

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-823

MEDICAL REVIEW(S)

Encl.

K1.2



K1.2

N20823



N20823

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ExelonTM
(Rivastigmine Tartrate)

1.5 mg, 3.0 mg, 4.5 mg, & 6.0 mg

NDA 20-823

Clinical/Statistical
(Volume 2, Post-May 12, 1999
Approvable letter)

CLINICAL/STATISTICAL (vol. 2)

(Post- May 12, 1999 Approvable Letter)

NDA 20-823

Exelon™

(Rivastigmine Tartrate) Capsules

1.5 mg, 3.0 mg, 4.5 mg, & 6.0 mg

Classification: 1S

<u>Date</u>	<u>Document</u>	<u>Reviewer</u>	<u>Tab</u>
5/12/99	APPROVABLE LETTER		H
8/1/99	Clinical Review, "Briefing Book"	R. Mani, M.D.	I
8/13/99	Safety Review, "Lewy Body Trial"	G. Burkhart, M.D.	J
8/29/99	Clinical Review, "CRF Lists"	R. Mani, M.D.	K
4/7/2000	Clinical Review, Safety	R. Mani, M.D.	L
4/7/2000	Clinical Review, Labeling	R. Mani, M.D.	M
4/9/2000	Team Leader Memorandum	R. Levin, M.D.	Mc
4/18/2000	Division Director Memorandum	R. Katz, M.D.	N
4/20/2000	Office Director Memorandum	R. Temple, M.D.	P

D.V

MAY 12 1999

NDA 20-823

Novartis Pharmaceuticals Corporation
Attention: Robert W. Kowalski, Pharm.D.
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr. Kowalski:

Please refer to your new drug application (NDA) dated April 7, 1997, received April 7, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exelon® (rivastigmine tartrate) Capsules: _____ mg, 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg.

We acknowledge receipt of your submissions dated:

November 11, 1998
November 19, 1998

January 26, 1999
February 11, 1999

February 26, 1999
March 11, 1999

Your submission of November 11, 1998 constituted a complete response to our July 7, 1998 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Mortality

Our review of the findings from your case-control analyses and our own analyses using both case-control and person-time methodology continue to show a weak suggestion that Exelon® could have an unrecognized life-threatening risk. For the reasons given below we also believe it likely that the weak signal of risk does not result from Exelon® related toxicity, and is more likely attributable to chance.

There are two findings that raised concern. First, there is an association between mortality and Exelon® in the randomized control trials, albeit statistically weak with a p-value of about 0.3. This finding alone, given the small numbers of events and

absence of an excess of deaths in the 10/12 mg group, would not be considered a signal of risk. Second, there is greater mortality at 10/12 mg than at lower doses in the open experience. Based upon the FDA team's review (findings attached to this letter) of the blinded materials submitted to Drs. Kane and Jeste, it appears that 10/12 mg use has about a 1.6 fold increase in mortality compared to lower doses across the full dataset of deaths within 7 days of discontinuing Exelon® and not implausibly related to Exelon® use. When using Dr. Kane's findings the relative increase is 3.4. I should note that most of the deaths follow no pattern and are characteristic of the usual deaths seen in an Alzheimer's population. The magnitude of the apparent increase thus depends upon which deaths are counted as implausible in the analysis, as well as how the data are divided into dose groups. We agree with your assertion that the "titration" dataset should not be excluded from the evaluation of any Exelon® risk, and that it tends not to suggest a risk. We also agree that the apparent increase in risk when considering body weight is difficult to evaluate and of uncertain meaning.

In general, we would view such findings as 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, unless there were other supportive findings (i.e., a specific cause of the events, dose response, or early hazard). That conclusion does not, however, represent certainty and the finding, if true, would be important. We therefore note that there are over 4300 patients (1400 in the U.S.) who have been enrolled in trials for whom we currently have no information, other than a few expedited safety reports, and ask that you analyze this data, as well as the updated "extended data set", for mortality using the same methods as were used in previous analyses.

Depending on the results of these analyses, we may ask that you perform and provide the results from a large simple trial designed to evaluate both all-cause mortality and sudden unexpected death. The trial should compare the mortality rates for patients randomized to 12 mg/day of Exelon®, high dose Aricept® (10 mg/day) and low dose Aricept® (5 mg/day). The study should be powered to exclude a 1.5 fold increase in all-cause mortality in patients treated for at least 12 to 18 months. Whether this trial should be performed after marketing or prior to approval will depend upon the results of the analyses of the additional 4300 patients and updated "extended data set".

Package Insert

We ask that you adopt as labeling for Exelon®, the draft package insert attached to this letter, modified as requested (i.e., as per this letter and the notes embedded within the text of the attached package insert).

1. Warnings section:

We have asked that you include in labeling a WARNING statement that describes what is known at present about the occurrence of excess mortality in patients treated with Exelon®. Based upon the results of the additional analyses described above, however, there may be no need for a discussion of mortality in labeling.

2. Clinical Pharmacology/Clinical Trials subsection:

We ask that you include a description of each of your studies (5) conducted in which the safety and efficacy of Exelon® was examined under adequate and well controlled conditions. Your description of these studies should follow the format utilized for study 352, but can be briefer where the results are less supportive. Only the results from the ADAS-cog and CIBIC-plus analyses should be presented.

3. Dosage and Administration section:

We have revised the dosage recommendations to describe 12 mg/day as the effective dose. Our analysis of your data reveals that doses of 9 mg/day and below were not consistently effective.

We have also recommended a titration schedule that is closer to the one studied in your controlled trials than the one proposed in your draft labeling. This schedule would require the availability of all dose strengths listed in the proposed labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Professional Sample Package Labeling/Brochure - "The EXELON Support Program"

We note that you have included professional sample package labeling and a Q&A brochure in the NDA that briefly describes the benefits of a patient support program entitled "The EXELON® Support Program". The brochure explains the benefits of the program, provides a Question and Answer format brochure and instructions/toll-free telephone numbers for patients for enrollment in the program. Please provide additional details about this program and whether or not it is the intent of the program to solicit ADR reports. If so, please describe how these reports will be collected and reported to the Agency and also, how the collection of reports might effect the spontaneous reporting rates for post-marketing ADRs.

We also note that the proposed label uses the word "NEW" in juxtaposition with Exelon[®]. We consider this language promotional. Please revise the labeling to remove the word "NEW".

Safety Report

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data, including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials, including "The EXELON[®] Support Program", that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

**Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857**

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Robbin Nighswander, R.Ph., Regulatory Management Officer, at (301) 594-5531.

Sincerely,


Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachments (2)

**APPEARS THIS WAY
ON ORIGINAL**

cc:

Archival NDA 20-823

HFD-120/Div. Files

HFD-120/Katz

/Levin/Mani/Oliva

/Burkhart

/Fitzgerald/Rosloff

/Guzewska/Rzeszotarski

/Nighswander

HFD-101/Temple

HFD-860/Sahajwalla

HFD-002/ORM

HFD-101/ADRA

HFD-95/DDMS

HFD-40/DDMAC (with labeling)

HFD-810/DNDC Division Director

DISTRICT OFFICE

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RW 5/12/99

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Drafted by: rmn/April 28, 1999

Initialed by:

final:

filename: _____

APPROVABLE (AE)

cc:

Archival NDA 20-823

HFD-120/Div. Files

HFD-120/Katz

/Levin/Mani/Oliva

/Burkhart

/Fitzgerald/Rosloff

/Guzewska/Rzeszotarski

/Nighswander

HFD-101/Temple

HFD-860/Sahajwalla

HFD-002/ORM

HFD-101/ADRA

HFD-95/DDMS

HFD-40/DDMAC (with labeling)

HFD-810/DNDC Division Director

DISTRICT OFFICE

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Drafted by: rmn/April 28, 1999

Initialed by:

final:

filename: _____

AUG - 1 1999

NDA(Serial Number)	20823
Sponsor:	Novartis
Drug:	Exelon®
Proposed Indication:	Alzheimer's disease
Material Submitted:	Response to Approvable Letter Briefing Package for Meeting
Correspondence Date:	6/8/99
Date Received / Agency:	6/8/99
Date Review Completed	8/1/99
Reviewer:	Ranjit B. Mani, M.D.

1. Background

This Agency issued an "approvable" letter for this NDA on 5/12/99. The sponsor wishes to discuss a number of issues raised by that letter at a forthcoming meeting. This submission is a briefing package for that meeting.

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

This NDA was originally submitted on 4/7/97; 19 submissions in connection with the same application were subsequently received, the last on 5/26/98. Based on the Efficacy and Safety Reviews and related supervisory memoranda, a "not-approvable" letter was issued by Robert Temple, M.D., Office Director, on 7/7/98 on the grounds that the application "fails to provide reports of all tests reasonably applicable to show that the drug will be safe for use under the conditions for use recommended". Please refer to the above reviews, memoranda and "not-approvable" letter for full details. The "not-approvable" action was based upon an unresolved concern that Exelon®, in doses that have been shown to be effective in treating Alzheimer's disease, may have been responsible for an increased risk of mortality. The action letter stated that while the available evidence did not clearly show that the risk of death increased as a function of the dose or duration of exposure to Exelon®, that possibility needed further examination.

Based on subsequent submissions, discussions with the sponsor and analyses by the sponsor and Division, an "approvable" letter was issued, as noted above on 5/12/99. Please see the letter and supporting reviews, memoranda and meeting minutes for full details.

2. Items In Approvable Letter For Discussion

The following refers only to items in the approvable letter that the sponsor wishes to discuss.

2.1 Safety Update

The "approvable" letter requested a safety update to the NDA that would contain all safety information now available concerning Exelon® and covering all studies and uses of the drug including those involving indications not being sought under the current NDA , other dosage forms and other doses. The updated information requested was further listed as follows:

- Retabulation of all safety data including results of trials ongoing at the time of the NDA submission: tabulation could take the same form as in the original NDA and tabular comparisons of adverse events submitted earlier now versus those submitted in the proposed safety update would be helpful
- Retabulation of dropouts with new dropouts identified and accompanied by a discussion, if appropriate
- Details of any significant findings or changes
- A summary of the world-wide safety experience with Exelon®
- Case Report Forms for all deaths and dropouts due to adverse events
- English translations of any approved foreign labeling not previously submitted
- Information suggesting a substantial difference in the rate of occurrence (between the data previously submitted with the NDA and the proposed safety update?) of common, but less serious adverse events

2.2 Mortality Analyses

As the actual contents of this section of the "approvable" letter appear to differ from what the sponsor states in the current submission, that section of the letter is copied below

Our review of the findings from your case-control analyses and our own analyses using both case-control and person-time methodology continue to show a weak suggestion that Exelon® could have an unrecognized life-threatening risk. For the reasons given below we also believe that it is likely that the signal does not result from any Exelon® related toxicity, but is more likely attributable to chance.

