

MEMORANDUM

DATE: April 17, 2006

TO: Members, Peripheral and Central Nervous Systems (PCNS) Drugs Advisory Committee and Invited Guests

FROM: Staff
Division of Neurology Products

SUBJECT: Background Document for PCNS Drugs Advisory Committee Meeting of May 17, 2006

NDA 20823 (SE1-016); Exelon® (rivastigmine tartrate); Novartis

Proposed New Indication: "Treatment of mild to moderate dementia associated with Parkinson's Disease"

1 Background

As you know, a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee of the Food and Drug Administration will be held on May 17, 2006 to discuss the above Supplemental New Drug Application. This paper has been prepared in an effort to brief you on the specific issues that we believe need to be addressed by the Agency when considering this application. In addition to this memorandum, we are forwarding copies of Agency clinical and statistical reviews and a number of publications, which we hope will provide a more detailed background for the meeting.

1.1 Purpose Of Meeting

The purpose of this Advisory Committee meeting is to achieve a consensus as to whether the proposed entity of dementia associated with Parkinson's Disease (also referred to in the application and in Agency reviews as "Parkinson's Disease Dementia") is an entity that justifies a new claim, and, if so, whether the data submitted in this application indicate that Exelon® is both effective and safe in the treatment of that condition

1.2 Dementia Associated With Parkinson's Disease

While it is widely accepted that there is an increased prevalence of dementia in Parkinson's Disease, the nosological status of that dementia does not appear to have been fully resolved.

The medical literature indicates that in patients with Parkinson's Disease who develop dementia, the neuropathological findings are varied; while a number of the pathological abnormalities seen, such as cortical Lewy bodies and prominent cell loss in the medial substantia nigra are considered distinctive for that condition, Alzheimer's-type lesions (such as neurofibrillary tangles and amyloid plaques) frequently co-exist, as do abnormalities attributed to cerebrovascular disease. The relative contribution of these various pathologies to the dementia in these patients has been a matter of some uncertainty and controversy.

More recently published studies (see Braak et al, Aarsland et al) are considered by some to indicate that earlier histopathological data may have underestimated the extent to which Lewy bodies were present in the brain (and especially in the neocortex and limbic cortex) of patients with Parkinson's Disease and dementia since these studies were done prior to the availability of modern immunohistochemical techniques such as stains for ubiquitin and alpha-synuclein. These studies have further suggested that pathological and neurochemical abnormalities specific to Parkinson's Disease may be more contributory to dementia in these patients than the Alzheimer-type changes.

Many medical authors have also stated that the cognitive deficits that are seen in the dementia that occurs in Parkinson's Disease are fairly distinctive. The higher cortical functions selectively compromised, and affected to a degree greater than in patients with Alzheimer's Disease, are reported to include attention, executive functions, free recall memory, visuospatial function, verbal fluency, and the speed of mental processing; abnormalities of behavior and personality have also been stated to be more characteristic of Parkinson's Disease than in Alzheimer's Disease. It is unclear to what extent this reportedly distinctive pattern of cognitive deficits may have been correlated with the neuropathological abnormalities outlined earlier, and especially with those that have been detected using more modern staining techniques.

These reportedly distinctive cognitive features of the dementia associated with Parkinson's Disease also find mention in what appear to be the only published formal diagnostic criteria for such a condition. These criteria, for diagnosing "Dementia Due To Parkinson's Disease" are available in DSM-IV 294.1, but their wording suggests that they are of very limited clinical utility. They begin with the statement that *"the essential feature of Dementia Due To Parkinson's Disease is the presence of dementia that is **judged** to be of direct pathophysiological consequence of Parkinson's disease"* but do not provide any further indication as to how such a judgment is to be made beyond stating that dementia associated with Parkinson's Disease is "characterized by cognitive and motor slowing, executive dysfunction, and impairment in memory retrieval." These criteria are primarily descriptive, and, importantly, do not specify how this entity is to be distinguished from other dementias such as Alzheimer's Disease; they have never been pathologically validated.

