in the draft label for Exelon®, as originally recommended in the Agency version of the draft label sent to the sponsor with the approvable letter of 5/12/99.

#### 8.2.2 Sponsor's View Of Effective Dose

In the approvable letter of 5/12/99 the Agency had stated that the only consistently effective dose was 12 mg. The Agency's draft label accompanying

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The Agency's argument was based upon the following:

- The 6-12 mg daily dose range having been shown to be effective in Studies B 303 and 352 studies on both primary outcome measures (see "Tabular Summary of Key Efficacy Studies")
- None of the 3 doses (3 mg, 6 mg or 9 mg) having been shown to be effective on both primary outcome measures in the B 351 study; the 6 mg and 9 mg doses were superior to placebo on the ADAS-Cog, but not on the CIBIC-Plus.
- Neither the 4 mg nor the 6 mg dose having been demonstrated to be effective on either a global or a cognitive measure in a 15-week Phase II study, B 103 (see below)
- The 1-4 mg dose in Studies B 303 and 352 being inconsistently effective on both outcome measures (i.e., the 1-4 mg dose did not show a statistically significant superiority to placebo on either ADAS-Cog or the CIBIC-Plus in the B 303 study)

### 8.2.3 Sponsor's View Of Effective Dose

The sponsor contends that the effective dose range for Exelon® is 6-12 mg daily, and not 12 mg. The basis for this contention is as follows:

- The prospectively-defined randomized dose group of 6-12 mg/day has been demonstrated to be superior to placebo in Studies B 352 and B 303 on both primary outcome measures (in the intention-to-treat, last-observation-carried-forward and observed cases datasets). This satisfied the regulatory requirement that the efficacy of this drug should be demonstrated in 2 randomized controlled trials.
- No studies investigated the efficacy of a fixed dose of 12 mg daily
- The high dropout rate in Study B 351 "negatively impacted" the results, i.e., in this study both the 6 mg and 9 mg daily doses could not be demonstrated to be superior to placebo on the CIBIC-Plus.
- A pooled analysis, reported in the Integrated Summary of Efficacy, that included efficacy data from B 303, B 304 and B 352 compared the 6-12 mg daily dose with the 1-4 mg daily dose and placebo. In this analysis the 6-12/day and 1-4 mg/day dose groups were superior to placebo on both primary outcome measures

The sponsor therefore believes that as agreed at the August 4, 1999 meeting, the dose range of 6-12 mg per day should be described as being effective in labeling, with the stipulation that higher doses were generally more effective.

### 8.2.4 Reviewer's Comments

- At the August 4, 1999 meeting the Division had largely agreed with the sponsor's contention that the effective dose of Exelon® ranged from 6 to 12 mg. The Division had suggested that the labeling for the drug include a statement that higher doses, **within the 6-12 mg range**, were generally more effective; the sponsor agreed with this recommendation
- The lack of efficacy at both the 6 mg and 9 mg daily doses, on a global outcome measure, in the B 351 study, is still problematic, if the label is to state that the effective dose is 6-12 mg daily. The sponsor's argument that this can be blamed on the high dropout rate in that study may not be valid. The dropout rate for the 6 mg dose group in B 351 is no different from that for the 6-12 mg dose groups in the B 303 and B 352 studies; the dropout rate for the 9 mg dose group in B 351 is higher. Moreover, it is unclear that the lack of a statistically significant result on the CIBIC-Plus for the 6 mg and 9 mg dose groups in B 351 is entirely attributable to a smaller sample size caused by dropouts: the actual effect size (Observed Cases) with the 6 mg dose was much smaller than with the 6-12 mg doses in B 303 and B 352 while that with the 9 mg dose was smaller than with the 6-12 mg dose in the B 303 study.
- It is also noteworthy that in B 103, a large, randomized, double-blind, placebo-controlled, 13-week study, that used a cognitive (Mini Mental Status Examination) and global (CGIC) outcome measure, the 6 mg dose was ineffective versus placebo
- I would suggest that the labeling state the following:

### 8.3 Activities Of Daily Living Results

#### 8.3.1 Background

In all four Phase III randomized controlled trials, the Progressive Deterioration Scale (PDS), an activities of daily living scale was used as one of several secondary efficacy measures. A full list of secondary efficacy measures in all four Phase III trials is in the table below

Study #	Secondary Efficacy Measures
B 303	Progressive Deterioration Scale
B 304	ADAS-CogA (ADAS-Cog plus attention item from ADAS-NonCog)
B 351	Global Deterioration Scale*
B 352	Mini Mental Status Examination* Caregiver Activity Survey**

\*These were designated in the protocol as "staging measures", rather than secondary efficacy measures, but the protocol did stipulate that they were to be analyzed in a manner similar to the secondary efficacy measures

\*\*This measure was to be analyzed only on pooled data from all 4 studies and was designated as a tertiary efficacy variable; it was introduced late during each protocol

The **Progressive Deterioration Scale** is a 29-item caregiver-rated instrument assessing selected "activities of daily living". Each item is scored by placing an "X" on a line (8.3 cm in length in the Case Report Forms) that extends between 2 extreme descriptions of that function (e.g., "drives car safely" and "driving is too dangerous-must be restricted"). The rater is asked to place the "X" at a point nearest to the characteristic that best describes the patient. Scores for individual items range from 0 to 100 with higher scores indicate improvement. The total score is the mean of individual item scores.

Note that personal care skills such as bathing, eating, dressing (except to a limited degree), grooming, toileting, and mobility are not assessed at all by this scale, which is a measure of instrumental activities of daily living, leisure activities and performance in social settings. It has been developed and is described in the medical literature as a "quality-of-life" scale. There is limited evidence of its reliability and validity in the medical literature

The protocols for the above efficacy studies described 2 types of analysis for the Progressive Deterioration Scale:

- An analysis comparing the mean change from baseline in total scores among treatment groups
- A responder analysis comparing the treatment groups. For this analysis patients were to be dichotomized into 2 groups:  $\geq 10\%$  improvement in score (responders) vs  $< 10\%$  improvement

Analyses were performed using both the intent-to-treat and last-observation carried forward datasets; the protocols also implied that other datasets could be used including observed cases, retrieved dropouts and observed cases +

retrieved dropouts. A main analysis for this measure was not stipulated in any protocol.

The sponsor's original draft labeling, and the draft labeling provided with this submission, describe in graphical form the results of the Progressive Deterioration Scale analyses that used the mean change from baseline score. These descriptions have been provided for the B 303 and B 352 studies individually, and for a pooled analysis of B 303, B 352 and B 351. In the draft labeling attached to the approvable letter of 5/12/99, the Division had excluded the description of the Progressive Deterioration Scale results.

At the meeting on August 4, 1999, the Division agreed to reassess the Progressive Deterioration Scale data

### 8.3.2 Results Of Progressive Deterioration Scale Analysis

The results of the Progressive Deterioration Scale analysis are provided below, study by study.

#### B 303

The mean change from baseline at Week 26 for each treatment group is shown in the following table

Dataset	6-12 mg/day	1-4 mg/day	Placebo	p-values
Intent-to-treat	0.05	-3.37	-2.18	6-12 mg/day vs placebo: 0.066 1-4 mg/day vs placebo: 0.326
LOCF	0.5	-3.31	-2.23	6-12 mg/day vs placebo: 0.043 1-4 mg/day vs placebo: 0.406

The percentage of responders in each treatment group is shown in the following table

Dataset	6-12 mg/day	1-4 mg/day	Placebo	p-values
Intent-to-treat	29	19	19	6-12 mg/day vs placebo: 0.010 1-4 mg/day vs placebo: 0.892
LOCF	33	20	20	6-12 mg/day vs placebo: 0.002 1-4 mg/day vs placebo: 0.933

#### B 352

The mean change from baseline at Week 26 for each treatment group is shown in the following table

Dataset	6-12 mg/day	1-4 mg/day	Placebo	p-values
Intent-to-treat	-1.52	-5.19	-4.90	6-12 mg/day vs placebo: 0.000 1-4 mg/day vs placebo: 0.765
LOCF	-1.01	-5.33	-5.17	6-12 mg/day vs placebo: 0.000 1-4 mg/day vs placebo: 0.874

The percentage of responders in each treatment group is shown in the following table

Dataset	6-12 mg/day	1-4 mg/day	Placebo	p-values
Intent-to-treat	23	11	14	6-12 mg/day vs placebo: 0.018 1-4 mg/day vs placebo: 0.398
LOCF	25	12	15	6-12 mg/day vs placebo: 0.006 1-4 mg/day vs placebo: 0.432

**B 351**

The mean change from baseline at Week 26 for each treatment group is shown in the following table

Dataset	9 mg/day	6 mg/day	3 mg/day	Placebo	p-values
Intent-to-treat	-2.15	-2.53	-2.93	-3.13	9 mg/day vs placebo: 0.371 6 mg/day vs placebo: 0.583 3 mg/day vs placebo: 0.851
LOCF	-2.06	-2.69	-2.59	-3.02	9 mg/day vs placebo: 0.454 6 mg/day vs placebo: 0.795 3 mg/day vs placebo: 0.726

The percentage of responders in each treatment group is shown in the following table

Dataset	9 mg/day	6 mg/day	3 mg/day	Placebo	p-values
Intent-to-treat	19	19	20	14	9 mg/day vs placebo: 0.240 6 mg/day vs placebo: 0.207 3 mg/day vs placebo: 0.202
LOCF	22	21	21	16	9 mg/day vs placebo: 0.187 6 mg/day vs placebo: 0.138 3 mg/day vs placebo: 0.207

**B 304**

The mean change from baseline at Week 26 for each treatment group is shown in the following table

Dataset	2-12 mg/day (b.i.d)	2-12 mg/day (t.i.d)	Placebo	p-values
Intent-to-treat	-2.69	-1.54	-4.95	2-12 mg/day (b.i.d) vs placebo: 0.03 2-12 mg/day (t.i.d) vs placebo: 0.001
LOCF	-2.35	-1.00	-4.74	2-12 mg/day (b.i.d) vs placebo: 0.032 2-12 mg/day (t.i.d) vs placebo: 0.001

The percentage of responders in each treatment group is shown in the following table