There are two findings that raised concern. First, there is an association between mortality and Exelon® in the randomized control trials, albeit statistically weak with a p-value of about 0.3. This finding alone, given the small numbers of events and absence of an excess of deaths in the 10/12 mg group, would not be considered a signal of risk. Second, there is greater mortality at 10/12 mg than that at lower doses in the open experience. Based upon the FDA team's review (findings attached to this letter) of the blinded materials submitted to Drs. Kane and Jeste, it appears that 10/12 mg use has about a 1.6 fold increase in mortality compared to lower doses across the full dataset of deaths within 7 days of discontinuing Exelon® and not implausibly related to Exelon® use. When using Dr. Kane's findings the relative increase is 3.4. I should note that most of the deaths follow no pattern and are characteristic of the usual deaths seen in an Alzheimer's Disease population. The magnitude of the apparent increase thus depends upon which deaths are counted as implausible in the analysis, as well as how the data are divided into dose groups. We agree with your assertion that the "titration" dataset should not be excluded from the evaluation of any Exelon® risk, and that it tends not to suggest a risk. We also agree that the apparent increase in risk when considering body weight is difficult to evaluate and of uncertain meaning.

In general, we would view such findings as a non-compelling weak suggestion of an association between drug use and mortality, occurring in a set of non-randomized data, and most likely to represent a chance occurrence were other supportive findings (i.e., a specific cause of the events, dose response, or early hazard). That conclusion does not, however represent certainty, and the finding, if true, would be important. We note that there _____) who have been enrolled in trials for whom we currently have no information, other than a few expedited safety reports and ask that you analyze this data, as well as the updated "extended data set", for mortality using the same methods as were used in previous analyses.

the analyses of the additional _____

2.3 Effective Dose

In the "approvable" letter the Agency stated that in the proposed Package Insert for Exelon®, the "Dosage and Administration" section had been revised (by the Agency) so that the dosage recommendations now describe 12 mg daily as the effective dose. The "approvable" letter further stated that the Agency analysis revealed that doses ≤ 9 mg daily were not consistently effective.

2.4 Titration Rate

In the version of the label that was attached to the "approvable" letter, the following titration schedule was recommended:

The recommended starting dose of EXELON® is 1.0 mg twice a day. If this dose is well tolerated, the dose may be increased every week by 0.5 to 1.0 mg/day to achieve 6 mg b.i.d. over a 9-12 week period. The maximum dose is 6 mg b.i.d (12 mg/day).

2.5 Specifics of Claim in Labeling

In the version of the label that was attached to the "approvable" letter, the following is stated in the "Indications And Usage" section: "Exelon® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type"

2.6 Display of Adverse Event Tables

In the version of the labeling proposed by the Agency and attached to the approvable letter, the following request was made in relation to the subsection entitled "Adverse Events Reported in Controlled Trials".

"This section should include a table with three columns, one each for patients treated with doses 10-12 mg, patients treated with doses less than 10 mg, and those on placebo. This table should include all adverse events that occur with a frequency of at least 2% in the higher dose Exelon treatment group and whose frequency is numerically greater than the placebo rate in the higher dose group, listed in descending order of frequency within body system"

2.7 Agency Plausibility Analysis

A special Agency group reviewed all deaths in the Exelon® database in a blinded manner (see previous review by me under this NDA, completed 4/29/99). Of the deaths that they considered not implausibly related to study drug and occurring during or within 7 days of last dose, the Agency concluded that there was a 1.6-fold increase in mortality at the 10-12 mg dose as compared with lower doses; this analysis was referred to in the "approvable" letter

3. Contents of Briefing Package

The submission contains the sponsor's discussion of the items outlined in the previous section, in addition to a listed meeting agenda. The sponsor's discussion of the above items will be outlined using the same headings, and in the same order as in Section 2

3.1 Safety Update

The size of the database contained in the proposed Safety Update, and the proposed cut-off dates are outlined in the table below

Study Grouping	Number of Patients	Database Cut-Off Date	Additional Exposure Since 120-Day Update
[Redacted Table Content]			

In this respect, the sponsor also states the following:

- [Redacted]
- [Redacted]

3.2 Mortality Analyses

According to the sponsor:

- The "approvable" letter stated that the weak signal of (life-threatening) risk does not result from Exelon®-related toxicity (see the actual contents of letter above which are different from what the sponsor states)
- The "approvable" letter stated that the apparent increase in mortality risk is more likely attributable to chance
- The small excess of deaths in Exelon®-treated patients in the randomized, controlled trials did not occur at the highest dose
- Exhaustive analyses performed by the sponsor as well as the FDA review team indicated that the results of post-hoc analyses performed on non-randomized data were predicated upon the definition of dose, the time off medication, the rater determining the plausibility relationships and the datasets used. Therefore, "it is evident that repeating these analyses on larger datasets of non-randomized patients are highly unlikely to provide any meaningful information or add clarity to the multitude of post-hoc analyses performed already"

The sponsor therefore feels that there will be no purpose in performing additional mortality analyses on the updated extended dataset plus the over _____ on whom this Division currently has no information other than a few IND safety reports. The sponsor states that 90 % of the patients in this combined dataset would be from open-label, non-randomized, uncontrolled trials. The limitations of a post-hoc analysis of mortality in such trials would not add any more clarification to the analyses of the Phase 3 randomized, controlled trials.

3.3 Effective Dose

The sponsor states that the Agency's conclusions regarding the effective dose, as stated in the "approvable" letter and attached labeling, are *"inconsistent with the standard analyses performed in the Integrated Summary of Efficacy and the conclusions which demonstrated that the a-priori, protocol-defined randomized dose group of 6 –12 mg per day demonstrated superior benefits to placebo on the pre-specified primary outcome measures (ADAS-Cog and CIBIC-Plus) in more than one trial"*

3.4 Titration Rate

The sponsor wishes to know why the Agency does not agree with the titration rate that the sponsor proposed in the draft package insert that was included in the NDA. The titration rate that the sponsor proposed was as follows:

The recommended starting dose is 1.5 mg twice a day. If tolerated, the dose may be increased to 3 mg bid after a minimum of two weeks. Subsequent increases to 4.5 mg and then 6 mg bid should be based on good tolerability of the current dose and may be considered after a minimum of two weeks treatment at that dose level. The maximum dose is 6 mg bid.

In support of its titration rate proposal the sponsor states the following:

- The Agency's recommendations for titration are based upon being similar or identical to the rate at which doses were increased in the randomized controlled trials of Exelon®
- The sponsor's proposed titration rate is based upon the results of the B 355 open-label study that assessed the safety and tolerability of weekly increases of 3 mg per day
- The tolerability of the 3 mg weekly rate of increase in the B 355 study was similar to that seen in patients randomized to 6 to 12 mg daily in the randomized, controlled trials (in which patients were titrated using a regime similar to that recommended by the Agency in the package insert). There were no "substantive" differences in the adverse event dropout rates or overall incidence of adverse events in Study B 355 as compared with the randomized controlled trials
- The Division had agreed in a communication to the sponsor on 3/13/96 that the protocol and design for Study B 355 were acceptable. The Division had also agreed with the inclusion of the faster titration rate in the labeling provided that data on an adequate number of patients was available in the NDA. Although the original protocol planned for about 200 patients, the sample size was increased at the request of the Division (who asked for about 300 –400 patients to be studied) and eventually 542 patients were enrolled in this study. The sponsor believes that it has more than met the Division's original expectations for the study

For convenience I have provided a comparison of the Agency and sponsor titration proposals/recommendations in the table below

	Sponsor's Proposal	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

3.5 Specifics of Claim in Labeling

The sponsor quotes the Agency as stating in the not-approvable letter of 7/7/98 that "there are more than one adequate and well-controlled investigations that Exelon® (rivastigmine tartrate) is effective for the treatment of **mild to moderately severe dementia of the Alzheimer's type**". The sponsor wishes to know why the Agency now limits the indication to **mild to moderate dementia of the Alzheimer's type**, and appears to have reversed its earlier conclusion; the sponsor believes that patients with moderately severe dementia genuinely benefit from Exelon® treatment

3.6 Display of Adverse Event Tables

In response to the Division's request to include in the subsection of the package insert entitled "Adverse Events Reported in Controlled Clinical Trials" a table comparing the incidence of adverse events in those receiving Exelon® doses of < 10 mg, those receiving doses of 10-12 mg and those receiving placebo, the sponsor has outlined the following difficulties:

- No patients were randomized specifically to the 10-12 mg dose; all patients were titrated to their maximum tolerated dose within specific dose range groups in the variable dose studies. The maximum dose used in the fixed dose studies was 9 mg
- Since most adverse events occurred during titration and not specifically at the 10-12 mg dose, the data in a table of the kind proposed by the Agency, if focussed on adverse events that occurred at the 10-12 mg dose, would be "inconsistent and misleading"
- Such adverse events would be inconsistent with the Agency's assertion that the effective dose is 12 mg daily and the sponsor's contention that the effective dose ranges from 6-12 mg daily

3.7 Agency Plausibility Analysis

Using deaths identified by the Agency review group as being not implausibly related to study drug and occurring during study drug treatment or within 7 days of last drug use, the sponsor has compared those receiving < 9 mg with those receiving > 9 mg with those receiving < 9 mg and found a relative risk for the higher dose range versus the lower dose range of 1.2. It believes that the Agency conclusion that the

relative risk for those receiving 10-12 mg versus those receiving lower doses for the same deaths was in error

4. Comments

- The sponsor should endeavor to transcribe the actual text of Agency letters in a more accurate manner than has been done in this submission
- The sponsor appears to indicate that the proposed Safety Update will not include the majority of, if not all, _____ regarding whom this Division currently has no information other than a few expedited IND Safety Reports. It appears clear that the sponsor's proposed Safety Update will include no data at all from _____ participating in non-US trials of Exelon®, other than narratives for deaths, and adverse events leading to treatment discontinuation. If my understanding of the proposed contents of the Safety Update is correct, excluding such a large body of data from the proposed Safety Update may be difficult to justify
- The sponsor proposes not to include any electrocardiogram or lab data in the Safety Update. Given our continued concerns about excess mortality in relation to Exelon® use and IND Safety Reports of at least 2 (and possibly 3) cases of fatal liver failure in patients treated with Exelon®, the sponsor should include an analysis of liver function tests and electrocardiogram data in the proposed Safety Update
- The sponsor does not wish to perform any mortality analyses at all on a database that _____, on the grounds that 90 % of such patients will be drawn from open-label, non-randomized, uncontrolled trials. Although there will clearly be limitations to the analyses that can be performed on such a cohort, it is also hard to pre-judge the conclusions of such analyses as being non-revealing.
- Until our continued concerns about excess mortality related to Exelon® use are better resolved it would not, in my opinion, be justified to expose _____ healthy people with Mild Cognitive Impairment to Exelon® for periods as long as 36 months. In addition, patients with Mild Cognitive Impairment may not be entirely representative of those with mild-to-moderate Alzheimer's disease for whom drug approval is currently being sought.
- The Agency's contention in the "approvable" letter that doses ≤ 9 mg daily had not been shown to be consistently effective, and that the effective dose was 12 mg daily is based upon the following (the studies listed below are all randomized controlled trials of adequate duration):
 - In the B303 and B352 efficacy studies patients were randomized to one of 3 groups: placebo, Exelon® 1-4 mg daily and Exelon® 6-12 mg daily. In both these studies the Exelon® 6-12 mg (variable dose) group was superior to placebo at a statistically significant level on both the ADAS-Cog and CIBIC-Plus. However a post-hoc subgroup analysis performed by Randy Levin, MD, suggested that only patients receiving doses of 10.5 to 12 mg daily had evidence of efficacy based on the ADAS-Cog and CIBIC-Plus
 - In the B351 efficacy study patients were randomized to one of 4 treatment groups: placebo, Exelon® 3 mg daily, Exelon® 6 mg daily and Exelon® 9 mg daily. None of the Exelon® groups showed a statistically significant superiority to placebo on both the