A further aspect of the nosological status of dementia associated with Parkinson's Disease (Parkinson's Disease Dementia) is its relationship to the entity of dementia with Lewy bodies, which also combines the motor features of Parkinson's Disease with dementia and for which most explicit clinical diagnostic criteria have been published. In the more recent medical literature, this entity has generally been distinguished from Parkinson's Disease Dementia by the (arbitrary) "one-year rule" criterion where the onset of dementia within 12 months of the onset of parkinsonism is stated to be consistent with dementia with Lewy bodies whereas if parkinsonism has been present for more than 12 months prior to the onset of dementia, the condition is considered to represent Parkinson's Disease Dementia. The neuropathological abnormalities that underlie both conditions are considered to be similar with changes considered distinctive for Parkinson's Disease being combined with other pathology, notably Alzheimer-type changes. Whether these entities are the same disease or separate distinct entities is still a matter of some controversy, although the consensus view appears to be that they are the same neurobiological entity (see McKeith et al [2 articles] below).

We do not doubt that the goal of ameliorating the effects of any form of dementia is a laudable one. However, from a regulatory perspective, a number of issues need to be addressed in regard to the entity of dementia associated with Parkinson's Disease in the context of this application, given the uncertainties about its nosological status that have already been outlined in this section.

1.3 FDA Role

The FDA approves a drug for marketing based on a determination that such a treatment is both effective and safe, when used to treat one or more specific clinical entities. The entity for which such a treatment is intended, is referred to as the "claim" or "indication" for that drug and is described in the "Indications and Usage" section of the label. Proposed labeling must accompany the New Drug Application (NDA) submitted by the sponsor.

The Federal Food, Drug, and Cosmetic Act (the Act) requires that the approval of a drug treatment for a specific condition be supported by (among other things) "...substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling...". Substantial evidence is further defined as evidence from "adequate and well controlled...clinical investigations...". These definitions make clear that approval of a drug product is inextricably linked to our ability to adequately describe the population for whom the drug is intended and the drug's effects in that population in labeling.

In order to do this, the following must generally be true:

- The condition can be defined without ambiguity using criteria that have wide acceptance, and are both valid and reliable
- Appropriate instruments be used for measurement of the clinical effect of the drug on that condition; such instruments must measure what they are intended to under the conditions under which they are actively employed
- Clinical trials should be appropriately designed to measure that effect

- The effect measured should be clinically meaningful

For the most part, 2 classes of clinical entities are considered appropriate for new drug claims:

- Specific diseases or clinical syndromes, such as multiple sclerosis or chronic renal failure.
- Non-specific symptoms such as pain or urinary frequency

On occasion, claims may be also be directed at symptoms of specific diseases, e.g., excessive daytime sleepiness associated with narcolepsy.

The Act also states that the Secretary may refuse to approve an application “if based on a fair evaluation of all material facts, such labeling is false or misleading.” Labeling that states that a particular drug is indicated for the treatment of a specific clinical entity could be considered misleading if the condition is not well-defined, the effect of the drug on that condition is not appropriately measured, or the clinical trial in which that effect was measured was not appropriately designed.

In deciding whether a proposed clinical entity justifies a new claim, criteria used by the FDA have generally consisted of the following:

- The existence of the entity must be broadly accepted by medical experts representing the relevant clinical discipline
- The entity should be operationally definable

If a new claim is sought for a drug that is already approved for a specific indication, a sponsor would be required to establish that the new indication is meaningfully different from the existing claim. Otherwise, the implication in labeling that the 2 indications were different entities when, in fact, they were not, could be considered misleading.

1.4 Current Basis For Approving Drugs For Dementia

In the last 15 years, five drugs have been approved by the FDA for the treatment of dementia and all have been approved specifically for Alzheimer’s Disease: tacrine, donepezil, rivastigmine, galantamine, and memantine. Tacrine, donepezil, rivastigmine, and galantamine have been approved for an identical indication: the treatment of mild to moderate dementia of the Alzheimer’s type. Memantine has been approved for the treatment of moderate to severe dementia of the Alzheimer’s type. Their approval has been based upon clinical trials, the key elements of which have been summarized below.

The current Supplemental New Drug Application is the first to seek approval for a drug to treat dementia associated with Parkinson’s Disease.