Dataset	2-12 mg/day (b.i.d)	2-12 mg/day (t.i.d)	Placebo	p-values
Intent-to-treat	18	24	15	2-12 mg/day (b.i.d) vs placebo: 0.343 2-12 mg/day (t.i.d) vs placebo: 0.018
LOCF	20	26	17	2-12 mg/day (b.i.d) vs placebo: 0.354 2-12 mg/day (t.i.d) vs placebo: 0.016

**8.3.3 Sponsor's Arguments For Retaining Progressive Deterioration Scale Data In Labeling**

These are listed below:

- In each Phase III randomized controlled trial, the Progressive Deterioration Scale was a prospectively-defined measure of efficacy
- The Progressive Deterioration Scale measures a domain of the disease that is important to patients, physicians and caregivers; since efficacy has been demonstrated in 3 randomized controlled trials on this measure it should be included in the package insert
- The Progressive Deterioration Scale is a validated measure of activities of daily living in Alzheimer's Disease patients where it has been used in other anti-dementia trials to assess the effect of drugs on activities of daily living. It is completed by the caregiver who has the best perspective on the patient's function

- In the B 303 and B 352 studies the mean change from baseline analysis revealed that the 6-12 mg daily dose of Exelon® was superior to placebo at a statistically significant level in the LOCF population. The responder analysis for the 6-12 mg daily dose was positive in both the intent-to-treat and LOCF populations in both studies
- A pooled analysis of B 303, B 351 and B 352 again revealed that the 6-12 mg dose was superior to placebo on both the mean change from baseline and on the responder analysis
- In the B 304 study both the b.i.d and t.i.d groups showed a statistically significant superiority to placebo on the mean change from baseline analysis; only the t.i.d group showed a statistically significant superiority to placebo on the responder analysis.

#### **8.3.4 Reviewer's Comments**

- The Progressive Deterioration Scale was one of several secondary efficacy measures in the protocols for each of the 4 Phase III efficacy studies. At least 2 methods of analysis were stipulated for this measure with each analysis being performed on 2 datasets (intent-to-treat and LOCF). No method of analysis was designated as being primary
- In setting a Type 1 error for analysis of this measure no adjustment has been made for multiple comparisons. Thus the conclusion that Exelon® had evidence of efficacy based on the Progressive Deterioration Scale in the B 303 study may be questionable. The evidence for efficacy in the B 352 study based on this measure is less questionable given the very low p-values
- The B 351 study was clearly negative in regard to this measure at both 6 mg/day and 9 mg/day doses. These negative results cannot be explained based on a high dropout rate alone
- The Progressive Deterioration Scale measures only a restricted spectrum of activities of daily living, as well as other functions
- There is only very limited evidence in the medical literature of the validity of the Progressive Deterioration Scale as a measure of activities of daily living.
- The analog method of scoring each item on this scale uses a line only 8.3 cm in length, from which a score ranging from 0 to 100 is derived; each cm on this line thus represents a change of 12.05 points. The maximum drug-placebo difference on this scale recorded in any of the 4 studies above is 4.16 points, representing 3.45 mm on the line. It appears doubtful that changes of such a small magnitude can be reliably recorded.
- Considering the above, it would appear appropriate for the Progressive Deterioration Scale data to be deleted from labeling.

#### **8.4 Weight Loss**

As requested by the Division at the 8/4/99 meeting, the sponsor has supplied data for the incidence of clinically notable weight loss (> 7 % decrease from baseline) for the Phase III placebo-controlled studies, in patients exposed to doses > 9 mg/day. The data are derived from a table supplied in the 120-Day

Safety Update and are provided to substantiate a statement in the "Warnings" section of the label.

Gender	Treatment Group	Incidence Of Weight Loss Of > 7 % From Baseline In Patients Receiving > 9 Mg/Day
Women (n = 332)	Exelon®	26 %
	Placebo	6 %
Men (n = 272)	Exelon®	18 %
	Placebo	4 %

There are no additional comments needed about this table which is acceptable

## **8.5 Inclusion Of Additional Efficacy Studies In Labeling**

### **8.5.1 Background**

In the draft label that accompanied the approvable letter of 5/12/99 the Division had asked the sponsor to include the results of the B 351, B 304 and B 103 studies in the Clinical Trials section of the label; the sponsor had included only the results of the B 303 and B 352 studies

### **8.5.2 Sponsor's Views Regarding Inclusion Of Additional Efficacy Studies**

The sponsor has argued against including data from the B 351 and B 103 studies in the label. The arguments are as follows.

In regard to the B 103 study the sponsor states that:

- This was a Phase II study in which the highest dose used was 6 mg
- None of the efficacy measures (ADAS-Cog, CIBIC-Plus or Progressive Deterioration Scale) used in the Phase III program were employed

In regard to the B 351 study the sponsor states that:

- This was distinct from the other Phase III randomized controlled trials in that it employed both a forced titration and a fixed dose design. This "inadequacy of design" lead to a high drop-out rate (of about 50 %) in the 9 mg/day group which was higher than in any other group in the Phase III randomized controlled trials. As a consequence of the high dropout rate only one of the two primary endpoints (the ADAS-Cog) showed a statistically significant superiority to placebo.
- When Exelon® is available for prescription neither a forced titration nor a fixed dose design will be used
- Since the dosing schedule in this study is not reflective of how Exelon® will be used on the market, the results of this study should not be included in labeling

### **8.5.3 Reviewer's Comments**

- The B 351 study should be described in labeling for the following reasons
  - The forced titration schedule employed for the 9 mg dose used increases of 0.5-1.0 mg/week which was no greater than for the other randomized controlled trials (which also used forced titration) and slower than that recommended by the sponsor in the draft package insert. For the 6 mg and 3 mg dose groups the titration rate was even slower.

The ~~only~~ difference is that for the randomized controlled trials B 352 and B 303, the high dose range was flexible varying from 6 to 12 mg (for the B 304 study it ranged from 2-12 mg) whereas in the B 351 study the higher doses were fixed at 6 mg and 9 mg. Thus the dosing regime for B 351 may not have been as substantially different from the other randomized controlled trials as the sponsor contends.

- For the 6 mg dose group in this study, the incidence of discontinuations was no higher than for the high-dose groups in the other randomized controlled trials. However the 6 mg dose was not superior to placebo on the CIBIC-Plus. This is information which should be useful for the prescribing physician.
- It could also be argued that the B 103 study should be included in labeling since it was a large study of 13 weeks duration, used a cognitive and a global outcome measure (Mini Mental Status Examination and CGIC, respectively) and since the sponsor has contended that the 6 mg dose is effective
- It may also be appropriate to include the B 304 study in labeling based upon the observation that 86 % of patients completing the study were at doses  $\geq$  6 mg per day (i.e., within the "effective" dose range) at the end of the study.

### 8.6 Analysis Supporting Efficacy Of 6-12 Mg Daily Dose Versus 1-4 Mg Daily Dose

#### 8.6.1 Background

In the draft labeling accompanying the approvable letter the sponsor was asked to supply data supporting statements that the 6-12 mg daily dose of Exelon® was superior to the 1-4 mg daily dose.

#### 8.6.2 Sponsor's Response

The sponsor has supplied the following table in support of the above. The table lists analyses that were statistically significant.

**Efficacy Comparisons in which 6-12 mg/day was Statistically Superior (p<0.05) to 1-4 mg/day in the ITT Population**

Efficacy Measure	Study B352	Study B303	Pooled Studies
ADAS-Cog Mean Change	√	√	√
ADAS-Cog $\geq$ 4 point improvement	√	√	√
CIBIC-Plus Mean Rating of Change		√	√
CIBIC-Plus Improvement			
PDS mean change	√	√	√
PDS $\geq$ 10% Improvement	√	√	√
MMSE mean Change	√	√	√

The exact p-values for some of the items above that are relevant to labeling are in the table below; I have not included any data from the pooled studies:

Efficacy Measure	Study B 352	Study B 303
ADAS-Cog Mean Change	0.000	0.009

CIBIC-Plus Mean Rating Of Change	0.804	0.014
CIBIC-Plus Percentage Improving	0.976	0.136
Progressive Deterioration Scale Mean Change	0.000	0.005

### 8.6.3 Reviewer's Comments

In the draft labeling supplied with this submission, the sponsor has stated that the 6-12 mg daily dose was superior to the 1-4 mg daily dose in regard to the following:

- The mean change in ADAS-Cog in the B 303 and B 352 studies
- The mean change in Progressive Deterioration Scale in the B 303 study

In describing the CIBIC-Plus data for the B 352 and B 303 studies in the draft label the sponsor has not claimed that the 6-12 mg daily dose was superior to the 1-4 mg daily dose

## 8.7 Cardiovascular Effects Of Exelon®

### 8.7.1 Background

In response to a request from the Division in the draft labeling that accompanied the approvable letter, the sponsor has provided a review of the cardiac effects of Exelon®. The review is based on data from randomized, double-blind, placebo-controlled studies. The analysis has focussed on cardiovascular vital signs, electrocardiograms and cardiac-related adverse events

### 8.7.2 Cardiovascular Vital Signs

The sponsor has used the results of the B 351 fixed-dose study to determine if there is a dose-response effect on cardiovascular vital signs. The results of the analysis for supine pulse rate are presented in the following table. The sponsor has concluded that there were no clinically important changes in heart rate with any dose of Exelon® over the 26 weeks of the trial and no dose-response effect. The sponsor has also further stated that there was no dose-response or clinically important effect for systolic and diastolic blood pressure values, and that similar results for pulse and blood pressure were obtained for Studies B 352 and 303, individually.

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**Mean ± SD and Median Baseline and Week 26 Values, and Change from Baseline for Supine Pulse, Study B351**

Variable	N	Exelon Doses			
		9 mg/day	6 mg/day	3 mg/day	Placebo
Pulse (bpm)					
Baseline Mean ± SD	90	66.5 ± 8.19	68.7 ± 8.62	68.4 ± 8.37	69.2 ± 8.95
Baseline Median		64.0	68.0	68.0	68.0
Week 26 Mean ± SD		66.5 ± 7.13	68.2 ± 9.06	67.7 ± 8.76	68.8 ± 8.47
Week 26 Median		67.0	68.0	66.0	68.0
Change in Mean ± SD		0.0 ± 8.91	-0.5 ± 9.87	-0.7 ± 9.00	-0.4 ± 8.51
Change in Median		0.0	-2.0	0.0	0.0

Note: Change was post-pre, and no statistically significant ( $p < 0.05$ ) differences were noted for change from baseline values between any of the treatment groups using pairwise comparison *t* tests.