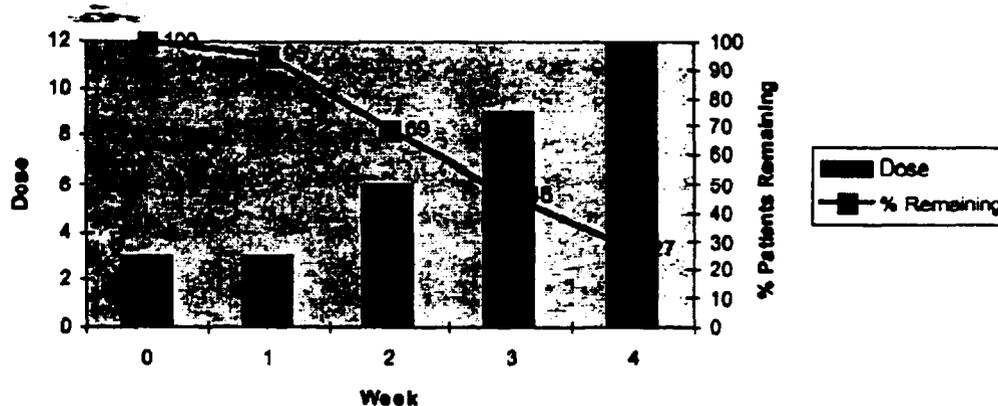
ADAS-Cog and CIBIC-Plus. However the 6 mg and 9 mg groups did show a statistically significant superiority on the ADAS-Cog alone. It was concluded that the effective dose appeared to > 9 mg daily

- In the B304 efficacy study patients were randomized to one of 3 groups: placebo, Exelon® 2-12 mg b.i.d and Exelon® 2-12 mg t.i.d. Only the Exelon® b.i.d group was superior to placebo on both the ADAS-Cog and CIBIC-Plus. A post-hoc subgroup analysis performed by Randy Levin, MD, indicated that doses ≤ 9 mg daily were not superior to placebo on either of these outcome measures
- In the B103 efficacy study patients were randomized to placebo, Exelon® 4 mg daily and Exelon® 6 mg daily groups. Neither of the Exelon® groups was superior to placebo on either the ADAS-Cog or CGIC

This reviewer is of the view that the labeling could be modified to indicate that only doses > 9 mg daily have been consistently shown to be effective. The labeling cannot state that doses ranging from 6 to 9 mg have been shown to be effective.

- The dose titration schedule that the sponsor wishes to include in labeling has never formally been assessed in a clinical trial. In the B 355 study, dose increases were made every one week, whereas in labeling the sponsor is proposing to make the same increases every 2 weeks; the titration schedule remains more rapid than in the randomized controlled trials. The Division noted in reviewing the NDA that in Study B 355, of 548 enrolled patients, only 27 % of patients were able to reach the 12 mg dose and remain in the study at 4 weeks (see figure below); these were all patients who were able to adhere to the maximum titration rate designated in the protocol. On the other hand, in the randomized controlled trials that used a slower rate of titration a mean of 36.3 % of patients were able to reach the 12 mg dose and remain in the study at 26 weeks. The figure below which I have copied from Dr Armando Oliva's NDA Safety Review shows the tolerability of the accelerated titration schedule for the B 355 study by week and daily dose. Note that the percentage remaining refers to those able to continue with the upward titration schedule, not the number able to actually remain in the study. The majority of discontinuations were due to adverse events.

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The incidence of deaths, adverse events leading to treatment discontinuation and all adverse events is compared between the B355 study and all Exelon® treated patients in randomized controlled trials is shown in the table below

Variable (%) (through Week 26)	Exelon®-treated patients in Phase 3 randomized, controlled trials (n = 1913)	Patients in B 355 study (n = 544)
Deaths	0.03 %	1.5 %
Adverse events leading to discontinuation	15.5 %	20.2 %
All adverse events	85.5 %	94.6 %

Although there are clearly a number of confounding variables (maximum dose reached, duration on maximum dose, etc) that could influence the data shown in the above table, the table does suggest that the titration schedule used in the randomized controlled trials is better tolerated than that used in the B355 study. The sponsor does propose in the draft labeling supplied with the NDA to use a titration rate that is slower than in the B 355 study but not as slow as in the randomized controlled Phase 3 trials (which is identical to what the Agency is recommending). Although the titration scheme proposed by the sponsor would be expected to be better tolerated than that in the B 355 study, the former titration schedule has never been formally studied.

- Although the Agency did state in the "not-approvable" letter of 7/7/98 that "there are more than one adequate and well-controlled investigations that Exelon® (rivastigmine tartrate) is effective for the treatment of mild to moderately severe dementia of the Alzheimer's type", it does not appear that the Agency made a distinction between "mild to moderately severe dementia" and "mild to moderate dementia".

In the Integrated Summary of Efficacy (Section 11; Summary and Conclusions) the sponsor too states that "these findings demonstrate that, among patients with mild to moderate, probable Alzheimer's disease, ENA has both a statistically significant and clinically meaningful therapeutic effect in reducing symptoms of the deterioration in cognition, global functioning, and ADL, and ameliorating the increase in disease severity associated with the progression of this illness".

The sponsor appears to believe that the drug is effective for patients with moderately severe dementia, in addition to those with mild to moderate dementia. This belief, and/or supportive data are not clearly stated in this submission or in the original NDA.

The sponsor, in fact, states (the opposite) in the Integrated Summary of Efficacy that, using the baseline Global Deterioration Scale (GDS) as an indication of disease severity, among patients treated with Exelon®, the percent of ADAS-Cog responders increased with the severity of Alzheimer's Disease at baseline. The opposite was true of CIBIC-Plus responders. No consistent relationship was evident between both the numbers of ADAS-Cog and CIBIC-Plus responders and the baseline GDS rating of illness severity. These statements appear based on a post-hoc sub-group analysis, the full details of which are not provided.

Baseline efficacy data for pooled studies B303 and B352, that the sponsor considers pivotal, are outlined in the table below. As will be seen measures of central tendency and variance for baseline Mini Mental Status Examination score in these studies are not substantially different from those of patients participating in efficacy studies of approved and in-development cholinesterase inhibitors for whom the approved/proposed claim is for mild to moderate dementia of the Alzheimers's type. Baseline Mini Mental Status Examination scores for patients participating in another efficacy study B 351 are within the same range (10-26). Baseline Mini Mental Status Examination scores for yet another efficacy study, B 304, are not provided in the NDA, although the selection criteria stated that patients with a Mini Mental Status Examination score of 10-26 would be enrolled in the study.

Dose Group	Exelon® 6-12 mg	Exelon® 1-4 mg	Placebo
N	828	650	647
Mean	20.0	19.7	19.9
Standard deviation	4.48	4.48	4.45
Median	21.0	20.0	21.0
Minimum			
Maximum			

In summary, therefore, there is no evidence provided to substantiate the sponsor's claim that Exelon® is effective for the treatment of mild to moderately severe dementia as opposed to mild to moderate dementia. The Agency has not, in any communication with the sponsor, sought to make a distinction between the terms "mild to moderate dementia" and "mild to moderately severe dementia".

- The sponsor may have a well-founded concern about the difficulty providing adverse event tables in the subsection of the draft package insert entitled "Adverse Events Reported in Controlled Trials" in the manner that the Agency has requested since the groups in the individual columns will not be based on randomization; such a table will need to be based on a post-hoc analysis.
- As noted above the sponsor cites a discrepancy between the analysis that it has performed, and that performed by the Agency, on deaths in the entire Exelon® database identified by a special review team as occurring during study drug treatment or within 7 days of last drug use, and which were not implausibly related to study drug. This difference is summarized below
 - The Agency concluded that the relative risk for mortality for those receiving 10-12 mg versus those receiving lower doses was 1.6
 - The sponsor has concluded that the relative risk for mortality for those receiving > 9mg versus those receiving < 9 mg was 1.2

There may be no real discrepancy in the 2 analyses as the groups chosen for comparison in one analysis are different from those chosen for the other. The apparent discrepancy can be resolved by comparing the 2 analyses. Note that at least one death in this category was in a patient receiving a final dose of 9 mg who would have been eliminated from the analysis performed by the sponsor.


Ranjit B. Mani, M.D.
Medical Reviewer

R. Levin, M.D. 

CC:
HFD-120
NDA 20823
electronic copy-Levin
Nighswander

ADDENDUM #1**8/2/99**

An additional item that the sponsor wishes to discuss is the paragraph in the Agency modification of the package insert that pertains to weight loss.

The sponsor states that it is unable to locate or generate the above numbers, which do not match those in the 120-Day Safety Update.

Comment: The data cited above appear to be based upon an analysis performed in the Safety Review of the original NDA.

ADDENDUM #2**8/4/99**

A meeting was held with the sponsor today. The Agency group attending the meeting was headed by Dr R. Temple.

The following were the key discussions/agreements to emerge from the meeting.