1.4.1 Diagnosis of Alzheimer's Disease

Patients enrolled in these trials have generally had “probable” Alzheimer's Disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Those criteria* are as follows

- Dementia established by clinical examination, and confirmed by a rating scale such as the Mini-Mental Status Examination, and by neuropsychological testing
- Deficits in two or more areas of cognition
- Progressive cognitive worsening
- No disturbance of consciousness
- Onset between ages 40 and 90
- Absence of systemic disorders, and other brain diseases that could account for the progressive cognitive impairment

*The NINCDS-ADRDA criteria for probable Alzheimer's Disease have been shown to be both valid and moderately reliable. They have a sensitivity of > 90%; their specificity is however lower (50 – 60%) and they are particularly lacking in specificity in distinguishing the frontotemporal dementias from Alzheimer's Disease, as well as in distinguishing those who have a combination of cerebrovascular neuropathology and Alzheimer's Disease from those who have pure Alzheimer's Disease.

1.4.2 Severity Of Dementia

The severity of their dementia has been assessed based on their Mini-Mental Status Examination scores at entry; the range of such scores that have been considered to fit the “mild to moderate” category has been from 10-26, whereas the corresponding range for the “moderate to severe” category has been from 0-14.

1.4.3 Design And Duration Of Clinical Trials

These trials have so far invariably been randomized, double-blind, placebo-controlled, parallel-arm studies. The period of double-blind treatment has ranged from 3-6 months.

So far, the approval of drugs for the treatment of Alzheimer's Disease has been based upon demonstrating efficacy in at least 2 such studies, each of at least 3 months' duration.

1.4.4 Outcome Measures For Assessing Drug Efficacy

Draft guidelines issued by this Agency have recommended that the efficacy of putative drugs for dementia be determined using assessments of the following as pre-specified co-primary outcome measures.

- Cognitive functions. The standardized test battery used most widely for this purpose in mild to moderate Alzheimer's Disease the Alzheimer's Disease

Assessment Scale-Cognitive (ADAS-Cog). The corresponding instrument used in moderate to severe Alzheimer's Disease is the Severe Impairment Battery

- A clinician's overall impression of how the patient's cognition, behavior and function have changed over the course of the study; this has been referred to as a "global" assessment. The most widely used method is the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). A similar measure termed the Alzheimer's Disease Cooperative Study – Clinician's Global Impression Of Change (ADCS-CGIC) has also been used.

A cognitive rating scale has been recommended as a primary outcome measure since the core symptoms of dementia are cognitive. However, since the clinical significance of a change on a cognitive rating scale may not be clear, a global scale or functional scale has been recommended as a second primary outcome measure; the functional measure used most commonly as a substitute for a global instrument has been the Alzheimer's Disease Cooperative Study – Activities Of Daily Living Scale (ADCS-ADL).

For approval to be granted it has been required that superiority of the drug over placebo be demonstrated separately on each of these 2 types of primary efficacy measure: cognitive and global/functional.

1.4.5 Symptomatic Effect Versus Disease Modification

The clinical trials on which the approval of drugs for Alzheimer's Disease have been based have thus far been considered not to be designed to distinguish between a purely symptomatic effect of the drug in question and a disease-modifying effect. In this context, the term "disease-modifying" refers to an effect on the underlying pathology of the disease.

Accordingly, the class labeling for these drugs states: "There is no evidence that -----(name of drug) alters the course of the underlying dementing process."

2 Summary Of Application

In this application, the sponsor has provided evidence from two completed clinical studies in support of the efficacy and safety of Exelon® for the proposed new indication. These are:

- Study 2311, which was randomized, double-blind, placebo-controlled, and parallel-arm in design
- Study 2311E1, the open-label uncontrolled extension to Study 2311

In addition, the sponsor has performed a non-interventional study (Study 2314) of the validity of a number of assessment scales in the Parkinson's Disease Dementia (and vascular dementia); partial results for that study have been included in this application.

The data for these studies as they pertain to the efficacy and safety of Exelon® in this population are summarized below, as are the results of the non-interventional validation study listed above.

2.1 Efficacy

The results of a single controlled clinical study (Study 2311, also referred to as the EXPRESS Study) of the efficacy of rivastigmine in the proposed entity of dementia associated with Parkinson's Disease have been submitted in this application.

The results of this study have been published (see Emre et al [2004]).