In the pooled Phase III placebo-controlled trials no “trends or clinically significant effects” were seen in supine pulse or in systolic and diastolic blood pressure. Changes in supine pulse rate from baseline to endpoint are summarized by the following table (detailed tables are provided for all vital signs)

	Statistic	ENA	Placebo	Total
Baseline	N	1914	865	2779
	Mean	69.8	69.5	69.7
	SD	9.35	8.85	9.20
	Median	70.0	68.0	68.0
Endpoint	N	1914	865	2779
	Mean	68.7	69.6	69.0
	SD	9.55	9.52	9.55
	Median	68.0	68.0	68.0
Change	N	1914	865	2779
	Mean	-1.1	0.1	-0.7
	SD	9.79	9.53	9.73
	Median	0.0	0.0	0.0

### 8.7.3 Evaluation Of Electrocardiograms

- Electrocardiogram parameters evaluated were heart rate, PQ or PR intervals, QRS interval, and corrected and uncorrected QT interval.
- In the B 351 study the following were the proportions of patients in each treatment group who were recorded to have no electrocardiogram change from baseline to post-baseline

Treatment Group	Proportion With No Change
Placebo	82 %
3 mg/day	83 %
6 mg/day	85 %

9 mg/day 82 %

- Similar results were seen in the B 303 and B 352 studies
- For the pooled Phase III controlled studies there were no significant differences between treatment groups in the incidence of electrocardiogram abnormalities that were new or had changed since the last visit as indicated in the following table.

Preferred Term	>=12 mg N = 611	>6-9 mg N = 359	>3-6 mg N = 698	<=3 mg N = 227	Placebo N = 861	Total N = 2756
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any abnormality	99 (16)	49 (14)	103 (15)	37 (16)	114 (13)	402 (15)
1ST DEGREE BLOCK	48 (8)	22 (6)	35 (5)	22 (10)	45 (5)	172 (6)
APC	3 (<1)	1 (<1)	7 (1)	2 (1)	7 (1)	20 (1)
ARTIFICIAL PACEMAKER	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	4 (<1)
ATRIAL FIBRILLATION	5 (1)	2 (1)	4 (1)	3 (1)	4 (<1)	18 (1)
ATRIAL FLUTTER	2 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	4 (<1)
AV WENCKEBACH	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	2 (<1)
ECTOPIC ATRIAL	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
INCOMPLETE RBBB	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
INTERIOR (2), 3, F	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)
INTRAVENTRICULAR COND. DELAY	1 (<1)	0 (0)	1 (<1)	1 (<1)	1 (<1)	4 (<1)
JUNCTIONAL	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
JUNCTIONAL RHYTHM	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)
LEFT ANTERIOR HEMIBLOCK	1 (<1)	2 (1)	2 (<1)	0 (0)	1 (<1)	6 (<1)
LEFT BUNDLE BRANCH BLOCK	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	3 (<1)
LEFT POSTERIOR HEMIBLOCK	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)
LEFT VENTRICULAR HYPERTROPHY	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)
RIGHT BUNDLE BRANCH BLOCK	4 (1)	2 (1)	1 (<1)	0 (0)	4 (<1)	11 (<1)
SEPTAL V1, V2, (V3)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
ST SEGMENT DEPRESSED	2 (<1)	1 (<1)	6 (1)	1 (<1)	3 (<1)	13 (<1)
T WAVES FLAT	3 (<1)	0 (0)	6 (1)	1 (<1)	2 (<1)	12 (<1)
T WAVES INVERTED	7 (1)	1 (<1)	11 (2)	2 (1)	8 (1)	29 (2)
U WAVES ABNORMAL	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)
VPC	35 (6)	16 (4)	45 (6)	8 (4)	47 (5)	151 (5)

- The treatment groups were nearly identical in regard to baseline electrocardiogram variables and no clinically significant differences were observed between the Exelon®- and placebo-treated groups in the mean change from baseline in these variables. The data for change from baseline in QT<sub>c</sub> intervals is in the following table; the first column indicates percentage change in QT<sub>c</sub>

	>=12 mg N = 610	>6-9 mg N = 359	>3-6 mg N = 701	<=3 mg N = 231	Placebo N = 862
	n (%)	n (%)	n (%)	n (%)	n (%)
<10%	496[81.32]	314[87.47]	595[84.88]	195[84.42]	724[83.99]
>=10% to <15%	77[12.62]	29[8.08]	73[10.43]	24[10.39]	87[10.09]
>=15% to <25%	10[1.64]	15[4.18]	10[1.43]	10[4.33]	40[4.64]
>=25%	7[1.15]	1[0.28]	3[0.43]	2[0.87]	11[1.28]

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### 8.7.4 Cardiovascular Adverse Events

The incidence of cardiovascular adverse events is summarized in the following table for Phase III placebo-controlled studies. The incidence in the Exelon® group is comparable with that in the placebo group as indicated by the following table. Note that the incidence of syncope is now similar between the treatment groups, whereas at the time of the original NDA submission it was slightly higher in those treated with Exelon® than in those treated with placebo.

**Incidence of Cardiovascular Adverse Events with an Incidence of  
 ≥1% in Either Treatment Group, Phase III Controlled Studies**

Body System and Event	Exelon (N=1923)	Placebo (N=868)
	n (%)	n (%)
Autonomic Nervous System Disorder	149 (8)	39 (4)
Syncope	47 (2)	15 (2)
Cardiovascular Disorders, General	153 (8%)	83 (7%)
Hypertension	62 (3%)	21 (2%)
Edema peripheral	36 (2%)	24 (3%)
Hypotension	21 (1%)	5 (1%)
Hypotension postural	18 (1%)	3 (<1%)
Chest pain	14 (1%)	5 (1%)
Cardiac failure	11 (1%)	4 (<1%)
Heart Rate and Rhythm Disorders	68 (4%)	28 (3%)
Palpitation	22 (1%)	5 (1%)
Fibrillation atrial	16 (1%)	4 (<1%)
Extrasystoles	5 (<1%)	7 (1%)
Myo-, Endo-, Pericardial and Valve Disorders	30 (2%)	7 (1%)
Angina pectoris	15 (1%)	3 (<1%)
Myocardial infarction	11 (1%)	1 (<1%)

**8.7.5 Reviewer's Comments**

I would agree with the sponsor's conclusions that, based upon vital sign, electrocardiogram and adverse event data from randomized controlled trials, there is no evidence that Exelon® has any deleterious effects on cardiac function. These conclusions support the sponsor's draft labeling.

**8.8 Gastrointestinal Effects Of Exelon®**

**8.8.1 Sponsor's Summary**

The most frequent adverse events in the Exelon® Phase III randomized controlled trials were nausea, vomiting, diarrhea and anorexia. The sponsor states that these were dose-dependent, manageable by dose reduction, and unrelated to the pharmacological effects of Exelon®.

The median duration for each of the above adverse events in Exelon®-treated patients in Phase III placebo-controlled trials was as follows

Adverse Event	Median Duration In Exelon®-Treated Patients
Anorexia	20 days
Nausea	2 days
Vomiting	1 day
Diarrhea	2 days

The incidence of selected adverse events in the Phase III randomized controlled trials is illustrated in the following table which was copied from the submission.

**Number of Patients (%) with GI Adverse Events with an Incidence of  $\geq 2\%$  in any Treatment Group (plus GI bleeds and ulcer for comparison), Phase III Controlled Studies**

GI System AEs	Exelon Dose Groups (mg/day maximum)								(N=868) Placebo	
	(N=611) >9-12		(N=359) >6-9		(N=703) >3-6		(N=250) $\leq 3$			
	n	(%)	n	(%)	n	(%)	n	(%)		
Nausea	267	(44)	209	(58)	184	(26)	58	(23)	105	(12)
Vomiting	176	(29)	137	(38)	110	(16)	22	(9)	49	(6)
Diarrhea	117	(19)	67	(19)	94	(13)	29	(12)	99	(11)
Anorexia	111	(18)	66	(18)	62	(9)	18	(7)	27	(3)
Abdominal Pain	73	(12)	57	(16)	54	(8)	25	(10)	51	(6)
Dyspepsia	52	(9)	39	(11)	38	(5)	18	(7)	38	(4)
Constipation	28	(5)	24	(7)	25	(4)	11	(4)	35	(4)
Flatulence	30	(5)	12	(3)	17	(2)	9	(4)	18	(2)
Eructation	17	(3)	6	(2)	8	(1)	3	(1)	6	(1)
GI Hemorrhage	0	(0)	1	(<1)	2	(<1)	3	(<1)	0	(0)
Gastric Ulcer	1	(<1)	0	(0)	2	(<1)	0	(0)	0	(0)

The 6 instances of gastrointestinal hemorrhage in Exelon®-treated patients did not show a dose response and were considered unrelated to the drug; in addition the frequency of this adverse event was low. The incidence of gastric ulcer was also infrequent and unrelated to dose.

The incidence of 3 different categories of ulcer in the Phase III placebo-controlled studies of Exelon® are displayed in the following table

**Exelon vs. Placebo Comparison of Ulcers - Phase III Controlled Studies\***

	Exelon (n=1923)		Placebo (n=868)	
	n	(%)	n	(%)
Gastric ulcer	3	(0.16)	0	
Duodenal ulcer	1	(0.05)	0	
Peptic ulcer	1	(0.05)	0	

\* For "All Controlled Studies" (including the above plus Phase II, with Exelon (n=2436) and placebo (n=1088), there is no change from Phase III controlled in the number of events.