- The sponsor presented a tabular summary of the mortality analysis for all randomized placebo-controlled trials completed to date. These included data from a recently completed European trial of Exelon® in Lewy body dementia. The pooled mortality analysis no longer showed a higher mortality rate for drug than for placebo. The Agency therefore stated that there was no longer a need for the mortality analysis recommended in the "Approvable" letter.
- The Safety Update is expected to be submitted by October 1999 and will contain the items already described. However, the cut-off date for submitting narratives and listings(world-wide) for deaths, and serious adverse events will

be extended to June 1999; Case Report Forms for specific patients will be submitted on request

- Post-marketing safety reports will also be submitted and will be as recent as possible
- The sponsor will supply safety and tolerability data from the B 356 open-label study of multiple titration regimes to support its proposed titration schedule
- The sponsor was informed that from the Agency's perspective there is no difference in meaning between the phrases "mild to moderate dementia" and "mild to moderately severe dementia"
- The Agency agreed with the sponsor that supplying (in the package insert) adverse event tables for controlled clinical trials that compared the 10-12 mg dose group against a < 10 mg group was not feasible
- In regard to what dose should be stated in labeling as being the effective dose, the Agency concurred that while the 6-12 mg dose range had been noted to be effective, the labeling should include a statement that doses at the upper end of that range are most likely to be effective
- The sponsor will submit its own figures in the package insert for the percentage of women and men receiving high doses of Exelon® who lost $\geq 7\%$ of their baseline body weight during clinical studies.
- Further discussion is needed as to what elements of the fixed dose efficacy study, B 351, should be included in labeling: none of the doses of Exelon® used in this study showed evidence of efficacy on both the cognitive and global outcome measures.

~~Ranjit B. Mani, MD
8/4/99~~

~~/S/
Randy Levin, MD~~

The sponsor is to send us a line listing of adverse events so we can designate those CRFs we want to be sent with the submission.

The sponsor is going to send additional data on the tolerability of patients to different titration regimen

The sponsor is going to send the results of the European double blind study including information in patients who died.

/S/

Review of Clinical Data

Mortality in ENA-INT-03 "Lewy Body Demitia Trial"

Seen

RM

8/13/1999-

Submission
attached

NDA: 20-823
IND: _____
Sponsor: Novartis
Drug: Rivastigmine
Route of Administration: Oral
Reviewer: Greg Burkhart, M.D., M.S.
Review Completion Date: August 13, 1999

15/13/99

On May 12, 1999, the agency issued an AE letter for rivastigmine, a treatment for Alzheimer's Disease. However, in the letter we expressed continued concern about excess mortality in the RCTs and slightly greater mortality at higher doses in the open extensions to the RCTs. The letter requested that Novartis analyze data from several thousand patients that had not been included in previous analyses to see if greater mortality at the highest doses persisted. These additional analyzes were to use the same techniques as those in previous analyzes.

In an August 4 meeting to discuss Novartis's plan to address the issues raised in the AE letter, they presented data showing that there had been 2 deaths within 7 days of the last dose of placebo in protocol ENA-INT-03, a study of rivastigmine in Lewy body dementia that had recently completed. On August 9, Novartis submitted a summary of this study, its protocol, narratives for the placebo deaths, and some descriptive statistics of its participants.

In short, the study enrolled fairly similar patients as those in the RCTs included in the NDA although they tended to be slightly older (46% were ≥ 75 compared to 42% in the RCTs) and were more likely to male (53% compared to 42% in RCTs). The only deaths were in placebo with both events that lead to death beginning within 7 days of the last dose of placebo. Both deaths were due to pneumonia. The AE profile in the study was similar to that seen with rivastigmine in the NDA.

In my April 27, 1999 review of Novartis's response to the NA letter, I described the aggregate findings in the NDA as still representing a weak signal of concern. The signal was based upon excess mortality in the RCTs (3 deaths verse 0 within 7 days of the last dose) and greater mortality at 10/12 mg than lower doses in the open experience (using

FDA classified ~~deaths~~ the mortality was 13.2 at 10/12 mg compared to 9.3 at lower doses [per 1000 person-years]).

The 2 deaths that have now been observed with placebo in an RCT with a similar population to that in the RCTs included in the NDA have a significant impact on my interpretation of the experience collected to date with rivastigmine. I no longer consider the mortality experience to represent any signal of concern. The greater mortality at 10/12 mg compared to lower doses in the NDA is not surprising given the non-random nature of determining a patient's dose. Likewise, there is nothing about the deaths that suggest a cause for concern. (Both of these points are discussed in detail in my April 27 review.)

My only recommended action is ask DSI to inspect ENA-INT-03, since the interpretation of the mortality experience with rivastigmine could turn on the experience of 2 placebo patients from a small study. I do not believe there is any need for a randomized study to clarify the safety of rivastigmine. Likewise, in my opinion, the additional 3000-4000 patients need only a standard safety update prior to approval, and finally, there is no need to discuss the mortality experience in labeling.

The experience in ENA-INT-03 may also impact the hold issued ~~_____~~ ↓ since the safety concern about mortality was mentioned as a contributing factor in the decision to issue the hold.

**APPEARS THIS WAY
ON ORIGINAL**

Review and Evaluation of Clinical Data

NDA	20823
Sponsor:	Novartis
Drug:	Exelon
Proposed Indication:	Alzheimer's Disease
Material Submitted:	Correspondence
Correspondence Date:	8/18/99
Date Received / Agency:	8/19/99
Date Review Completed	8/29/99
Reviewer:	Ranjit B. Mani, M.D.

1. Background

This submission contains a listing of deaths and serious adverse events that lead to treatment discontinuation that will be included in a proposed final safety update that is to be submitted soon.

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

The Agency issued an "approvable" letter for this NDA on 5/12/99. Items in the approvable letter were discussed at a meeting between the Division and sponsor held on 8/4/99. At that meeting the sponsor indicated that a final safety update for this NDA would be submitted in October 1999. This safety update would include Case Report Forms for selected patients who died or had serious adverse events that lead to treatment discontinuation. A full listing of patients who died or had serious adverse events that lead to treatment discontinuation has now been provided so that we may indicate what Case Report Forms may be desired. In the listings verbatim (rather than COSTART) terms are used

**APPEARS THIS WAY
ON ORIGINAL**

2. Tabular Listing of Case Report Forms Needed

This reviewer has selected the following Case Report Forms

Study #	Patient #	Verbatim Term
305	303301004	Abdominal pain-pancreatitis
305	303303018	Decrease of her general state
305	303304008	Death while sleeping
305	303307013	Death (cause unknown)
305	303312012	Dysphagia
305	303312022	Anemia
305	303338001	Death (sudden)
305	303338005	Sudden death
305	304402019	Difficulty in swallowing
305	304404011	Prolonged QT interval
305	304416017	Bleeding disorders
305	304429013	Bradycardia
353	303143026	Dysphagia
353	351108064	Renal failure
353	351111040	Respiratory failure
353	351113019	Respiratory failure
353	352208048	Difficulty swallowing
353	352209016	Dysphagia
353	352209017	Steatohepatitis
353	352215024	Thrombocytopenia
355	355007109	Neuromuscular disorder
355	355025108	Apnea
356	0050017	Fatigue and paralysis
356	0220003	Worsening of anemia
356	0670006	Cryptogenic cirrhosis of the liver
356	0620003	Jaundice
356	1050004	Paralysis
452	0070010	Increased lethargy, decreased hemoglobin, urinary tract infection, anemia and pneumonia
INT01	018.0001	Unsteadiness
INT01	030.0002	Slight pancreatitis
INT01	017.0005	Bradycardia
INT01	036.0011	Liver disease
INT01	002.0007	Sinus bradycardia
INT01	021.0002	Lipthymia
INT01	027.0007	Bradycardia with weakness and ischemic signs on electrocardiogram
INT01	010.0011	Weakness and dyspnea
INT01	021.0002	Anemia
INT01	002.0021	Bradycardia
INT01	002.0038	Weakness
INT01	002.0005	Weakness

3. Comments

The sponsor should be requested to supply us with the above Case Report Forms.

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

R. Levin, M.D.

rbm 8/29/99

cc:

HFD-120

NDA 20823

electronic copy-Levin

Nighswander

We may need to have additional CRFs
depending on our review.

CSO Note: The list of CRFs was FAXed to
firm on 9/7/99.

o 9/7/99

Review and Evaluation of Clinical Data

NDA (Serial Number)	20823 N(-A2)
Sponsor:	Novartis
Drug:	Exelon
Proposed Indication:	Alzheimer's Disease
Material Submitted:	Amendment
Correspondence Date:	10/21/99
Date Received / Agency:	10/21/99
Date Review Completed:	4/7/00
Reviewer:	Ranjit B. Mani, M.D.

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1. Background

This submission contains an amendment to the above New Drug Application (NDA). The amendment includes a safety update and other items listed below.

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

1.1 Brief History Of NDA

This NDA was originally submitted on 4/7/97; 19 submissions in connection with the same application were subsequently received, the last on 5/26/98. Based on the Efficacy and Safety Reviews and related supervisory memoranda, a "not-approvable" letter was issued by Robert Temple, M.D., Office Director, on 7/7/98 on the grounds that the application "fails to provide reports of all tests reasonably applicable to show that the drug will be safe for use under the conditions for use recommended". Please refer to the above reviews, memoranda and "not-approvable" letter for full details. The "not-approvable" action was based upon an unresolved concern that Exelon®, in doses that had been shown to be effective in treating Alzheimer's disease, may have been responsible for an increased risk of mortality. The action letter stated that while the available evidence did not clearly show that the risk of death increased as a function of the dose or duration of exposure to Exelon®, that possibility needed further examination.

Based on subsequent submissions, discussions with the sponsor and analyses by the sponsor and Division, an "approvable" letter was issued, as noted above on 5/12/99. Please see the letter and supporting reviews, memoranda and meeting minutes for full details.

A number of issues raised by that letter were discussed at a meeting between the Division and sponsor on 8/4/99. Please see my review of the briefing package for that meeting, which was submitted on 6/8/99 for full details. A summary of that meeting, on which the current submission is based, is in Section 1.2 of this review

1.2 Summary Of Meeting Between Division And Agency On 8/4/99

The Agency group attending the meeting was headed by Dr R. Temple.

The following were the key discussions/agreements to emerge from the meeting.