The main features of the protocol for this study were as follows

- This was a randomized, double-blind, placebo-controlled, parallel-arm study. Patients were randomized to Exelon® or placebo in an approximately 2:1 ratio
- The key inclusion criteria for the study were as follows
 - Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria
 - Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia within at least 2 years of the first diagnosis of idiopathic Parkinson's Disease
 - Mini-Mental Status Examination score of 10 – 24 at entry
- The study was of 24 weeks' duration
- The 2 parallel treatment arms were
 - Rivastigmine 3 to 12 mg/day (flexible dose) as BID dosing
 - Placebo
- The primary efficacy measures were the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study – Clinician's Global Impression Of Change (ADCS-CGIC).
- The secondary efficacy measures were the following: Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL); Neuropsychiatry Inventory-10; Mini-Mental Status Examination; Cognitive Drug Research Computerized Assessment System; Delis-Kaplan Executive Functioning System (D-KEFS) Verbal Fluency Test; and Ten Point Clock-Drawing Test
- Safety was assessed through adverse events, vital signs, safety laboratory tests, electrocardiograms, and Unified Parkinson's Disease Rating Scale motor scores

- The sponsor's primary efficacy analysis was performed on the intent-to-treat plus retrieved dropouts dataset using the following statistical models
 - The change from baseline to endpoint in the ADAS-Cog score was to be compared between the treatment groups using an analysis of covariance with treatment, country, and baseline ADAS-Cog score as explanatory variables
 - The ADCS-CGIC score at endpoint was to be analyzed using a Cochran-Mantel-Haenszel test with modified ridits scores and with country as a stratification variable

Key results for this study were as follows.

541 patients were randomized, of whom 442 patients completed the study. Their distribution by treatment group was as follows:

<u>Treatment Group</u>	<u>Exelon®</u>	<u>Placebo</u>
Number randomized	362	179
Number completed	263	147

The main efficacy results of this study were as follows

- The primary efficacy analysis, using Study Week 24 as the endpoint, revealed statistically significant differences between the treatment groups on the ADAS-Cog (difference in mean change from baseline score at endpoint: 2.90; $p < 0.001$) and ADCS-CGIC (difference in mean score between treatment groups at endpoint: 0.5; $p = 0.007$). Note that an Agency statistical reviewer has judged the distribution of ADAS-Cog data not to be normal and therefore in violation of the assumptions of the analysis of covariance model proposed; however, even with the use of a non-parametric model, the Wilcoxon rank sum test, the Exelon® group showed a statistically significant superiority over placebo on this measure
- Nominally statistically significant differences were seen between the treatment groups on all secondary efficacy variables at Week 24 in the same dataset as that used for the primary efficacy analysis
- Analyses of the primary efficacy parameters using other datasets (intent-to-treat last-observation-carried-forward, and observed cases) yielded similar results.

2.2 Safety

2.2.1 Study 2311

This study has already been summarized above. Salient safety findings for this study were as follows.

- The incidence of nausea, vomiting, and tremor was appreciably higher in the rivastigmine group than in the placebo group; a similar adverse event profile was seen in the key controlled clinical trials of Exelon® in Alzheimer's Disease

- Several treatment-emergent adverse events that may have represented a worsening in the motor manifestations of Parkinson's Disease, and tremor in particular, were more frequent in those treated with Exelon® than in those treated with placebo. However, changes in UPDRS total and individual motor scores, probably a more objective measure of change in the motor manifestations of Parkinson's Disease than the incidence of treatment-emergent adverse events, showed no meaningful difference between treatment groups.

2.2.2 Study 2311E1

This was a 24-week open-label uncontrolled extension to Study 2311 intended primarily to evaluate the safety and tolerability of Exelon® in the study population. Patients given the option of enrolling in this study had either completed the double-blind treatment phase of Study 2311, or discontinued early during that study, but returned for all the remaining scheduled efficacy assessments without significant protocol violations. Regardless of their previous treatment assignment, patients enrolled in the extension study were all re-titrated to a flexible dose of Exelon® that ranged from 1.5 mg BID to 6.0 mg BID, based on tolerability.

433 patients enrolled in Study 2311 were eligible to enroll in Study 2311E1, of whom 334 patients actually consented to participate in, and 273 patients, completed the latter study.

The adverse event profile of Exelon® in Study 2311 was broadly similar to that seen in Study 2311E1.