The incidence of the above 3 categories of ulcer in Exelon® and placebo-treated patients in the All Therapeutic Studies grouping in this submission is summarized in the next table

**Exelon vs. Placebo Comparison of Ulcers - All Therapeutic Studies (Phase II, III, and US IIIb) from FDA Pre-approval Safety Update (maximum exposure - 3.5 years)**

	Exelon (n=8297)		Placebo (n=1088)	
	n	(%)	n	(%)
Gastric ulcer	11	(0.21)	0	
Duodenal ulcer	14	(0.26)	0	
Peptic ulcer	6	(0.11)	0	

Based on the above 2 tables the sponsor has further concluded that

- In Phase III placebo-controlled studies of Exelon® there was a low incidence of all types of ulcers
- Increasing exposure from 6 months upto about 3.5 years resulted in only a slight increase in duodenal ulcer incidence and no increase in the incidence of other categories of ulcer

Most treatment-emergent gastrointestinal adverse events occurred during titration and the vast majority of such events were mild or moderate; most resolved without symptomatic treatment

The proportion of Exelon®-treated patients with "severe" anorexia, nausea, vomiting and diarrhea in Phase III controlled studies is illustrated below:

Adverse Event	Percentage Of Exelon®-Treated Patients With Severe Adverse Events
Anorexia	1
Nausea	2
Vomiting	2
Diarrhea	<1

In the all Phase III studies grouping the proportion of Exelon®-treated patients with anorexia, nausea, vomiting and diarrhea who were in the mild, moderate and severe categories is illustrated in the table below.

Adverse Event	Mild	Moderate	Severe
Anorexia	61 %	36 %	3 %
Nausea	45 %	49 %	6 %
Vomiting	38 %	55 %	7 %
Diarrhea	60 %	36 %	3 %

Based on the above the sponsor has proposed the following labeling in the "Warnings" section which is stated to be similar to class labeling.

### 8.8.2 Reviewer's Comments

The above labeling statement has largely been substantiated. I would however alter the last sentence to read as follows (the majority of instances of nausea, vomiting and diarrhea have been mild to moderate in intensity, and not merely mild)

## 8.9 Adverse Events

### 8.9.1 Sponsor's Presentation

The items in this section may be summarized as follows:

- The most common adverse events (i.e.,  $\geq 10\%$  incidence in either treatment group) in the Exelon® and placebo groups, in Phase III placebo-controlled trials were nausea, vomiting, dizziness, diarrhea, headache, anorexia and abdominal pain
- The median duration for each of the above common adverse events, in Phase III placebo-controlled trials, with the exception of anorexia, ranged from 1-4 days; the median duration of anorexia was 20 days
- In the Phase III placebo-controlled studies the incidence of severe adverse events was similar in the Exelon® (15%) and placebo (12%) groups; the vast majority of adverse events in these studies were therefore mild to moderate in severity
- The most common adverse events in Phase III placebo-controlled trials were much more common during the titration phase than during the maintenance phase as indicated in the following table. The titration regimes used for these studies required a fixed dose escalation with no possibility of a dose reduction. Outside the confines of a clinical trial it is likely that titration will be individualized, tolerance will improve and adverse events will be infrequent.

Comparison of Common ( $\geq 10\%$  incidence) Adverse Events by Treatment Group during Titration and Maintenance, for Patients in the Phase III Controlled Studies Who Entered Maintenance (i.e., Week 13 of treatment)

Treatment Group	Adverse Event	All AEs*	Nearly-emergent <sup>b</sup> AEs
		Wks 1-12 (n=1582)	Wks 13-26 (n=1582)
Exelon	Nausea	476 (30)	123 (8)
	Vomiting	242 (15)	66 (4)
	Dizziness	222 (14)	43 (3)
	Diarrhea	200 (13)	39 (2)
	Headache	202 (13)	41 (3)
	Anorexia	160 (10)	16 (1)
Placebo <sup>c</sup>		(n=788)	(n=788)
	Headache	72 (9)	11 (1)
	Nausea	70 (9)	7 (1)
	Dizziness	63 (8)	8 (1)

\* Includes all patients entering maintenance phase (Week 13 of treatment)  
<sup>b</sup> Includes AEs with an initial occurrence in maintenance phase AEs (includes AEs with a severity greater than in titration)  
<sup>c</sup> Less than 10% incidence included for the purposes of comparison

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- No systematic effects of gender, race or age on the incidence of adverse events could be determined in Phase III placebo-controlled trials.
- The following text is suggested for labeling:  
 "Treatment with Exelon® is associated with an increased incidence of nausea, vomiting, dizziness, diarrhea and anorexia. These are generally mild in intensity, of short duration and attenuate on continued dosing. These effects are generally seen during titration and are more frequent with higher doses"

8.9.2 Reviewer's Comments

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- I would modify the sponsor's labeling text above as follows (see addition in blue) to make the statement more accurate  
 "Treatment with Exelon® is associated with an increased incidence of nausea, vomiting, dizziness, diarrhea and anorexia. These are generally mild to moderate in intensity, of short duration and attenuate on continued dosing. These effects are generally seen during titration and are more frequent with higher doses"
- The sponsor's own analysis presented in the Integrated Summary of Safety with the original NDA indicated that female patients had a higher incidence of nausea, vomiting, anorexia, and abdominal pain than male patients

### 8.10 Statement On Predictors Of Response

The sponsor has conducted a review of response to Exelon® in the Phase III placebo-controlled trials based on age, race and sex; it has found that these factors do not influence response

The following proposed statement in labeling is therefore acceptable:  
 "Patients' age, gender or race did not predict clinical outcome"

## 9. Tabular Summary Of Key Efficacy Studies

### 9.1 Dose And Number Of Patients Completing

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

### 9.2 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)

### 9.3 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*	-0.32*
	Exelon® 6-12 mg/day	4.94*	-0.35*

\*p < 0.05

## 10. Tabular Summary Of B 103 (Phase II) Study

The B 103 study enrolled a sufficient number of patients for it to be considered to contribute to the overall assessment of efficacy. It may also be considered for inclusion in labeling since it was a large study of 13 weeks duration, used a cognitive and a global outcome measure (Mini Mental Status Examination and CGIC, respectively) and since the sponsor has contended that the 6 mg dose is effective. This study is summarized below:

Design	Randomized, double-blind, placebo-controlled, parallel-arm		
Key Inclusion Criteria	Probable Alzheimer's Disease		
Duration	13 weeks		
Study Arms and Dosage	Placebo	Exelon® 4 mg daily	Exelon® 6 mg daily
Number Randomized	133	136	133
Number in "intent-to-treat"	128	132	126
Number Completing	125	119	113
Primary Outcome Measures	Mini Mental Status Examination CGIC		
Efficacy Results For Mini Mental Status Examination INTENT-TO-TREAT Drug-Placebo Difference at endpoint	4 mg vs placebo: -0.3 6 mg vs placebo: 0.1 Not statistically significant		
Efficacy Results For CGIC INTENT-TO-TREAT Drug-Placebo Difference at endpoint	4 mg vs placebo: 0.15 6 mg vs placebo: 0.02 Not statistically significant		

## 11. Dr Greg Burkhardt's Assessment Of Mortality

In the approvable letter of 5/12/99 the Agency indicated to the sponsor that analyses performed until that time had continued to show a weak suggestion that Exelon® could have an unrecognized life-threatening risk. This concern was based upon:

- An excess mortality, albeit statistically weak, in those treated with Exelon® as compared with those treated with placebo in the randomized controlled trials
- A greater mortality, in open-label extension studies, at 10-12 mg in comparison with lower doses.

The Agency acknowledged that it was likely that the above signal did not result from any Exelon®-related toxicity, but was more likely attributable to chance. As a mechanism for resolving this remaining concern the Agency recommended the following to the sponsor:

- A further mortality analysis using methods similar to those already used on a cohort of patients that consisted of about 4300 individuals about whom the Division had little information, and the updated extended dataset
- Depending on the results of the analysis, a further large simple randomized trial comparing the mortality associated with Exelon® 12 mg daily with that associated with donepezil in doses of 5 mg and 10 mg daily.

Following the meeting between the sponsor and Division on 8/4/99, the sponsor submitted a summary of the recently completed placebo-controlled trial INT-03 that was conducted in patients with Lewy Body Disease. Dr Greg Burkhart, Safety Team Leader, in a review, dated 8/13/99, used the results of this study in an overall analysis of the mortality experience with Exelon®.

Taking the results of the INT-03 study into consideration, the mortality experience with Exelon® in Phase III placebo-controlled trials is summarized by the following table:

	Exelon® (n = 1982)	Placebo (n = 929)
Number of Deaths (within 30-day window)	6	3
Mortality Rate	0.30 %	0.32 %
Total Exposure	829.5 patient-years	417.0 patient-years
Number of Deaths per 100 Years of Exposure	0.72	0.72

Dr Burkhart concluded that he:

- No longer had a concern that Exelon® contributed to excess mortality
- Did not feel that a further randomized controlled trial of Exelon® to evaluate safety was needed
- Did not believe that a mortality analysis of the type recommended in the Agency's approvable letter was warranted

Please see Dr Burkhart's review for full details

## 12. Vomiting

Vomiting (and several related symptoms such as anorexia, nausea and diarrhea) appear to be common with Exelon® and in view of its implications (fluid depletion, aspiration, esophageal tears, and patient/caregiver distress) is discussed in a separate section

### 12.1 Recording Of Vomiting In Case Report Forms

Along with all other adverse events, the following aspects of vomiting were recorded in Case Report Forms during the development of Exelon®

- Does it meet the definition of serious?
- Severity (mild, moderate or severe)
- Event causality
- Relationship to study medication
- Start and stop dates
- Frequency
- Therapy prescribed
- Effect on study course

The definitions of the terms mild, moderate and severe are in the following table:

1	Mild	Symptom barely noticeable to patient; does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.
2	Moderate	Symptom of a sufficient severity to make patient uncomfortable; performance of daily activities influenced; patient is able to continue in study; treatment for symptom may be needed.
3	Severe	Symptom causes severe discomfort. May be of such severity that patient cannot continue. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

It is hard to see how the term "mild" as defined above could be applied to any episode of vomiting; on the other hand it is also unclear if investigators actually used this definition to indicate the severity of vomiting

**12.2 Incidence Of Vomiting (And Related Symptoms)**

The incidence of vomiting and related symptoms in all controlled clinical trials is illustrated below

Adverse Events	Exelon® (n=1923)	Placebo (n=868)
Nausea	37 %	12 %
Vomiting	23 %	6 %
Anorexia	13 %	3 %
Diarrhea	16 %	11 %