- The sponsor presented a tabular summary of the mortality analysis for all randomized placebo-controlled trials completed to date. These included data from a recently completed European trial (INT-03) of Exelon® in Lewy body dementia. The pooled mortality analysis no longer showed a higher mortality rate for drug than for placebo. The Agency therefore stated that there was no longer a need for the mortality analysis recommended in the Approvable letter.
 - * In the Approvable letter the Agency had stated that mortality analyses continued to suggest that Exelon® had an unrecognized life-threatening risk, albeit weak and non-compelling. The Agency had therefore recommended further mortality analyses, using methods similar to those employed previously on the following patients: 4300 patients (1400 in the U.S.) who had been enrolled in trials for whom we had no information, other than a few expedited safety reports, and the updated "extended data set" for patients already included in the mortality analyses
- The Safety Update was expected to be submitted by October 1999 and would contain the items listed below. However, the cut-off date for submitting narratives and listings (world-wide)

for deaths, and serious adverse events leading to treatment discontinuation would be extended to June 1999; Case Report Forms for specific patients would be submitted on request

The contents of the Safety Update were to include

- Patient narratives for deaths and serious adverse events leading to treatment discontinuation that had occurred since the 120-Day Safety Update, in global clinical trials of Exelon®
- Other safety data from US Phase 3 trials currently ongoing or begun since the original NDA submission [these would not include electrocardiogram or clinical laboratory tests (hematology, chemistry and urinalysis)]
- Post-marketing safety reports would also be submitted and would be as recent as possible
- The sponsor would supply safety and tolerability data from the B 356 open-label study of multiple titration regimes to support its proposed titration schedule
- The sponsor was informed that, from the Agency's perspective, there was no difference in meaning between the phrases "mild to moderate dementia" and "mild to moderately severe dementia"
- The Agency agreed with the sponsor that supplying (in the package insert) adverse event tables for controlled clinical trials that compared the 10-12 mg dose group against a < 10 mg group was not feasible
- In regard to what dose should be stated in labeling as being the effective dose, the Agency concurred that while the 6-12 mg dose range had been noted to be effective, the labeling would include a statement that doses at the upper end of that range were most likely to be effective
- The sponsor would submit its own figures in the package insert for the percentage of women and men receiving high doses of Exelon® who lost $\geq 7\%$ of their baseline body weight during clinical studies.
- Further discussion was needed as to what elements of the fixed dose efficacy study, B 351, should be included in labeling: none of the doses of Exelon® used in this study showed evidence of efficacy on both the cognitive and global outcome measures.

1.3 Case Report Forms In Safety Update

A submission dated 8/18/99 contained a listing of deaths and serious adverse events that led to treatment discontinuation that were to be included in the Safety Update. A listing of the Case Report Forms requested by us from this listing is contained in a review by me dated 8/29/99; this list was subsequently transmitted to the sponsor.

2. Contents Of Submission

This submission contains:

- A Safety Update (referred to by the sponsor as the Pre-Approval Safety Update)
- Interim Safety Reports for Studies B356 and INT-03
- Interim reports for Studies W368, W370 and B357 which have been completed since the 120-Day Safety Update
- Revised draft labeling, and a discussion of labeling issues
- A description of a caregiver support program
- Introductory promotional materials
- A Chemistry, Manufacturing and Controls Amendment providing an alternative source of manufacture, and samples of the 6 mg capsule proposed for use
- Financial disclosure certification information.

3. Safety Update

3.1 Overall Extent Of Data

In regard to the Safety Update, the following are noteworthy, as per the sponsor:

- This Safety Update is cumulative. Data collected for the Integrated Summary of Safety in the original NDA submission and 120-Day Safety Update have been included in this Safety Update, as have data collected subsequently. Data collected for the Integrated Summary of Safety in the original NDA and for the 120-Day Safety Update (which was itself cumulative) have been pooled where applicable with data collected subsequently.
- The cut-off date for all safety data included in the analyzable Integrated Safety Database (also referred to as the key safety population) is June 30, 1998. This cut-off date is applicable to all updated and new studies with the exception of the ongoing Phase IIIb studies INT-01, INT-02 and INT-03
- Narratives for deaths and serious adverse events are available through June 30, 1999
- Narratives for adverse events that led to treatment discontinuation are available through December 31, 1998.

3.2 List Of Studies Included In Safety Update

A full listing of studies included in the sponsor-designated **analyzable integrated safety database** for this submission are listed in the following table copied from the submission. Various sub-groupings are also listed in the table.

All Therapeutic Studies (Phase II and III)

Phase II Studies	B103, B103-01, B103-04, B103-06, B901/B902, B104, B104-01, B104-02, B105
Phase II Japanese Studies	ENA/AD/EP-II (292), ENA/VD/EP-II (293), ENA/OR1/ALZ/PH2L/01 (291)
Phase III Controlled Studies	B303, B304, B351, B352
Phase III Uncontrolled Studies	B305, B353, B354, B355, B357
Phase IIIb US Studies	B356, B452

All Phase III Studies

Phase III Controlled Studies	B303, B304, B351, B352
Phase III Uncontrolled Studies	B305, B353, B354, B355, B357

All U.S. Phase IIIb Studies

B356, B452

Several additional studies have contributed information to the safety update but have not been included in the analyzable Integrated Safety Database. These are:
INT-01 (an international study identical to B356)

INT-02 (an international study identical to B452)
 INT-03 (a randomized, double-blind, placebo-controlled study in Lewy Body Dementia)
 C152 (a study that used a transdermal formulation of Exelon®) *
 B153 (a bioequivalence study comparing the oral solution formulation with the capsule formulation) **

* This study has been carried out under that IND have previously been reviewed by me

**A full report of this study has been submitted under NDA 21025 for the oral solution formulation of Exelon® and has been reviewed by me.

3.3 Comparison Of Content Of Current Update and 120-Day Safety Update

The two safety updates are compared in the following table which has been copied from the submission

The Following Data were included in the 120-Day Safety Update	The Pre-approval Safety Update includes all Data from the 120-Day Safety Update as Well as the Following Additional Data
All Phase II Studies	Phase II Study C152 (TDS study—see section 9)
Patients who completed clinical pharmacology studies by June 30, 1997	
Completed Phase III Controlled Studies B351, B352, B303, and B304	
All data from Week 27 up to Week 52 for patients who were enrolled in the Phase III Uncontrolled Extension Studies (B305 ^a or B353 ^b) before July 1, 1996 (52-Week Data)	All data available through June 30, 1996 for patients enrolled in the Phase III Uncontrolled Extension Studies B305 and B353
All data from Week 27 up to Week 76 for patients who were enrolled in the Phase III Uncontrolled Extension Studies (B305 ^a or B353 ^b) before January 1, 1996 (76-Week Data)	All data available through June 30, 1996 for patients enrolled in the Phase III Uncontrolled Extension Studies B305 and B353
Completed Phase III Uncontrolled Titration Study B354	
Weeks 15-26 for all patients who entered Phase III Uncontrolled Titration Study B355 ^a	All data available through June 30, 1996 for patients enrolled in the Phase III Uncontrolled Titration Study B355
	All data from Phase III Uncontrolled Study B357 (Antiemetic study)
	All data available through June 30, 1996 for patients enrolled in the Phase III US Studies B356 and B452
Adverse events that resulted in death, premature discontinuation, or were serious through March 31, 1997 ^c	Adverse events that resulted in death or were serious through June 30, 1999 and adverse events that resulted in premature discontinuation through December 31, 1996 ^d
<ul style="list-style-type: none"> ^a Includes corrections to Studies B305, B353, and B355 because of error in the ISS database, which were identified after the ISS database was locked. ^b Although the Integrated safety database for the 120-Day Safety Update was locked on June 8, 1997, data on deaths, premature discontinuations, and serious adverse events were presented manually through March 31, 1997 in Theme 6.2 of the 120-Day Safety Update. ^c This includes the Phase III European Studies INT-01, INT-02, and INT-03. 	

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Note that there are no new data for placebo-treated patients included in the analyzable Integrated Safety database ("key safety population").

3.4 Short Description Of New Studies Included In Safety Update

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~~_____~~

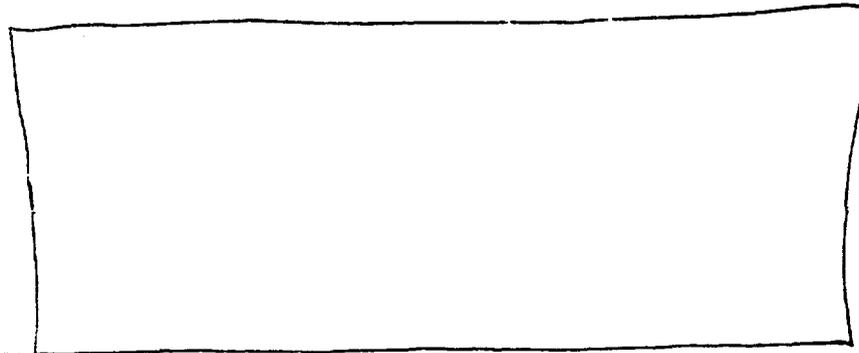
was complete,

_____ in the United States.

This study is reviewed in greater detail in a subsequent section.

B357 is a pilot-open label study assessing the effect of anti-emetic treatment on nausea and/or vomiting associated with rising doses of Exelon® treatment in patients with probable Alzheimer's Disease. 82 new patients have been recruited to this study. A separate report has been provided for this study.

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INT-03 was a randomized, double-blind, placebo-controlled, parallel-arm, 20-week study of the safety, tolerability and efficacy of Exelon® in patients suffering from probable Dementia with Lewy Bodies. Patients were randomized to receive either Exelon® or placebo. All patients receiving Exelon® were initially treated with 1.5 mg b.i.d; those unable to tolerate that dose were discontinued from the study. During the titration phase, the dose was increased at a maximum interval of 2 weeks at a maximum tolerated daily maintenance dose of 6, 9, or 12 mg (given b.i.d) was reached

120 patients were enrolled in this study which was conducted entirely outside the United States. A final study report is included in this submission. (Note that the INT-03 study has not been included in the analyzable Integrated Safety Database; only narratives for deaths, serious adverse events and adverse events leading to treatment discontinuation have been made available in this submission)

C152 was an open-label, ascending-dose, sequential cohort study of 5 different variants of an Exelon® transdermal system in patients with mild to moderate Alzheimer's Disease. Each patient would receive upto 4 weeks of treatment with a single patch variant. A separate report for this study has not been provided; neither are data for this study included in the submission. Neither are data from the study included in the analyzable Integrated Safety Database. Narratives for

deaths, serious adverse events and adverse event dropouts do appear to have been made available

3.5 Exposure

Cumulative exposure data for the All Therapeutic Studies Group is provided in the following table. This group comprises all Phase 2 and 3 studies included in the analyzable Integrated Safety Database

The sponsor states that the data in the table represent 5713 patient-years of exposure to Exelon®.