2.3 Non-Interventional Validation Study (Study 2314)

This 4-week cross-sectional study was intended to evaluate the validity and reliability of several measures of cognition, activities of daily living, executive function and behavior in patients with Parkinson's Disease Dementia and vascular dementia, and to compare the performance of the same measures in those conditions with their performance in Alzheimer's Disease. This submission contains an interim report that only pertains to Parkinson's Disease Dementia.

The interim report indicates that 55 patients with Parkinson's Disease Dementia (diagnosed using the DSM-IV criteria) and 58 patients with Alzheimer's Disease (diagnosed using the NINCDS-ADRDA criteria) were enrolled in the study; patients with each diagnosis were further grouped into mild and moderate categories based on Mini-Mental Status Examination scores of 18 to 24 and 10 to 17, respectively, at study entry. The efficacy instruments evaluated were the ADAS-Cog, Global Deterioration Scale, ADCS-ADL, D-KEFS Verbal Fluency Test, Ten-Point Clock Test, Trailmaking Tests A and B, Neuropsychiatry Inventory, including Neuropsychiatry Inventory-Distress, and Cognitive Drug Research Computerized Assessment System tests for the assessment of attention. Each enrolled patient was to be evaluated using these measures at

baseline and Week 4; all but 2 patients, both in the Parkinson's Disease Dementia group, completed their evaluations.

The results of this study have been interpreted as demonstrating the following:

- That the ADAS-Cog score can differentiate between dementia associated with Parkinson's Disease of mild and moderate severities, as can the scores for several of the other instruments evaluated in this study
- That the ADAS-Cog and several other efficacy measures had test-retest reliability in dementia associated with Parkinson's Disease
- That the ADAS-Cog scores correlated with those of several other efficacy instruments in dementia associated with Parkinson's Disease, whether the latter measures assessed cognition or other domains
- A factor analysis that compared populations with Parkinson's Disease Dementia and Alzheimer's Disease on ADAS-Cog sub-item scores had indicated that the sub-items grouped differently in each population, suggesting that the cognitive and behavioral profiles in these populations might differ

3 Issues For Discussion

Study 2311 may be considered to have demonstrated the efficacy of Exelon® in the study population based solely on the prospectively-specified criteria for efficacy. Please note that the dual efficacy outcome measure paradigm used for demonstrating the efficacy of Exelon® in this study is the same as used to demonstrate the efficacy of drugs approved for the treatment of Alzheimer's Disease.

However, from a regulatory perspective, the main question that needs to be addressed in the context of this application is whether the results of Study 2311 establish that Exelon® is effective in the treatment of an entity (i.e., "dementia associated with Parkinson's Disease") that is sufficiently distinct from mild to moderate dementia of the Alzheimer's type [for the treatment of which Exelon® is already approved] to justify the approval of that drug for "dementia associated with Parkinson's Disease" as a separate indication.

The above question and others, together with the discussion in Section 1, form the basis for the issues listed below that we hope can be fully addressed at the forthcoming Advisory Committee meeting.

3.1 Is there a distinct form of dementia associated with Parkinson's Disease (and, in particular, a dementia that is distinct from Alzheimer's Disease) and do widely accepted, valid, and reliable criteria exist for its clinical diagnosis?

As already noted in Section 1.2, the neuropathological findings in patients with Parkinson's Disease and dementia are varied and may include features seen in Alzheimer's Disease such as neurofibrillary tangles and senile plaques, as well as abnormalities considered distinctive for Parkinson's Disease, and cerebrovascular pathology. More recently published studies have been interpreted by some as indicating that in such patients, pathological changes that are relatively specific to Parkinson's Disease are more important in contributing to dementia than those due to Alzheimer's Disease.

As also noted in Section 1.2, a number of authors have concluded that the profile of cognitive deficits seen in those who have Parkinson's Disease with dementia is different from that seen in patients with Alzheimer's Disease with selective compromise of attention, executive functions, free recall memory, visuospatial function, verbal fluency, and the speed of mental processing in the former. However, it is less clear that this reportedly distinctive cognitive profile for dementia associated with Parkinson's Disease has been correlated with the neuropathological abnormalities that some consider more specific to that condition.