The incidence of vomiting and related symptoms in all studies included in the All Therapeutic Studies grouping is illustrated below

Adverse Event (COSTART)	Exelon® (n=5297) %	Placebo (n=1088) %
Nausea	47.2	10.9
Vomiting	31.6	5.2
Diarrhea	21.5	9.8
Anorexia	18.2	2.8

The incidence of these adverse events in selected dose groups for selected randomized controlled trials and titration studies is illustrated in the table below

**APPEARS THIS WAY  
 ON ORIGINAL**

	Study number/Randomization group						
	B352: 6-12mg (n = 231)	B303: 6-12 mg (n = 243)	B304: 810 (n = 227)	B355 (n = 544)	B356: 1 wk titr. (n = 438)	B356: 2 wk titr. (n = 305)	B356: 4 wk titr. (n = 489)
Dose Increases	0.5-1.0/wk	0.5-1.0/wk	0.5-1.0/wk	3.0/wk			
Nausea n (%)	125 (54)	121 (50)	123 (54)	314 (58)			
Vomiting n (%)	75 (33)	82 (34)	88 (39)	181 (33)			
Diarrhea n (%)	57 (25)	40 (17)	40 (18)	99 (18)			
Anorexia n (%)	53 (23)	34 (14)	47 (21)	77 (14)			

### 12.3 Severity Of Vomiting And Related Adverse Events

The severity of vomiting and related symptoms in all Phase III studies is illustrated below

Adverse Event	Mild	Moderate	Severe
Anorexia	61 %	36 %	3 %
Nausea	45 %	49 %	6 %
Vomiting	38 %	55 %	7 %
Diarrhea	60 %	36 %	3 %

The severity of vomiting in the subset of Phase III randomized controlled trials (consisting of the vast majority of patients participating in such trials) submitted with the original NDA is illustrated below

Severity Of Vomiting	Treatment Group	
	Exelon® (n=1696)	Placebo (n=763)
Mild	10 %	3 %
Moderate	10 %	2 %
Severe	2 %	< 1 %

### 12.4 Discontinuations Due To Vomiting And Related Symptoms

These are illustrated for the following table which is applicable to selected studies and treatment groups

**APPEARS THIS WAY  
 ON ORIGINAL**

	Study number/Randomization group						
	B352: 6-12 mg (n = 231)	B303: 6-12 mg (n = 243)	B304: BID (n = 227)	B355: (n = 544)	B356: 1 wk titr. (n = 438)	B356: 2 wk titr. (n = 305)	B356: 4 wk titr. (n = 489)
Dose Increases	0.5-1.0/wk	0.5-1.0/wk	0.5-1.0/wk	3.0/wk	3.0/wk		
Overall (any) n (%)	67 (29)	55 (23)	41 (18)	108 (20)	79 (18)		
Nausea n (%)	30 (13)	30 (12)	11 (5)	40 (7)	48 (11)		
Vomiting n (%)	13 (6)	18 (7)	10 (4)	13 (2)	28 (6)		
Diarrhea n (%)	5 (2)	3 (1)	2 (1)	5 (1)	20 (5)		
Anorexia n (%)	12 (5)	8 (3)	4 (2)	7 (1)	24 (6)		

**12.5 Other/Overall Attributes Of Vomiting And Nausea**

These are summarized in the following table which is applicable to all randomized controlled trials of Exelon®

	Nausea		Vomiting	
	Exelon (n = 1923)	Placebo (n = 868)	Exelon (n = 1923)	Placebo (n = 868)
Percent of Patients with Event	37%	12%	23%	6%
% Severe*	2%	<1%	2%	<1%
% Discontinued	7%	1%	4%	<1%
% Serious	<1%	0%	<1%	<1%
Duration of Episodes (days)				
N	1553	136	831	65
Mean	12	9	4	5
Median	2	2	1	1
Mode	1	1	1	1
Number of Episodes per patient				
Mean	2	1	2	1
Median	2	1	1	1
% Resolved	95%	93%	99%	98%

**12.6 Reviewer's Comments**

- Vomiting, nausea and anorexia appear to be common with Exelon®. They appear to be more common during the titration phase than during the maintenance phase of clinical trials. Of these symptoms vomiting is of the greatest concern given its consequences

- Vomiting appears to most common in the dose range (6-12 mg/day) at which the drug also has evidence of efficacy
- In patients titrated to the 6-12 mg/day dose range, the incidence of vomiting appears unaffected by the titration regime used
- Discontinuations due to vomiting are relatively uncommon as compared with the total incidence of this symptom
- While most episodes of vomiting appear not to be "severe", "moderate" and "mild" episodes appear to occur with about equal frequency. The applicability of the term "mild" to any episode of vomiting, using the criteria proposed by the sponsor, is questionable. It is not possible for this symptom to be barely noticeable to the patient.
- It is unclear if the frequency of episodes of vomiting represents the frequency of individual episodes of emesis or of contiguous periods of time where multiple episodes of vomiting may have occurred. Clearly, it is very unlikely that the mean duration of individual episodes of vomiting will last 4 days.
- 

### 13. Draft Labeling Review

A detailed review of the draft labeling supplied by the sponsor has been made in a separate document ('\_\_\_\_\_'). Please refer to that document for full details.

### 14. Financial Disclosure Certification

The sponsor states the following:

*All new submitted studies in this Complete Response (i.e., Studies B 356, B 357, W 368, W 370, and INT-03) are not considered "covered studies" as defined by 21 CFR 54.2 (e) since they do not establish that the product is effective nor does one investigator in these studies make a "significant contribution to the demonstration of safety". Thus, financial disclosure certification, as defined by 21 CFR 54.4, is not applicable to the present submission*

I have reviewed the cited regulations and agree with the sponsor.

### 15. Comments

- The efficacy of Exelon® in the symptomatic treatment of mild to moderate Alzheimer's Disease has already been established as meeting current regulatory standards. There is some evidence to support efficacy across the entire 6-12 mg dose range, and, to a less convincing extent, even at lower doses, but the most consistent effectiveness may have been at doses in the higher part of the 6-12 mg range. The effect size with Exelon® has been exceedingly modest.
- Although there no direct ("head-to-head") comparisons have been carried out, there is no clear indication that Exelon® has any advantages over donepezil,

an approved cholinesterase inhibitor, which appears to be the drug in that class currently most widely used for the treatment of Alzheimer's Disease. In fact donepezil appears to have the following advantages over Exelon®:

- Once-daily dosing
- A much less complex titration regime, with even the initial dose being demonstrated to have evidence of efficacy
- A much lower incidence of nausea and vomiting: 11 % and 5 %, respectively, in donepezil-treated patients in placebo-controlled trials (both these adverse events occurred at about twice the rate as in placebo-treated patients)
- A lower incidence of anorexia: 13 % for Exelon®-treated patients and 4 % for donepezil-treated patients, in placebo-controlled trials (the incidence in Exelon®-treated patients was 4 times higher than in placebo-treated patients; that in donepezil-treated patients was about 2 times higher than in placebo-treated patients)
- The major safety concern associated with Exelon® use is the high incidence of vomiting (occurring in about one-third of patients titrated to the effective dose range of the drug), regardless of titration regime and especially high with the dose range believed to be effective. To a lesser degree the same concern extends to the high incidence of nausea and anorexia at the doses recommended for use. Vomiting is of especially great concern given
  - its potentially serious, even life-threatening consequences, namely aspiration, fluid depletion and its consequences, and esophageal tears or rupture
  - the highly distressing nature of this symptom both for patients and caregivers
  - the age and frailty of many patients likely to be exposed to the drug

Although most instances of vomiting have been classed by investigators as being "mild" or "moderate" in severity (it is unclear to what extent investigators have adhered to the protocol-specified definitions for these terms) and although the incidence of adverse event discontinuations due to vomiting is low (7 % for those randomized to the 6-12 dose group in the studies B 303 and B 352,

event, the occurrence of even single, short-lived periods of vomiting at such a high incidence in this population is of major concern.

While vomiting is readily evident to an observer and the drug could be discontinued or reduced in dosage when a first episode occurs, even that first episode could have serious consequences, e.g., if it occurs while a patient is asleep

The high incidence of anorexia, and nausea are also of concern given that many elderly individuals, and especially those who are cognitively impaired, are undernourished to begin with. The many possible consequences of undernutrition do not need further description here but it is noteworthy that in women doses of Exelon®  $\geq 9$  mg (the most effective doses) are associated with a 26 % incidence of weight loss in excess of 7 % of baseline body weight.

The available data suggest that the incidence of nausea and vomiting may

not be related so much to the titration rate as to the absolute daily dose administered during titration

- There does not appear to be any other major hazard associated with Exelon® use that would preclude approval. The Division no longer has a concern that Exelon® contributes to increased mortality. Pancreatitis attributable to Exelon® appears to be very infrequent, as are (largely asymptomatic) elevations of transaminases and bilirubin.
- Major issues pertaining to labeling that need to be discussed further with the sponsor, if the drug is finally approved, include:
  - Titration rate: that proposed by the sponsor has been associated with a high incidence of nausea and vomiting
  - Inclusion of data from analysis of a secondary efficacy measure (Progressive Deterioration Scale) in labeling: I would recommend against inclusion of these data for the reasons stated above
  - Inclusion of efficacy data from studies other than B 303 and B 352: I would favor a description of B 351 as well

If approved the high incidence of nausea, vomiting and anorexia with this drug needs to be clearly emphasized in the package insert, wherever indicated.

- Based on the above, the key elements of the risk-benefit equation in the case of Exelon® are as follows:
  - The very modest efficacy of the drug most apparent at higher doses which are also the doses at which the most common and troublesome adverse events occur
  - The lack of any readily apparent advantage, and the presence of several readily apparent disadvantages, when Exelon® is compared to donepezil, which currently appears to be the most commonly used cholinesterase inhibitor in this country
  - The very high incidence of nausea, vomiting and anorexia, and their potentially serious consequences especially in this population. The consequences of vomiting are potentially serious regardless of whether episodes are short-lived and non-recurrent, or frequent
- To this reviewer the risk-benefit equation above is weighted against approval of the drug. Approval of the drug might be possible if it could be demonstrated that a different dosing regime was associated with a much lower incidence of nausea, vomiting and anorexia.