Study Grouping	Exposure (Weeks) **								
	Any Exp.	>= 1	>= 2	>= 4	>= 12	>= 26	>= 38	>= 52	>= 65
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Therapeutic Studies	5297 (100)	5245 (99)	5154 (97)	4962 (94)	4326 (82)	3407 (64)	2627 (50)	2150 (41)	1757 (33)

Study Grouping	Exposure (Weeks) **						
	>= 78	>= 91	>= 104	>= 130	>= 156	>= 182	>= 208
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Therapeutic Studies	1537 (29)	1414 (27)	1250 (24)	638 (12)	160 (3)	4 (<1)	1 (<1)

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3.6 Demographics

A comparison of demographics between those treated with Exelon® and those treated with placebo in the All Therapeutic Studies group is summarized in the following table

Variable	Exelon® (n=5297)	Placebo (n=1088)
Mean Age (years)	73.7	72.7
% Male	41	40
% Caucasian	89	91
Mean Weight (kg)	66.6	75.5

Mean weight is that recorded at baseline

These demographics are very similar to those in the original Integrated Summary of Safety and in the 120-Day Safety Update

3.7 Disposition

Patient disposition in the Exelon® and placebo groups in the All Therapeutic Studies grouping are indicated in the following table which compares percentages

Outcome	Exelon® (n=5297)	Placebo (n=1088)
Completed	51 %	84 %
Discontinued	49 %	16 %
Discontinued due to adverse event	24 %	8 %
Withdrawal of consent	12 %	3 %
Death	2 %	0 %

The data in the above table are very similar to those in the 120-Day Safety Update except for a higher overall discontinuation rate (16 % in the 120-Day Safety Update)

3.8 All Adverse Events

The following table extracted from the submission provides a listing of all COSTART-designated adverse events that have occurred in $\geq 5\%$ of Exelon®-treated patients in the All Therapeutic Studies listing. Note that the Exelon®-placebo comparisons in the table below are not particularly compelling since they are not solely based on randomized controlled trials of equal length

Adverse Event (COSTART)	Exelon® (n=5297)		Placebo (n=1088)	
	Number	%	Number	%
Any adverse event	4852	91.6	791	72.7
Accidental trauma	921	17.4	83	7.6
Fatigue	516	9.7	45	4.1
Asthenia	479	9.0	22	2.0
Weight decrease	469	8.9	3	0.3
Malaise	288	5.4	20	1.8
Dizziness	1232	23.3	107	9.8
Headache	1011	19.8	124	11.4
Somnolence	466	8.8	25	2.3
Tremor	316	6.0	13	1.2
Nausea	2501	47.2	118	10.9
Vomiting	1672	31.6	56	5.2
Diarrhea	1139	21.5	107	9.8
Anorexia	962	18.2	30	2.8
Abdominal Pain	748	14.1	65	6.0
Dyspepsia	574	10.8	42	3.9
Constipation	394	7.4	39	3.6
Back Pain	400	7.6	43	4.0
Arthralgia	305	5.8	27	2.5
Myalgia	290	5.5	10	0.9
Bone fracture	265	5.0	19	1.8
Agitation	987	18.7	78	7.2
Insomnia	685	12.9	60	5.5
Confusion	606	11.4	68	6.3
Depression	590	11.1	44	4.0
Anxiety	399	7.5	26	2.4
Aggressive Reaction	327	6.2	22	2.0
Hallucination	316	6.0	32	2.9
Upper respiratory infection	760	14.4	85	7.8
Urinary tract infection	492	9.3	54	5.0
Coughing	374	7.1	42	3.9
Rhinitis	275	5.2	28	2.6
Urinary incontinence	436	8.2	19	1.8

The above adverse events were similar in their nature to those seen in the original Integrated Summary of Safety and the 120-Day Safety Update. The frequency of a number of the more common adverse events was somewhat higher in the current submission than in the 120-Day Safety Update; the sponsor's explanation is that the current submission represents a longer period of data collection and increased aging of the population included in the database.

3.9 Adverse Events Leading To Treatment Discontinuation

The following table extracted from the submission provides a listing of all COSTART-designated adverse events that have occurred in $\geq 5\%$ of Exelon®-treated patients in the All Therapeutic Studies listing. Note that the Exelon®-placebo comparisons in the table below are not particularly compelling since they are not solely based on randomized controlled trials of equal length

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The above adverse events were similar in their nature to those seen in the original Integrated Summary of Safety and the 120-Day Safety Update. The frequency of a number of the more common adverse events was somewhat higher in the current submission than in the 120-Day Safety Update; the sponsor's explanation is that the current submission represents a longer period of data collection and increased aging of the population included in the database.

3.10 Serious Adverse Events

The following table extracted from the submission provides a listing of all COSTART-designated serious adverse events that have occurred in $\geq 1\%$ of

Exelon®-treated patients in the All Therapeutic Studies listing. Note again that the Exelon®-placebo comparisons in the table below are not particularly compelling since they are not solely based on randomized controlled trials

Adverse Event (COSTART)	Exelon® (n=5297)		Placebo (n=1088)	
	Number	%	Number	%
Any adverse event	1458	27.5	137	12.6
Syncope	97	1.8	4	0.4
Overdose	243	4.6	46	4.2
Accidental trauma	93	1.8	4	0.4
Procedure	66	1.3	9	0.8
Bone fracture	136	2.6	8	0.7
Agitation	65	1.2	2	0.2
Pneumonia	83	1.6	4	0.4
Cerebrovascular Disorder	87	1.6	4	0.4

All narratives for serious adverse events have been read, supplemented with Case Report Forms when needed. Significant narratives are discussed separately.

3.11 Deaths

Deaths referred to in this section include only those that have occurred during treatment and within 30 days of study drug discontinuation.

A total of 135 deaths have occurred in the Exelon® studies that have been included in the analyzable Integrated Safety Database (key safety population); however 4 of these deaths were, in error, not included in the analyzable Integrated Safety Database. These include deaths already contained in the original Integrated Summary of Safety and in the 120-Day Safety Update. As already noted the cut-off date for the analyzable Integrated Safety Database is June 30, 1998.

A further 124 deaths occurred up to the later cut-off date of June 30, 1999.

The distribution of all deaths that have occurred in the Exelon® development program through June 30, 1999 is illustrated by the following table copied from the submission.

	Deaths in the Analyzable Database		Deaths through June 30, 1999	
	ENA	Placebo	ENA	Placebo
All Studies	133	2	255	4
Phase I Study (B129)	0	0	1	0
Phase II Studies	5	1	5	1
Phase III Studies	105	1	141	1
Phase IIIb Studies	23	0	108	2

Narratives for all deaths up to the June 30, 1999 cut-off date, except for those already included in the original Integrated Summary of Safety and 120-Day Safety Update, have been supplied. These narratives have been read by me and

supplemented with Case Report Forms if necessary. Significant narratives have been discussed in greater detail in a separate section.

3.11.1 Causes Of Death

The following table copied from the submission groups deaths in Exelon®-treated patients according to their general cause. The deaths are those in Phase III studies only

Causes of death	Through June 30, 1998 (in the database)	Through June 30, 1999
	N=4648	N=7567
Cardiac	45	83
Infection	32	60
Cancer	15	22
Cerebrovascular	14	30
Alzheimer's disease	6	13
Vascular disorder	5	10
Gastrointestinal disorder	3	9
Accidental trauma	3	5
Hemorrhage	2	3
Pulmonary	0	2
Renal disorder	1	2
Suicide	1	2
Hepatic disorder	0	1
Metabolic disorder	0	4
Unknown	0	2
Total	127	348

3.11.2 Mortality In Phase III Placebo-Controlled Trials

A total of 9 deaths have occurred in ALL Phase III placebo-controlled trials (these include studies that have not contributed to the analyzable Integrated Safety Database). Both the crude mortality rate and the mortality rate adjusted for exposure to study treatment were similar between the Exelon® and placebo groups as evidenced by the following table

	ENA N=1982	Placebo N=929
Number of deaths (within 30-day window)	6	3
Mortality rate	0.30%	0.32%
Total exposure	829.5	417.0
Number of deaths per 100 years of exposure	0.72	0.72

Phase III Controlled Studies (Exelon N=1923; Placebo N=868): B303, B304, B361, and B362.
 Phase IIIb Controlled Study (Exelon N=59; Placebo N=61): INT-03.

3.11.3 ~~Tabular~~ Summary Of Deaths

The sponsor has presented a tabular summary of all 259 deaths that have occurred during the Exelon® development program through June 30, 1999. The tables are too extensive to be reproduced in full in this review. The causes of death listed in the tables are almost entirely those that are common in older patients. The deaths in the original Integrated Summary of Safety and 120-Day Safety Update have already been subjected to extensive review. The tables however do include a patient who is listed as having cryptogenic cirrhosis as the cause of death

The patient (#INT01.067.006) who died of cryptogenic cirrhosis was an 82 year old woman who received Exelon® for a total of 531 days, last in a dose of 3 mg daily. She is described in greater detail in a later section.

3.12 Review Of All Narratives For Deaths, Serious Adverse Events And Adverse Events Leading To Treatment Discontinuation

All narratives in this submission have been read.

Many narratives are presented in tabular format; they vary greatly in detail.

Cut-off dates for narratives, as already stated, are as follows:

Category	Cut-off date
Deaths and serious adverse events	6/30/99
Adverse events leading to discontinuation	12/31/98

Adverse events that warrant further attention have been discussed below under "Adverse Events of Special Concern"

4. Post-Marketing Safety Reports

Exelon® is currently approved for marketing in a number of countries outside the United States. In this submission the sponsor has provided 4 consecutive Post-Marketing Surveillance Update Reports covering the following periods

Report	Dates Covered
Periodic Safety Update Report # 1	8/1/97 to 1/31/98
Periodic Safety Update Report # 2	2/1/98 to 7/31/98
Periodic Safety Update Report # 3	8/1/98 to 1/31/99
Periodic Safety Update Report # 4	2/1/99 to 7/31/99

The consecutive Periodic Safety Update Reports contain line listings for adverse events among other items. In addition to all spontaneous reports generated by the marketed drug, serious adverse events from clinical trials which were attributable to the drug have been included. I have read all the line listings. Adverse events that warrant further attention have been discussed below under "Adverse Events of Special Concern"

5. Adverse Events Of Special Concern

Based on a review of narratives, and selected Case Report Forms for deaths, serious adverse events and adverse events leading to treatment discontinuation, and on post-marketing safety reports, I have discussed the following adverse events in greater detail.

5.1 Vomiting

This is discussed in a separate section below

5.2 Pancreatitis

The following is based upon information supplied in this safety update, as well as a separate submission dated 1/10/2000. In the latter submission the sponsor supplied, in response to an Agency request, an updated listing of all cases of pancreatitis reported in clinical trials, and in post-marketing safety reports, through 1/26/00. A total of 19 cases had been listed by the sponsor (18 in patients receiving Exelon® and 1 in patients receiving placebo). I have been able to find 20 cases (19 in patients receiving Exelon® and 1 in a patient receiving placebo)

In Phase III placebo-controlled trials the incidence of pancreatitis in the Exelon® and placebo groups was as follows.

	Exelon® (n = 1923)	Placebo (n = 868)
Pancreatitis	1 (0.052 %)	1 (0.12 %)

The incidence of pancreatitis in the above table corresponded to 123 per 100,000 patient-years (1/811 patient-years) of exposure for Exelon® and 253 per 100,000 (1/396 patient-years) for placebo

In the All Therapeutic Studies grouping the incidence of pancreatitis, both as an adverse event, and as a serious adverse event, in those treated with Exelon® and placebo is as below:

	Exelon® (n = 5297)	Placebo (n = 1088)
Pancreatitis	9 (0.17 %)	1 (0.09 %)

The incidence of pancreatitis in the above table corresponded to 158 per 100,000 patient-years (9/5713 patient-years) of exposure for Exelon® and 208 per 100,000 (1/481 patient-years) for placebo

Note: Based on 2 additional cases of pancreatitis in Exelon®-treated patients that should have been in the All Therapeutic Studies grouping, the actual incidence of pancreatitis in Exelon®-treated patients should be 0.21 % in the Exelon®-treated group or 193 per 100,000 patient-years of exposure.