The only published diagnostic criteria that may be applicable to dementia associated with Parkinson's Disease are those contained in DSM-IV (294.1). These criteria are limited in their utility as already stated in Section 1.2, and have, moreover, never been neuropathologically validated. Nevertheless, DSM-IV remains a standard reference manual.

It is also noteworthy that a recently-published American Academy of Neurology Practice Parameter (see Miyasaki et al) has both concluded that the etiology of dementia in Parkinson's Disease is unclear and that a specific pattern of cognitive deficits (impaired executive function, visuospatial abnormalities, impaired memory, and language deficits) is characteristic of that condition and should be incorporated into cognitive batteries that are intended to screen for Parkinson's Disease Dementia. The same publication also states that the DSM-IV criteria for diagnosing dementia per se may not be entirely appropriate for diagnosing dementia in Parkinson's Disease, presumably because the pattern of cognitive deficits in that condition is distinctive.

3.2 *Was the population enrolled in Study 2311 selected appropriately in the context of the proposed new indication, such that the effects of Exelon® in that population could be considered distinct from those already established as occurring in patients with Alzheimer's Disease?*

In this study, the key inclusion criteria used to identify patients as having dementia associated with Parkinson's Disease were prospectively specified as consisting of the following:

- Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria
- Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia within at least 2 years of the first diagnosis of idiopathic Parkinson's Disease

In practice, the criteria used to diagnose dementia associated with Parkinson's Disease in Study 2311 appear to have consisted of the following:

- Presence of Parkinson's Disease
- Presence of dementia syndrome, **without that dementia syndrome needing to have a pattern considered characteristic for dementia associated with Parkinson's Disease**
- Evidence of Parkinson's Disease prior to, but within 2 years of, the onset of dementia
- Exclusion of other causes of dementia

Thus, there was no requirement for those enrolled in Study 2311 to have a pattern of cognitive deficits that was in any way distinct from that seen in those patients who were enrolled in the key pre-approval efficacy trials of Exelon® in mild to moderate probable Alzheimer's Disease, upon which the current approval of Exelon® is based. Admittedly, the NINCDS-ADRDA criteria for the diagnosis of probable Alzheimer's Disease, which were used to enroll patients in the pre-approval efficacy trials of Exelon® required the exclusion of patients with Parkinson's Disease, if strictly applied.

In addition:

- The effects of rivastigmine on the primary efficacy measures in Study 2311 were not very different from those observed for rivastigmine, and, indeed other acetylcholinesterase inhibitors, on the same measures in the key pre-approval efficacy trials of those drugs in mild to moderate probable Alzheimer's Disease
- The clinical course of the placebo group in Study 2311 was similar to that of the placebo groups in the pre-approval efficacy trials of Exelon® in Alzheimer's Disease, as measured using the same instruments
- The overall design of Study 2311 was similar in many ways to the now-standard study design used to demonstrate the efficacy of drugs intended for the treatment of Alzheimer's Disease; the similarity extended to the outcome measures used

Alzheimer's Disease is a common condition, and it is intuitively to be expected that full-fledged Alzheimer's Disease (i.e., pathological abnormalities due to Alzheimer's Disease that could be considered sufficient to account for dementia) must be present merely by chance not uncommonly in patients with Parkinson's Disease and dementia.

All these observations raise the question of whether the apparent efficacy of Exelon® in Study 2311 was different from that seen with Exelon® in patients with mild to moderate probable Alzheimer's Disease as has already been

demonstrated in the pre-approval efficacy trials of Exelon®. Even if neuropathological abnormalities specific to Parkinson's Disease predominate in these patients, is it still possible that the effects of Exelon® in these patients are mediated through an effect on co-existing Alzheimer-type pathology? It is, however, also noteworthy that several authors (see Emre [2003]) have described the occurrence of marked loss of cholinergic neurons in the nucleus basalis of Meynert as an abnormality that is specific to Parkinson's Disease and may provide a potential, albeit hypothetical, mechanism by which an acetylcholinesterase inhibitor drug such as Exelon® may have a beneficial effect in that condition.

3.3 Was the population enrolled in Study 2311 otherwise selected appropriately?

Among the pre-specified exclusion criteria for Study 2311 was the presence of other causes of dementia, including, but not limited to, other primary neurodegenerative diseases.