## 16. Recommendation

I recommend that this application not be approved on the grounds that the risks of using the drug outweigh the possible benefits

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Ranjit B. Mani, M.D.  
Medical Reviewer

R. Levin, M.D. \_\_\_\_\_

*SL*  
(see my memo)

rbm 4/7/00

cc:

HFD-120

NDA 20823 N(-A2)

electronic copy-Levin

**APPEARS THIS WAY  
ON ORIGINAL**



**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*22 pages*

*DRAFT LABELING*

**MEMORANDUM**

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

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

**Date:** April 9, 2000  
**From:** Randy Levin, M.D., Neurology Team Leader  
**Subject:** NDA 20-823 Exelon  
**To:** File

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**Background**

The application was submitted on 4/7/97. A not approvable letter was issued on 7/7/98 because of a concern for increase risk in mortality for patients on drug. Based on the sponsor's response to these concerns, an approvable letter was issued on 5/12/98. In the approvable letter, they were also asked to adopt the draft labeling, provide additional information on the patient support system and to update the safety data for the drug.

The sponsor provided information in response to the approvable letter, completing their response on 10/21/99. In this response, they provided a safety update, interim safety reports for study B356 and INT-03, interim reports for three completed studies (W358, W370 and B357). These reports were used to support proposed changes to the labeling. They also included information on a caregiver's support program and launch material. A CMC amendment for an alternate source for the capsule was also provided.

**CMC**

Drs. Rzeszotarski and Guzewska reviewed the cmc section of the submission and subsequent amendments addressing specific cmc issues and found the information adequate for approval. The sponsor noted that they had an alternate source of the capsule. This site was found to be acceptable based on profile information. There were also issues regarding the readability of the label which the sponsor agreed to correct.

**Safety update**

The safety update was reviewed by Dr. Mani. Issues related to the concern for an increase in mortality were addressed by Dr. Burkhart as well.

The cut off date for the safety update was through 6/30/99 for narratives for deaths and serious AEs. The cut off date for discontinuation for adverse events leading to discontinuation was 12/31/98.

**Exposure and disposition** - A total of 5297 patients were exposed to Exelon with over 2000 exposed for more than 1 year. The sponsor calculated a total of 5713 patient years of exposure. In the clinical trials, 1088 patients were given placebo. The mean age of the patients was about 73. Approximately 60% were female and 90% were white. 49% of patients on Exelon discontinued from studies completed to 16% in the placebo group. 24% of patients discontinued for adverse events. The reasons for discontinuation was consistent with the most common adverse events summarized in Table 1.

**Mortality , serious adverse events and adverse events leading to discontinuation** - There were a total of 259 deaths reported up to 6/30/99. Mortality rates were similar between patients on drug and placebo. The issue of increased mortality in patients exposed to Exelon was also addressed by Dr. Burkhart who concluded that based on the current safety database, there was not a signal for increased risk for mortality in Exelon treated patients.

Dr. Mani reviewed the narratives of the deaths and serious adverse events in the safety update. He noted some concerns with the following adverse events:

**Pancreatitis** - Dr. Mani noted 20 cases of pancreatitis in patients on Exelon, 10 occurring in the clinical trials. One case was reported in a patient on placebo giving an incidence of 0.17% in Exelon treated patients compared to 0.12% in placebo treated patients. 7 out of the 10 patients had gallstones. From all of the patients exposed, 9 did not have a concurrent condition to explain the pancreatitis. Two patients were able to resume treatment.

**Liver disease** - Dr. Mani reviewed the cases with LFT abnormalities. All elevations of LFTs were < 5 times the ULN except for a single patient. This patient was noted to have an elevation of ALT to 222. She was kept of drug for a total of 39 weeks prior to discontinuation for persistent elevation of LFTs. The ALT peaked at 1190 one week after discontinuation and resolved 3 weeks after drug discontinuation.

In the clinical trials, two patients experienced an elevation of LFTs with an elevation of bilirubin. These patients were on other drugs that may have contributed to the elevation (methotrexate in one patient and trimethoprin sulfamethoxazole in another). Two postmarketing cases were also reported but the information is limited. One patient was treated for decubitus ulcers and malnutrition. The second patient was on Exelon for 55 days prior to developing an ALT of 630. Exelon was discontinued and one week later the SGPT was 130. No other information was available.

**Discontinuation for adverse events** - 24% of patients discontinued for adverse events. The reasons for discontinuation was consistent with the most common adverse events which are summarized in Table 1.

Table 1: Common Adverse Events (%)

Adverse Event	Exelon (n=5297)	Placebo (n=1088)
Nausea	47.2	10.9
Vomiting	31.6	5.2
Dizziness	23.3	9.3
Diarrhea	21.5	9.8
Headache	19.8	11.4
Agitation	18.7	7.2
Anorexia	18.2	2.8
Accidental trauma	17.4	7.6
Upper respiratory infection	14.4	7.8
Abdominal Pain	14.1	6.0
Insomnia	12.9	5.5
Confusion	11.4	6.3
Depression	11.1	4.0
Dyspepsia	10.8	3.9
Fatigue	9.7	4.1
Urinary tract infection	9.3	5.0
Asthenia	9.0	2.0
Weight decrease	8.9	0.3
Somnolence	8.8	2.3
Urinary incontinence	8.2	1.8
Back Pain	7.6	4.0
Anxiety	7.5	2.4
Constipation	7.4	3.6
Coughing	7.1	3.9
Aggressive Reaction	6.2	2.0
Tremor	6.0	1.2
Hallucination	6.0	2.9
Arthralgia	5.8	2.5
Myalgia	5.5	0.9
Malaise	5.4	1.8
Rhinitis	5.2	2.6
Bone fracture	5.0	1.8

### Labeling issues

The sponsor has provided comments to the proposed labeling in the approvable letter. Changes included inclusion of the PDS results in the labeling, exclusion of information of the "negative" studies, changes in the description of cardiovascular and GI adverse events, description of weight loss, presentation of adverse event rates, dosage strength availability and titration regimen.

living.” The sponsor stated in the application “The PDS was identified in study protocols as a secondary efficacy criterion. It provided evidence supportive of the primary efficacy results. This assessment scale is useful in the evaluation of a treatment-linked improvement in everyday functioning.” Caregivers rated the patient on the following (item number). While some of the items appear to be the same, on the form there are differences in the anchors of the line that are sometimes subtle but change the meaning:

- Active participation in family finance, balances checkbook, takes care of finances (1)
- Handles money, checks, bills adequately and accurately (6)
- Actively participates in family finances, planning budget, takes care of finances (16)
- Always correctly balances checkbook and accurately cares for family finances (21)
  
- Meaningfully discusses TV, movies, similar event (2)
- Discusses current events, politics, or topics of interest (4)
- Attendance at social gatherings at high or increased levels (25)
- Increases amount of time doing hobbies or recreational pursuits (26)
- Does hobbies or other leisure time pursuits (29)
- Does hobbies or similar activities error free, accurately and properly (18)
  
- Drives car safely (3)
- Drives own car (27)
- Maintains pattern of doing usual household chores (5)
- Does jobs or need tasks (28)
- Looks up, dials numbers, uses phone without any assistance (7)
- Looks up, dials numbers, and typically uses phone without help (22)
- Always uses tools, household implements, etc appropriately to the task (15)
- Proper eating behavior, uses proper utensils, manners, all/most of time (23)
- No noticeable difficulties telling time (9)
- Has a clear concept of time can tell how long a half hour is (13)
- Has little or no difficulty in telling time correctly (14)
  
- Travels independently on public or in private vehicles (8)
- Walks or travels a considerable distance from home and returns unaided (10)
- Can walk about without getting lost in immediate neighborhood (19)
- Is comfortable or feels at home in unfamiliar settings (11)
  
- Always remembers where she/he puts things (12)
- Places items in customary spots Does not engages in needless rearranging (17)
- Typically needs no help or advice to dress appropriately for climate or conditions (20)
- Takes normal precautions in daily activity (24)

The following was taken from the sponsor’s ISE to describe how the test was administered: “Each activity item is presented as a bipolar pair of descriptors, at opposite ends of an unmarked line. The line was used by the rater as an analog scale. The rating of each item involved placing an “X” at a proximity on the line proportional to the degree

that either of the characteristics or statements at the extremes best described the patient. Each PDS completed in these studies was scored by \_\_\_\_\_ personnel trained by \_\_\_\_\_, one of the scale's authors. Scoring was accomplished with the aid of a digitizing tablet and pen, which returned the location of the pen point (X-Y coordinates) to a computer. The scoring program calculated the mean and standard deviation of items for each patient and returned for each item a transformed score (T), where  $T = M + (10/S) * (X-M)$ , M = mean of all scored items, S = standard deviation of all scored items, and X = untransformed item score. The total score on a PDS questionnaire was the mean of all available item scores: the mean of untransformed scores equals the mean of transformed scores. Higher scores were better.

The PDS was to be completed at screening (practice only, CRF remained at the study site and was not forwarded to Sandoz), baseline, Weeks 12, 18, and 26, and within 24 hours of the last dose of study medication in patients who discontinued early. The PDS was identified in study protocols as a secondary efficacy criterion. It provided evidence supportive of the primary efficacy results. This assessment scale is useful in the evaluation of a treatment-linked improvement in everyday functioning. Post-baseline minus baseline total score changes were compared among treatment groups in the ITT and LOCF populations. The possible range of change scores was \_\_\_\_\_ Positive differences indicated improvement.”

The PDS was included in 4 efficacy studies as a secondary outcome measure. The results for the intent to treat analysis are summarized in Table 2.

**Table 2 Results of PDS change scores**

Study	303	352	351	304
High dose	0.05	-1.52	-2.15	-2.35
Placebo	-2.18	-4.90	-3.13	-4.74
P value	0.066	0.000	0.371	0.03?

The sponsor argues that the PDS results are an important feature to be included in labeling in order to help inform the prescribers, caregivers, and patients on the drug's effect on quality of life or activities of daily living. There are some issues about the sponsor's argument.