The sponsor further states that 8760 patients have been exposed to Exelon® in clinical trials worldwide until mid-1999. 15 Exelon®-treated patients have developed pancreatitis during these trials yielding a crude incidence of 15/8760 or 0.17 %

The sponsor has also estimated that until 7/31/99 there had been 36,026 patient-years of exposure to marketed Exelon® yielding a crude incidence of spontaneous reports of pancreatitis of 8.3 per 100,000 patient-years of exposure (3/36026). Using a total of 4 cases derived from spontaneous reports I have estimated a crude incidence of 11.1 per 100,000 patient-years of exposure.

A listing of individual cases of pancreatitis that I have been able to identify is provided below. Separate tables are provided for the All Therapeutic Studies grouping, clinical trials not included in the latter grouping and spontaneous post-marketing reports.

5.2.1 All Therapeutic Studies

Patient ID #	Age/ Gender	Symptoms	Laboratory and imaging data	Relevant concurrent conditions
303301004	70/M	Abdominal pain, vomiting	Abdominal plain X-rays and ultrasound: normal. Amylase 358 U/L	None
304402001	77/M	Unclear	No information provided	Duodenal ulcer, gallstones
304430007	77/M	Vomiting, diarrhea	Abdominal ultrasound: gallstones Serum amylase > 2000 IU/L	Cholelithiasis
304432014	73/F	Nausea, vomiting, epigastric pain	Abdominal ultrasound: gallstones, cholecystitis and pancreatitis	Gallstones, cholecystitis
351112008	70/M	Vomiting, weakness	Abdominal ultrasound: enlarged common bile duct and numerous gallstones. Abdominal CT: Dilated gallbladder and common bile duct; thickened gallbladder wall and common bile duct Amylase 195 U/L Lipase 838 U/L	Cholecystitis, cholangitis
351102061	75/F	Abdominal pain	Abdominal ultrasound: gallbladder sludge. Serum amylase > 900 U/L	Cholelithiasis
US.ENAINT01.005.0008	57/F	Abdominal pain	Abdominal CT scan and gallbladder ultrasound normal Amylase 184 U/L Lipase 1372 U/L	Olanzapine treatment
US.ENAINT01.028.0008	70/F	Vomiting and shortness of breath	Gallbladder ultrasound: solitary stone Abdominal CT: Mild pancreatitis ERCP: A few gallstones; normal bile ducts Amylase 185 U/L	Cholelithiasis
US.ENAINT01.054.0018	74/F	Abdominal pain	Gallbladder ultrasound: many gallstones "Markedly elevated amylase"	Cholelithiasis
US.ENAINT02.002.0004	85/F	Nausea, vomiting and fainting	Amylase 110 U/L Lipase 396 U/L	None

Patient ID #	Exelon® daily dose at time of onset of pancreatitis	Duration of open-label Exelon® treatment at onset of pancreatitis	Outcome
303301004	12 mg	769 days	Resolved after drug was interrupted. Drug was later continued for a further month
304402001	2 mg	573 days	Patient recovered after treatment with intravenous antibiotics. Exelon® continued for a further 56 weeks after acute illness
304430007	12 mg	181 days	Patient recovered and continued in study
304432014	12 mg	58 days	Patient underwent cholecystectomy and recovered. Exelon®

351112008	6 mg	575 days	continued after acute illness Patient received broad-spectrum antibiotics, underwent cholecystectomy and recovered. Exelon® continued after acute illness
351102061	Placebo	90 days	Patient's pain resolved; she underwent a cholecystectomy and was able to continue with study drug for an additional 13 weeks
US.ENAINT01.005.0008	9 mg	524 days	Exelon® continued after acute illness for an uncertain period
US.ENAINT01.028.0008	9 mg	451 days	Patient underwent cholecystectomy and recovered. Exelon® continued after acute illness for an uncertain period
US.ENAINT01.054.0018	6 mg	216 days	Patient underwent cholecystectomy and recovered. Exelon® continued after acute illness for an uncertain period
US.ENAINT02.002.0004	12 mg	42 days	Study medication discontinued. Patient recovered

2 additional cases that should have been in the All Therapeutic Studies grouping but have not been included in the adverse event/serious adverse event listings for that grouping are below. The sponsor appears to have become aware of these cases after the Safety Update was submitted since they were not included in that update:

Patient ID #	Age/ Gender	Symptoms	Laboratory and imaging data	Relevant concurrent conditions
US.ENAINT01.028.0011	83/M	Not provided	No data provided	Cholelithiasis
US.ENAINT01.032.0008	80/F	Diarrhea, and features consistent with sepsis and thrombophlebitis	HIDA scan and abdominal CT scan negative for cholecystitis Amylase and lipase data not provided	Diabetes mellitus Cholelithiasis

Patient ID #	Exelon® daily dose at time of onset of pancreatitis	Duration of open-label Exelon® treatment at onset of pancreatitis	Outcome
US.ENAINT01.028.0011	12 mg	2 months	Underwent cholecystectomy; outcome unclear
US.ENAINT01.032.0008	6 mg	22 months	Improving; Exelon® appears to have been continued

5.2.2 Clinical Trial Patients Not In All Therapeutic Studies Grouping

Patient ID #	Age/ Gender	Symptoms	Laboratory and imaging data	Relevant concurrent conditions
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ENAC/152/0/3/3/1/USA	82/F	Nausea, diarrhea, shortness of breath, dizziness	Abdominal ultrasound: negative Amylase: 333 U/L Lipase: 1220 U/L	None
ENAC/152/0/3/2/1/USA	66/F	Abdominal pain, vomiting	Amylase: 175 U/L Lipase: 1137 U/L	None
CD.ENAINT01.030.0002	73/F	Nausea, vomiting, abdominal pain and dizziness	Abdominal ultrasound: negative Amylase: 832 U/L Lipase: 939 U/L	None

Patient ID #	Exelon® dose at time of onset of pancreatitis	Duration of Exelon® treatment at onset of pancreatitis	Outcome
ENAC/152/0/3/3/1/USA Initials: BB	12 mg daily	6 months	Resolved: Exelon® continued after acute illness for an uncertain period
ENAC/152/0/3/2/1/USA Initials: SR	12 mg daily	1 year	Study medication interrupted; subsequent course unclear
CD.ENAINT01.030.0002	6 mg daily	2.5 months	Recovered; study medication discontinued permanently

5.2.3 Spontaneous Post-Marketing Reports

Patient ID #	Age/Gender	Symptoms	Laboratory and imaging data	Relevant concurrent conditions
F/99/01224/Exelon	77/M	Nausea, vomiting	None provided	None stated
D/98/04338/Exelon	84/M	"Acute abdominal symptoms"	Lipase 810 U/L. Other unspecified diagnostic measures performed	None found
F/99/2713/Exelon	?/F	No information provided	No information provided	None stated
D/99/652/Exelon	77/M	No information provided*	No information provided	None stated

* "Acute necrotizing pancreatitis" diagnosed

Patient ID #	Exelon® dose at time of onset of pancreatitis	Duration of Exelon® treatment at onset of pancreatitis	Outcome
F/99/01224/Exelon	3 mg	2 weeks	Exelon® discontinued; outcome not stated
D/98/04338/Exelon	3 mg	3 weeks	Exelon® discontinued; patient recovered fully
F/99/2713/Exelon	9 mg	3 months	Exelon® discontinued; patient recovered
D/99/652/Exelon	3 mg	2 weeks	Exelon® discontinued. Outcome unknown

5.2.4 Overall Assessment Of Pancreatitis

A total of 9 cases of pancreatitis, in whom a concurrent predisposing condition was either absent or not stated in the adverse event report, have occurred in Exelon®-treated patients in the above groupings. It is noteworthy that, in several

of these, the clinical data available are sketchy and it is unclear to what extent contributory conditions such as gallstones were looked for. Of the 9 cases

- None occurred in Phase III placebo-controlled trials (one case of gallstone associated pancreatitis occurred in a placebo-treated patient)
- Only 2 occurred in the All Therapeutic Studies grouping with an incidence of 0.038 %. In one of these patients the diagnosis may have been questionable based on the serum amylase and lipase data
- 2 out of 7 were able to resume taking the drug after the acute illness had subsided, without a recurrence

Thus pancreatitis, without a predisposing condition such as gallstones, does appear to be a rare occurrence in Exelon®-treated patients, as it is with other cholinesterase inhibitors such as donepezil and metrifonate. It is quite possible that if sufficient information was available for several patients with no hitherto apparent predisposing cause, such a cause would be obvious. It is also, however, possible that of the many Exelon®-treated patients who had nausea, vomiting and abdominal pain in the entire clinical trial database, more would have been detected to have pancreatitis on detailed testing.

5.3 Cryptogenic Cirrhosis

A single patient diagnosed to have cryptogenic cirrhosis is described further in a narrative below. No other cases of cirrhosis appear to have occurred in the Exelon® database.

The patient was an 82 year old woman (ID # INT 01.067.006) participating in Study # B 356 and weighing 55.9 kg at study entry. At study entry she had a medical history of peptic ulcer disease, hypothyroidism, and rheumatoid arthritis; the latter condition had been treated with methotrexate for over 4 ½ years prior to study entry. Medications at study entry included levothyroxine, methotrexate, aspirin, conjugated estrogens and omeprazole. She had taken Exelon® for 76 weeks, last in a dose of 3 mg daily, when she presented to an emergency room with abdominal pain, dyspnea and ascites and was hospitalized; earlier she had been noted to decline over 3 months and to develop leg edema. A paracentesis, that revealed a transudate, was performed together with a number of treatment measures. Soon afterwards a diagnosis of cryptogenic cirrhosis was made by a gastroenterologist. She became febrile and received broad-spectrum antibiotics; she was then transferred to a skilled nursing facility, where she received comfort care with morphine and died 10 days after being hospitalized. Liver function test data are provided from screening until Week 52 and are normal; laboratory data pertaining to her hospitalization are not available. Exelon® was stopped at the time of her hospitalization. An autopsy does not appear to have been performed.

The diagnosis of a cryptogenic cirrhosis in this patient appears to have been clinical and not based on histopathology. If the patient did have cirrhosis, as her clinical history suggests, it is quite possible, as indicated by the sponsor, that it was related to methotrexate use and not to Exelon®. Cirrhosis appears to be a well-recognized adverse event associated with long-term (> 2 years) use of methotrexate, and the current label for the drug contains a "black box" warning to that effect.