However, under the protocol for Study 2311, brain imaging (i.e., computerized tomography or magnetic resonance scanning) was not required prior to entry into the study, and there is, currently, no information available through study Case Report Forms as to the proportion of patients, if any, enrolled in that study who may have undergone brain imaging as part of their screening diagnostic evaluation.

In this regard, the following may be pertinent:

- The American Academy of Neurology Practice Parameter for Dementia (see Knopman et al) recommends the use of a neuroimaging examination (either a non-contrast CT scan or MRI scan) "under most circumstances" at the time of the initial dementia assessment
- In key efficacy trials of drugs in Alzheimer's Disease, it is standard practice to perform either a CT scan of the head or MRI at screening, if not performed within the preceding 12 months
- A standard neurological examination directed at detecting focal neurological deficits is more difficult to perform in patients with Parkinson's Disease, and often considerably more difficult

In the absence of brain imaging, it may be difficult to determine to what extent patients with potential causes of dementia such as cerebrovascular lesions, tumors, subdural hematoma, and hydrocephalus may have been excluded from Study 2311.

3.4 Was the overall design of Study 2311 appropriate and were the primary efficacy measures used suitable for evaluating the efficacy

and safety of rivastigmine in mild to moderate dementia associated with Parkinson's Disease?

As outlined previously, the overall design for this study was very similar to the design of the key pre-approval efficacy trials of Exelon® in Alzheimer's Disease: the design (randomized, double-blind, placebo-controlled, and parallel-arm), duration, entry Mini-Mental Status Examination score range, cognitive and global primary efficacy measures, and criteria for determining efficacy were all virtually identical.

Whether such a design is an appropriate one for efficacy trials in dementia associated with Parkinson's Disease may need further discussion. Assuming that dementia associated with Parkinson's Disease is a distinct entity justifying a separate claim, the following may need consideration in addressing this question:

- The natural clinical course of dementia associated with Parkinson's Disease, for which information is lacking
- The nature of the cognitive deficits seen in that entity
- The appropriateness of the outcome measures used, particularly the ADAS-Cog, for dementia associated with Parkinson's Disease. The ADAS-Cog is not, for example, considered particularly useful for evaluating executive function. The validation study conducted by the sponsor (Study 2314) did not address whether the ADAS-Cog, had "content" validity in dementia associated with Parkinson's Disease, i.e., whether the components of the ADAS-Cog adequately evaluate the main cognitive domains believed to be impaired in that condition.

3.5 Do the results of Study 2311 warrant replication for a claim for the treatment of dementia associated with Parkinson's Disease to be granted?

All drugs approved by this Agency so far for the treatment of dementia of the Alzheimer's type (Alzheimer's Disease) have been approved based on the demonstration of efficacy in at least 2 adequate and well-controlled trials. This Division's view so far has been that the same principle should generally apply to other types of dementia unless they are variants or grades of severity of Alzheimer's Disease not subsumed under the current claim.

On that basis, if dementia associated with Parkinson's Disease is indeed a condition that is distinct from Alzheimer's Disease, it would seem appropriate to require that the results of the study be replicated.

3.6 Do the data presented in this application indicate that Exelon® is safe for use in this population at a dose range of 3 to 12 mg/day?

The adverse event profile of Exelon® in the study population was broadly similar to that seen in clinical trials in Alzheimer's Disease. In Study 2311, the incidence of nausea and vomiting was particularly high in the group treated with Exelon® as compared with the group treated with placebo, a finding consistent with that

seen with Exelon® in the controlled clinical trials in Alzheimer's Disease and addressed fully in the WARNINGS section of the current approved product label.

Several treatment-emergent adverse events that may have represented a worsening in the motor manifestations of Parkinson's Disease – tremor, in particular - were more frequent in those treated with Exelon® than in those treated with placebo. However, changes in Unified Parkinson's Disease Rating Scale total motor score, probably a more objective measure of change in the motor manifestations of Parkinson's Disease than the incidence of treatment-emergent adverse events, showed no meaningful difference between treatment groups.

4 Conclusion

In this memorandum, we have outlined the issues we would like the Committee to discuss in advising the Division in its review of this Supplemental New Drug Application. We are, of course, eager to hear your views not only on the issues we have identified, but on any other issue that you believe might be pertinent to the subject at hand. We look forward to seeing you and to a lively discussion at the meeting.

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