The fundamental issue is that the PDS is not a measurement of "quality of life". The PDS scale like the CIBIC uses clinical measures of functionality to assess efficacy. A change in the PDS scale like the CIBIC can be used to help demonstrate activity of the drug. For this application, the results in the studies do show small changes in functionality similar to that seen in the CIBIC except the changes are only associated with nominal p values < 0.05 for one of the two studies evaluating the 6 to 12 mg/day dose group (352) raising an issue of the statistical significance of the finding.

Even ignoring the issue of statistical significance, the PDS has the same limitations as the CIBIC. The clinical meaning of a demonstrated difference between drug and placebo on the PDS is not known. Specifically, the results of the PDS does not provide to the

prescriber, caregiver or patient with information on the drug's effect on the quality of life of a patient with Alzheimer's disease.

This point is described by the authors of the scale in an article provided by the sponsor in the application (DeJong, 1989). In this article, the authors concluded that "In interpreting the changes identified by the PDS in quality of life as AD progresses, a few points should be kept in mind. These findings are suggestive, not definitive. The changes of behavior can be either quantitative (a change in degree or extent) or qualitative." So, even though the PDS assesses function that can effect "quality of life" activities, a change in this scale does not mean that there was an improvement in the patient's quality of life. Take the example of the ability to use the telephone without help. If a patient's use of the telephone improves so they understand that they must pick up the receiver prior to dialing but still cannot dial, the patient's function has improved but their "quality of life" is unchanged in that they still cannot make a telephone call without help.

The PDS was not designed to assess the quality of life of the patient. The test was designed to detect changes in the patient's functioning. The sensitivity of the PDS is set at a level that evaluates changes that do not necessarily signify a change in the quality of life of the patient. A responder in this test is defined as someone who has at least a 10% change toward the goal of being able to perform the activity. To validly demonstrate that the drug actually improved the patient's "quality of life", the test needs to assess if the patient can perform activities that improve their quality of life. The activities described in the PDS that improve the quality of life are listed above. The sponsor has not demonstrated that the drug allowed patients to perform any of these activities. This does not mean that the drug is not active. It only means that the drug was not shown to enable patients to perform the activities listed in the PDS.

There are some other issues of concern about this measure. The validity of the findings in these studies are questionable for additional reasons. The blinding of the caregiver assessor could be effected by the high frequency of adverse events seen with the drug (50% of patients were reported to have nausea). Also, it is not clear if caregivers are able to distinguish some of the subtle changes in the measures described in the test. The authors of the PDS suggest that the PDS can be performed in 15 minutes. In a brief look at some of the questions, a rater can think that there is really no difference between two similar questions and rate them accordingly. In addition, the authors of the article also noted that "While statistically significant differences exist between stages of GDS on certain items descriptive of ADL, additional validation is needed, along with multiple and independent external criteria of AD."

In conclusion, instead of providing helpful information to the prescriber, caregiver and patient, the PDS results may be misleading. Claims associated with "activities of daily living" or "quality of life" scales can be easily misunderstood by the reader. In addition, the findings are not robust, are of unclear clinical significance, and are of questionable validity.

Description of studies - The sponsor did not include the description of the "negative" study. These were the fixed dose studies that did not show statistically significant findings on the dual outcome assessments for drug groups. The ADAS-cog comparison was associated with a p value < 0.05 for the 6 and 9 mg/day groups when compared to placebo but the CIBIC was negative. The sponsor claims there were extenuating circumstances to explain why these studies were not positive including the high drop out rate as a result of patients being forced to specific doses. Since the drop out rate for the 6 mg group was not different from the 6 to 12 mg/day group in the "positive" study, the drop out rate may not be the reason for the lack of efficacy. The question then remains whether the information seen in this study about the fixed doses would be helpful information. While the positive efficacy studies did show that the 6 to 12 mg/day dose group was statistically better than placebo, it did not show which doses from 6 to 12 mg/day were effective. Since the fixed dose studies provide better evidence about the efficacy of the specific dose and evidence for a dose response, a brief description would provide some additional information.

Warnings - cardiovascular - The same warnings for potential cardiovascular effects seen in the Aricept labeling should be included in the Exelon labeling. The sponsor has not included the statement that Exelon is associated with syncope. With Aricept, the incidence for syncope was 1 and 2% for placebo and drug. For Exelon it is 1.7 and 2.4 for placebo and drug, respectively. The statement "syncopal episodes have been reported in association with the use of Exelon" is consistent with Aricept labeling.

Warnings - nausea, vomiting and diarrhea - These events occurred at a high rate and led to a discontinuation of the drug in a number of patients. These symptoms can lead to serious problems in this patient population who generally are not as able to respond to stress such as weight loss, dehydration and aspiration that can be a result of these symptoms. The high incidence of these adverse events raise a question as to whether the drug should even be approved. Recently, a similar drug was not approved based on part in the high frequency and severity of these types of adverse events. The frequency and severity of the symptoms appeared to be greater in the drug that was not approved.

One problem in evaluating this issue is the difficult assessing the severity of the symptoms. One way to assess the severity is by the percentage of patients who discontinue because of the adverse event. This is difficult to assess in many of the studies since the dose titration is flexible allowing patients to remain on lower doses instead of discontinuing the drug. Determining the severity of the symptoms by the frequency is also difficult since this information is not captured in a reliable way in the case report forms. The statement used by the sponsor in labeling, "In most cases these events have been mild and transient and have resolved during continued use of Exelon" does not provide a useful impression of this problem. This issue needs to be prominently conveyed in labeling. A better description of the seriousness of the events is needed such as the incidence and severity.

Warnings - weight loss - The weight loss seen with Exelon was not like other cholinesterase inhibitors and this statement should not be included in labeling. Weight

loss and anorexia were significant problems and should be included with the symptoms of nausea and vomiting noted above. The sponsor provided the requested information about weight loss as summarized in Table 3.

**Table 3 Incidence Of Weight Loss Of > 7 % From Baseline In Patients Receiving > 9 Mg/Day**

Gender	Treatment Group	Incidence Of Weight Loss Of > 7 %
Women (n = 332)	Exelon	26 %
	Placebo	6 %
Men (n =272)	Exelon	18 %
	Placebo	4 %

Adverse events presentation - When providing percentages for adverse events, the sponsor will need to provide the incidence based on the people exposed to the 6 to 12 mg/day dose group not those exposed to the dose and all lower doses. In addition, the numbers used should be for patients in all controlled trials.

Adverse events - most frequent - In this section, the sponsor should discuss the differences in common adverse events with the different titration regimen.

Adverse events - other - The sponsor should continue to report serious adverse events even if they are present on this list.

Titration - Titration is a combination of three factors: starting dose, interval for dose increase and the amount of dose increase at each interval. The titration in the draft labeling was based on the experience from the controlled clinical trials. A comparison of the titration regimen is summarized in Table 4.

**Table 4 Comparison of Titration Regimen**

Titration	Initial dose	Interval for increase	Dose increase
Draft labeling	1 mg bid	Weekly	0.5 to 1 mg

The new proposed titration schedule has a number of advantages. It is consistent with European labeling, does not require 0.5 or 1 mg capsule and potentially can get patients to higher doses quicker. The disadvantages includes an increase risk for adverse events. This last point is difficult to assess since the regimens were not directly compared. They had three groups that only differed by the duration between increases in dosing. The incidence of adverse events did not seem to differ between the 1 and 2 or 4 week intervals. So the dosing interval does not appear to have an effect when using 3 mg/day increases. One of the problems with this conclusion is that patients were allowed to stay on lower doses instead of advancing so the weekly intervals may not accurately reflect what actually occurred.

The  
er,

Starting at 3 mg/day and advancing by 1 mg/day on a weekly basis would allow patients to get to the 12 mg/day dose in 9 weeks instead of 6 weeks by the proposed dosing and could possibly help reduce the adverse events and allow patients to reach the higher doses.

Dose availability- Since the adverse events appear to be dose related, patients may need to be maintained on lower doses. In addition, since the PK is non linear from 6 to 12 mg/day, smaller dosing increments might be useful to between the currently available 6, 9 and 12 mg/day. One possibility is to use unequal doses which may not eliminate the adverse effects and they might not offer more efficacy than the lower dose. The ability to move from 9 to 7 or 8 mg may help.

## Conclusions

The sponsor has provided evidence in more than one adequate and well controlled clinical trials of efficacy for the symptomatic treatment of patients with mild to moderate Alzheimer's disease. The treatment effect is modest and dose related.

The negative aspects of describing the PDS results in labeling outweigh any benefits for including it. Describing the PDS results in labeling may mislead prescriber, caregiver and patient rather than provide useful information. Claims associated with "activities of daily living" or "quality of life" scales like the PDS can be easily misunderstood by the reader. Because there was a difference between patients treated with drug or placebo, or there were more "responders" in the drug treated patients on the PDS "quality of life" scale, does not mean that the drug changes the patient's "quality of life". This also does not

mean that the drug is worthless. The PDS along with the ADAS-cog and CIBIC are helpful for detecting whether the drug is having some effect in patient's with Alzheimer's disease. However, they are not meant to quantify the benefit of the drug for the patient. In addition to this issue, the PDS findings are not robust, are of unclear clinical significance, and are of questionable validity.

Many patients had problems tolerating the drug because of nausea, vomiting and other GI symptoms that appears to be dose related. These adverse events are most prominent at the doses demonstrated to be effective which may interfere with the ability for patients to achieve therapeutic doses. In the clinical trials, these adverse events led to a reduction in dose or prevented the patients from being titrated to higher doses. It is not clear if a titration regimen involving a longer interval between dose increases or a smaller increase in dose with each step would improve the tolerability.

Based on the high incidence of adverse events and the modest treatment effect, the question is raised if the drug should be approved at all. This view point is expressed by Dr. Mani in his review. I agree with Dr. Mani that the most common adverse events, nausea, vomiting, diarrhea, anorexia, and weight loss are all potentially serious problems in this population. I also agree with Dr. Mani that these issues should be clearly and prominently conveyed in labeling to both prescribers (Warnings and Dose and Administration section) and caregivers (information to patients/caregivers section). The risk as a result of these adverse events may be reduced by close monitoring for these problems by the prescribers and caregivers.

### **Recommendations**

I recommend approval if the sponsor provides prominent warnings regarding the potentially serious adverse events, allows for more flexibility in dosing \_\_\_\_\_, and includes the other points recommended in this memo. In addition, the sponsor should be asked to report serious adverse events even for those listed in the adverse events section.