5.4 Symptomatic Hepatitis

With the exception of 2 patients listed as having cholestatic hepatitis/jaundice, and another patient described as having hepatitis, I have not been able to find any definite instances of symptomatic hepatitis in either the clinical trial database (among deaths, serious adverse events or adverse events leading to treatment

discontinuation) or among the post-marketing safety reports submitted to us. **There appear to have been no definite cases of liver failure among Exelon®-treated patients**

Narratives for the 2 patients with cholestatic hepatitis/jaundice are below:

Patient # 1

A 71 year old woman (ID # 352213006), participating in Study B353 weighed 71.8 kg at study entry. After taking Exelon® for a total of 184 weeks, last in a dose of 12 mg daily, she was hospitalized on account of changes in her mental state, vomiting, fever and unsteadiness. Her skin was icteric. For 1 week immediately prior to her hospitalization she was treated with trimethoprim-sulfamethoxazole for a urinary tract infection; she was reportedly known to be allergic to that drug. At hospitalization her liver function tests were as follows: SGOT 62 U/L; SGPT 131 U/L; total bilirubin 6.5 mg/dl; GGT 564 U/L. Abdominal (including liver and gall bladder) ultrasound and abdominal-pelvic CT scans were negative. Both Exelon® and trimethoprim-sulfamethoxazole were stopped. A urinary tract infection and atrial fibrillation were treated during hospitalization. The patient's course after discharge is not known.

Patient # 2

A brief post-marketing safety report from France describes a 77 year old man who "experienced cholestatic hepatitis" 10 weeks after starting Exelon® in an unspecified dosage, and 10 days after starting a combination of amoxicillin, mianserin and tiemonium. All his medications were discontinued and 3 weeks later the patient had not recovered. No further details are available. I presume that this patient was symptomatic.

A further patient diagnosed to have hepatitis is described below:

A post-marketing safety report describes a 76 year old woman (ID # F/99/0865/Exelon) diagnosed to have parkinsonism and senile dementia who was prescribed Exelon® 3 mg daily for 2 months although it is uncertain if she took that medication regularly. At the end of that 2-month period she was hospitalized with a worsened mental state, malnutrition and a large decubitus ulcer. In addition to Exelon® she was receiving ceftriaxone, piribedil, phenobarbital with caffeine, levothyroxine, pipemidique, acetaminophen, moclobemide, lactitol, ornithine oxoglutarate and a nutritional supplement. Liver functions at that time revealed the following: SGOT 337 U/L, SGPT 530 U/L, alkaline phosphatase 229 U/L and GGT 198 U/L. Exelon®, piribedil and phenobarbital with caffeine were stopped. 3 days later her laboratory tests were as follows: SGOT 41 U/L, SGPT 160 U/L, alkaline phosphatase 141 U/L and GGT 198 U/L. Abdominal ultrasound was normal except for biliary sludge. Serological testing was negative for hepatitis B and C, but positive for hepatitis A (indicating previous exposure?). Antinuclear antibodies were negative. Subsequently the patient worsened and died. There is no report of an autopsy having been performed.

In yet another patient diagnosed to have hepatitis, the only evidence that the patient may have been symptomatic is that she was hospitalized

A post-marketing safety report describes a 66 year old woman (ID # E/99/00184/Exelon) in Spain who had Alzheimer's Disease and a history of "hepatic and biliary lithiasis" who received Exelon® 3 mg daily for 55 days following which the dose was increased to 6 mg daily. 3 months later the patient was diagnosed to have hepatitis and needed hospitalization: laboratory tests at that time revealed the following: SGOT 609 U/L; SGPT 630 U/L. Exelon® was stopped at that time and a week later laboratory tests showed the following: SGOT 40 U/L; SGPT 130 U/L. No other information is available

In none of the above cases was there sufficient information or evidence to suggest a high likelihood of Exelon® being responsible for the hepatitis

5.5 Liver Function Abnormalities

In this section I will focus on asymptomatic liver function abnormalities listed as adverse events

In the four Phase III placebo-controlled trials, the incidence of "clinically notable" abnormalities (defined in the table) of liver function were similar between Exelon® and placebo, as illustrated in the sponsor's table below:

Incidence of clinically notable abnormalities
 Exelon® Phase III Controlled Studies (26-week)

Liver function test	Result	Exelon® N=1898 n (%)	Placebo N=862 n (%)
Total bilirubin	High (2 mg/dL)	19 (1.00)	14 (1.62)
Alkaline phosphatase	High (3 x ULN)	5 (0.26)	1 (0.12)
SGOT (AST)	High (3 x ULN)	5 (0.26)	4 (0.46)
SGPT (ALT)	High (3 x ULN)	11 (0.58)	7 (0.81)

Phase III Controlled Studies: B303, B304, B351, and B352
 ULN = upper limit of normal range

No analysis of laboratory data is presented in the Safety Update as per an agreement with the Agency.

Based on **(all) adverse event** reports the incidence of liver function abnormalities in the All Therapeutic Studies Grouping is as follows:

Adverse Event (COSTART)	Exelon® (n=5297)		Placebo (n=1088)	
	Number	%	Number	%
Hepatic enzymes increased	10	0.19	1	0.09
Hepatic function abnormal	10	0.19	0	0.00
Gamma GT increased	6	0.11	0	0.00
Hepatitis	4	0.08	0	0.00
SGPT increased	4	0.08	0	0.00
Bilirubinemia	3	0.06	0	0.00
Hepatitis cholestatic	3	0.06	0	0.00
Hepatocellular damage	3	0.06	0	0.00
Hepatomegaly	3	0.06	0	0.00
Jaundice	3	0.06	0	0.00
Hepatic failure	0	0.00	1	0.09
Liver fatty*	1	0.02	0	0.00
SGOT increased	1	0.02	0	0.00

*See "Serious Adverse Events" below

Among **adverse event dropouts** in the All Therapeutic Studies grouping the incidence of liver function abnormalities is as follows:

Adverse Event (COSTART)	Exelon® (n=5297)		Placebo (n=1088)	
	Number	%	Number	%
Hepatic enzymes increased	2	0.04	0	0.00
Hepatic function abnormal	3	0.06	0	0.00
Hepatitis	2	0.04	0	0.00
Bilirubinemia	1	0.02	0	0.00
Hepatitis cholestatic	1	0.02	0	0.00
Hepatocellular damage	1	0.02	0	0.00

Hepatic failure	0	0.00	1	0.09
Liver fatty*	1	0.02	0	0.00

*See "Serious Adverse Events" below

Among serious adverse events in the All Therapeutic Studies grouping the incidence of liver function abnormalities is as follows:

Adverse Event (COSTART)	Exelon® (n=5297)		Placebo (n=1088)	
	Number	%	Number	%
Hepatic enzymes increased	3	0.06	0	0.00
Hepatic function abnormal	1	0.02	0	0.00
Hepatitis	2	0.04	0	0.00
Hepatitis cholestatic	1	0.02	0	0.00
Hepatic failure	0	0.00	1	0.09
Liver fatty*	1	0.02	0	0.00

*A 71 year old woman weighing 61.8 kg first began showing very minor transaminase elevations (SGOT was 50 U/L) at Week 52 of Exelon® treatment at a time when she was receiving 12 mg daily. Exelon® was stopped at Week 60 and was then resumed for at least several months prior to the patient discontinuing participation in the study at Week 128. The greatest transaminase abnormalities were seen at Week 125: SGOT 157 U/L, SGPT 161 U/L, and alkaline phosphatase 175 U/L; however her alkaline phosphatase rose to 306 U/L about 2 months after she discontinued from the study at which time her other liver functions were as follows: SGOT 143 U/L, SGPT 104 U/L and gamma GT 757 U/L. Abdominal ultrasound, Hepatitis A and C serology and ERCP were negative. Liver biopsy revealed severe steatohepatitis. The patient was apparently asymptomatic throughout. It is unclear whether her liver function abnormalities eventually resolved

In those Exelon®-treated patients with liver function abnormalities that counted as serious adverse events or adverse events that lead to treatment discontinuation, transaminase elevations did not exceed 5 x upper limit of normal in the majority of instances. A single instance where transaminase elevations were more pronounced is described further below:

A 71 year old woman (ID # 355015112) was enrolled in Study # B 355. She had a past medical history of penicillin allergy, hypertension, arthritis, and gall bladder disease (with previous cholecystectomy). Concomitant medications included Claritin, Advil and Bumex. At baseline her liver function tests were as follows: AST 34 U/L; ALT 44 U/L; and alkaline phosphatase 93 U/L. A hepatitis screen showed a positive antibody to Hepatitis A virus (total).

During Week 2 of the study while taking Exelon® in a dose of 3 mg b.i.d, she developed nausea and vomiting leading to a reduction in dose to 1.5 mg b.i.d. At Week 4 her laboratory tests were as follows: AST 134 U/L; ALT 222 U/L and alkaline phosphatase 107 U/L. During the next 35 weeks these enzyme levels fluctuated considerably. Exelon® was finally discontinued at Week 39 when her laboratory tests were as follows: AST 586 U/L; ALT 614 U/L and alkaline phosphatase 163 U/L. About a week later these enzyme levels peaked at: AST 1260 U/L; ALT 1190 U/L and alkaline phosphatase 226 U/L. 3 weeks after the drug was stopped her liver function tests showed: AST 21 U/L; ALT 28 U/L and alkaline phosphatase 101 U/L. During the course of the study hepatitis screening was repeated several times and showed results similar to those at baseline.

Among clinical studies not included in the Safety Update and among post-marketing safety reports I have found 8 additional reports of abnormal liver functions comprising elevated transaminases and/or elevations in serum bilirubin. Most of these reports are sketchy and transaminase values in all instances reported have not exceeded 5 x upper limit of normal. All lead to discontinuation of Exelon® treatment.

Overall, liver function abnormalities appear to be infrequent with Exelon®. In Phase III placebo-controlled trials they were no more frequent in those treated with Exelon® than in those treated with placebo.

5.6 Autoimmune Disorder With Renal Failure

Such a disorder was spontaneously reported in a single patient who is described further below:

A 69 year old woman [redacted]; ID # D/99/00862/Exelon) in Germany who took Exelon® in a dose of 1.5 mg b.i.d for 3 months developed an illness comprising the following 3-4 weeks after beginning to take the drug: diffuse pain, hemolytic anemia, renal failure (with a diffuse necrotizing glomerulonephritis on biopsy), pulmonary infiltrates and positive p-ANCA (positive anti-neutrophil cytoplasmic antibody). She worsened despite treatment with cyclophosphamide and prednisone and died. Exelon® was apparently continued throughout her illness.

There is no evidence that Exelon® was responsible for this patient's autoimmune disease, which bears a resemblance to Wegener's granulomatosis.

6. B:

safety report

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6.2 Design

... subsequent protocol amendment (# 3) the design of the study was