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Randy Levin, M.D.  
Neurology Team Leader

## MEMORANDUM

DATE: April 18, 2000

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-100

TO: File, NDA 20-823

SUBJECT: Division 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 the cholinesterase inhibitor Exelon (rivastigmine tartrate) in patients with Alzheimer's Disease was submitted on 4/7/97 by Novartis. A Not Approvable letter was issued on 7/7/98, on the basis of a finding of increased mortality. This concern arose from data from the controlled trials, and appeared to be confirmed by analyses of the uncontrolled data. While the signal was weak, it was felt that additional analyses were required to further clarify the signal.

The sponsor provided additional analyses in a submission dated 11/8/98. These analyses were extensively reviewed (see, for example, my memo dated 5/3/99). As a result of these analyses, an approvable letter was sent on 5/12/99. This letter made clear that the Agency still was concerned about what was termed a "...non-compelling weak suggestion of an association between drug use and mortality, occurring in a set of nonrandomized data, and most likely to represent a chance occurrence...", in particular, because there was a considerable number of patients who had been exposed to Exelon for whom the Agency had no safety information at that time.

On 8/9/99, the sponsor submitted the results of Study ENA-INT-03, a randomized controlled trial of patients with Lewy body dementia, a population similar to the Alzheimer's population. In this study, there were 2 deaths within 7 days of the last dose of study medication, both in placebo patients. The addition of these deaths erases the signal of increased mortality originally seen in the controlled trials, and, in light of this, the weak signal seen at higher doses in the uncontrolled experience becomes of no concern. Dr. Burkhart, previous Team Leader of the Safety Team, reviewed this submission in a memo dated 8/13/99; he reaches the same conclusion.

The sponsor formally responded to the Approvable letter in a submission dated 10/21/99. This submission contained the Safety Update requested in the Approvable letter, draft labeling, and the results of Study B356, which examined a different dosing regimen than that used in the controlled trials. In this study, patients were treated with 3 mg/day increments either every week, every 2

weeks, or every 4 weeks. In the original controlled trials, patients were titrated to their maintenance dose by increments of about 1 mg/day.

This submission has been reviewed by Dr. Mani, medical officer (review dated 4/7/00), and by Dr. Randy Levin, Neurology Team Leader (review dated 4/9/00).

In this memo, I will offer my recommendations for action on this NDA.

## EFFECTIVENESS

We had previously determined that substantial evidence of effectiveness had been provided; this is, of course, still true. The issue of the effective dose, however, needs some comment.

In the Approvable letter, we described 12 mg/day as the effective dose, with doses below 9 mg/day not being consistently effective.

The 2 randomized controlled trials on which the finding of substantial evidence of effectiveness is based both employed a design in which patients were randomized to dose ranges of 6-12 mg/day, 1-4 mg/day, or placebo. In both studies, statistically significant differences in favor of drug were seen between the high dose range and placebo. Strictly speaking, then, it is appropriate to recommend the dose range of 6-12 mg/day as the effective dose range.

Presumably, the earlier conclusion that the higher doses were the effective ones was based on the results of 2 fixed dose studies, one in which patients were randomized to doses of 3, 6, or 9 mg/day of Exelon or placebo, and one in which patients were randomized to Exelon 4 or 6 mg or placebo. In the former trial, the 6 and 9 mg/day groups showed a statistically significant superiority to placebo on the ADAS-cog, but not on the CIBIC, although there were numerical trends in favor of the higher doses. In the latter trial, there were no real differences seen between the Exelon treated groups and placebo.

While I agree that these studies suggest that the higher doses are more effective, the RCTs on which a finding of effectiveness has been based were designed to evaluate the 6-12 mg/day group, and efficacy conclusions should be based on this grouping. Labeling should suggest that the higher doses are more effective, and the Dosing and Administration section should urge practitioners to attempt to get patients to the higher doses, as tolerated.

## SAFETY

As noted above, the primary safety concern throughout the review of the application has been the concern of increased mortality, and, as noted, this is no

longer a concern. Dr. Mani has reviewed the Safety Update included in the response to ~~the~~ Approvable letter. He identifies several AEs related to the gastrointestinal system that are of concern.

- 1) Nausea and Vomiting: In the controlled trials, 47% of patients who reach the therapeutic dose range of 6-12 mg/day experience at least one episode of nausea (compared to 12% of the placebo patients) and 31% of patients who reach the therapeutic dose range of 6-12 mg/day experience at least one episode of vomiting (compared to 6% of the placebo patients). While we have little to no information about the character of these episodes (for example, we do not know what constitutes an "episode" of vomiting), apparently 7% of the episodes were listed as being severe, with the rest equally distributed between Mild and Moderate. A total of 5% of patients discontinued treatment due to vomiting compared to <1% of placebo patients. A total of 8% of Exelon patients discontinued treatment secondary to nausea, compared to 4% of placebo patients.
- 2) Weight loss: A total of 26% of women who received doses of >9 mg/day experienced weight loss of at least 7% of their baseline body weight (compared to 6% of placebo patients) and 18% of men experienced a similar loss (compared to 4% of placebo patients). We have little information about the characteristics of this weight loss (e.g., time course).
- 3) Anorexia: A total of 17% of Exelon treated patients in the 6-12 mg range experienced anorexia, compared to 3% of placebo patients. According to the sponsor, only about 1% of Exelon treated patients had severe anorexia.

## LABELING

While the sponsor has proposed numerous changes to the draft label that accompanied the Approvable letter, there are 2 issues that remain unresolved.

- 1) The inclusion in the Clinical Trials Section of the results of the Progressive Deterioration Scale (PDS), an Activities of Daily Living Scale.

The sponsor evaluated a number of secondary measures in the controlled trials. Results on the PDS, a multi-item scale that ostensibly measures various activities of daily living in which various functions are assessed by the caregiver on a 10 cm visual analogue scale, reached nominal statistical significance in the 2 trials on which effectiveness was based.

However, examination of the estimate of the treatment effects seen in these trials reveals differences the clinical meaning of which are unknown. As Dr. Levin notes in his memo, there is no evidence that any patient was able to successfully perform any tasks (dialing a phone, handling finances, etc.) that they could not do before treatment. In his view (and mine), the PDS can best be understood as an alternate Global measure. Indeed, there were discussions prior to the study between the sponsor and the division about the PDS serving as the primary

global measure in the trial (ultimately, the sponsor chose to have the CIBIC-plus serve this function). The PDS appears to be sensitive to the small effect of the drug (as is the CIBIC), but appears to provide no meaningful information about the patient's status beyond what the global offers. For this reason, I believe it would be inappropriate to include the results in the labeling; to do so would mislead prescribers into concluding that Exelon has been shown to have a meaningful effect on specific functions, which I do not believe has been shown in this case. In addition, since the PDS is rated by the caregiver, it is at least reasonable to consider that the blind could have been broken (given the high rates of GI AEs), thereby further calling into question the (quite modest) results on the PDS.

2) Selection of the appropriate dosing regimen

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## RECOMMENDATION

Dr. Mani has recommended that the NDA not be approved, because of his view that the benefits do not outweigh the risks (primarily vomiting). Dr. Levin recommends that the application be approved, but that the lower dosage strengths be made available.

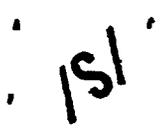
My own view is that the application can be approved with appropriate labeling. I agree with Dr. Mani that there is no evidence that Exelon confers a benefit beyond that associated with Aricept, although, of course, a direct comparison of the drugs has not been made. Further, it is also true that Aricept is not associated with the incidence of vomiting seen with Exelon, and that vomiting is an inherently worrisome adverse event in this population.

On the other hand, Exelon is clearly effective by current standards (although quite modestly so), and while the incidence of vomiting is high, it is not associated with serious outcomes, and the discontinuation rate due to vomiting is relatively low (about 5%). Although there is no evidence that Exelon offers a benefit not conferred by Aricept (or Cognex), and it presumably has the same mechanism of action (at least suggesting that patients who do not respond to the 2 approved drugs will not respond to Exelon), the paucity of approved treatments argues, in my view, for making Exelon available. This of course presupposes that labeling will adequately warn prescribers about the risks attendant to its use.

I have discussed the availability of the lower dosage strengths at length with the review team.

\_\_\_\_\_ vomiting than those seen with increments of 1.5 mg (the approved regimen in all of the approximately 60 countries in which Exelon is approved), I would not insist that these lower dosage strengths be made available at this time. I would, however, like to see the sponsor commit to performing an adequate Phase 4 study to further examine this question. If such a study demonstrates that smaller dosing increments are associated with substantially lower rates of vomiting, these strengths should be made available. At this time, however, labeling can recommend that patients be titrated (no more rapidly than every 2 weeks) by 3 mg/day; if this is not tolerated, the dose should be reduced by 3 mg/day, and if patients cannot tolerate daily doses of at least 6 mg, the drug should be discontinued.

We are forwarding this package with draft labeling that we believe the sponsor should adopt.

  
Russell Katz, M.D.

Cc:  
NDA 20-823  
HFD-120  
HFD-120/Katz/Levin/Mani/Nighswander

**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: APR 20 2000

FROM: Robert Temple, M.D.  
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Exelon, NDA 20-823

TO: Russell Katz, M.D.  
Director, Division of Neuropharmacologic Drug Products, HFD-120

I agree with your conclusion that Exelon should be approved. As you recall, I believe vomiting is not a trivial ADR in this population but all the evidence we have suggests that it is manageable. The labeling certainly conveys this adverse event. Given tacrine's q.i.d. regimen and extensive liver chemistry monitoring requirements, there is really only Aricept practically available and I believe alternatives are important. It is even possible the drugs are not really identical in their effects (e.g., because of different effects on particular cholinesterases). I agree that the current version of labeling is acceptable and that the lower strength tablets are not necessary. It does not appear that smaller titration steps made a major difference in nausea and vomiting rates.

  
Robert Temple, M.D.

cc:  
Orig. NDA 20-823  
~~HFD-120~~  
HFD-120/Project Manager  
~~HFD-101/R Temple~~  
drafted:sb/4/20/00  
final:sb/4/20/00

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