# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022568**

# SUMMARY REVIEW

**MEMORANDUM**

DATE: July 22, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-568

SUBJECT: Action Memo for NDA 22-568, for Aricept (donepezil hydrochloride extended release) 23 mg Sustained Release

NDA 22-568, for Aricept (donepezil hydrochloride extended release) 23 mg Sustained Release Tablet, was submitted by Eisai Medical Research, Inc., on 9/24/09. Aricept (immediate release tablets) is currently approved for the treatment of Alzheimer's Disease (AD); a dose of 5 mg is approved for use in patients with mild to moderate patients, and a dose of 10 mg is approved for patients with mild, moderate and severe Alzheimer's Disease. The current doses (5 and 10 mg) are approved for use once a day.

The current application proposes a 23 mg dose in the treatment of patients with moderate to severe AD. The application contains the results of a single controlled trial, Study 326, designed to establish the effectiveness of (and contribute to a finding of safety to) the product in patients with moderate to severe AD. In addition, the application contains longer-term safety data, and the requisite clinical pharmacology and chemistry information.

The application has been reviewed by Dr. Tristan Massie, statistician, Dr. Irene Chan, Division of Medication Error Prevention and Analysis (DMEPA), Dr. David Hawver, pharmacologist, Dr. Lois Freed, pharmacology supervisor, Dr. Xinning Yang, Office of Clinical Pharmacology, Dr. Hao Zhu, Pharmacometrics, Dr. Patrick Marroum, Office of New Drug Quality Assessment, Dr. Akm Khairuzzaman, chemist, Dr. Antoine El-Hage, Division of Scientific Investigations, and Dr. Ranjit Mani, medical officer. I will briefly review the relevant effectiveness and safety information, and offer the rationale for the division's action.

Effectiveness

As noted above, the sponsor has submitted the results of Study 326 to support the effectiveness of Aricept 23 mg as a treatment for patients with moderate to severe AD.

This was a multi-national, parallel group, double blind (and double dummy) trial in which patients were randomized to receive Aricept 23 mg or Aricept 10 mg once

a day, in a 2:1 pattern. The trial duration was 24 weeks, and patients must have been taking donepezil 10 mg once daily for at least three months. Patients must have had a baseline MMSE score of between 1-20, and a baseline SIB (see below) of no more than 90.

There were 2 co-primary outcome measures:

The Severe Impairment Battery (SIB), a cognitive measure used previously in the assessment of patients with severe AD. This is a multi-item instrument assessing elements of memory, language, orientation, attention, praxis, visuospatial ability, construction, and social interaction ranging from 0 (worst) to 100 (best). The SIB was to be analyzed with an ANCOVA with terms for baseline, country, and treatment.

Clinician's Interview Based Impression of Change (CIBIC-plus), in which the patient's condition is rated, with input from the caregiver, from 1 (markedly improved) to 7 (markedly worse). This was to be analyzed with a CMH test, adjusted for baseline CIBIS (Clinician's Interview Based Impression of Severity [with caregiver input] and country.

Other secondary outcome measures included the MMSE, and the ADCS-ADL.

The study was performed at 220 sites in 23 countries in Asia (including India), Oceania, Europe, North America, Africa, and South America. The following chart displays the patient flow:

| | Aricept 23 | Aricept 10 |
|---|---|---|
| Randomized | 981 | 486 |
| Completed | 685 (70%) | 399 (82%) |
| Reason for D/C | | |
| Adverse event | 182 (19%) | 39 (8%) |
| Withdrew consent | 61 (6%) | 22 (4.5%) |
| Lack of efficacy | 24 (2%) | 12 (2%) |

The following chart displays the results of the analyses of the SIB, including the protocol specified primary analysis (Change from Baseline to Week 24 for the ITT population, Last Observation Carried Forward), as well as other post hoc analyses:

Change from Baseline to Week 24, SIB

| Outcome | Aricept 23 (N) | Aricept 10 (N) | P-value |
|---|---|---|---|
| ITT, LOCF | 2.6 (907) | 0.4 (462) | 0.0001 |
| ITT, OC | 3.3 (684) | 0.9 (397) | 0.0001 |
| Concomitant Memantine | -0.2 (338) | -0.3 (163) | 0.003 |
| No Memantine | 3.1 (569) | 1.3 (299) | 0.007 |
| US Population, LOCF | 2.7 (292) | -1.2 (141) | 0.0002 |
| MMSE 3-14 | 1.1 (476) | -2.0 (256) | 0.0005 |
| MMSE 5-14 | 1.2 (436) | -1.4 (244) | 0.0034 |
| MMSE 0-16 | 1.6 (641) | -1.5 (331) | <0.0001 |

Change in Mean CIBIC+

| Outcome | Aricept 23 (N) | Aricept 10 (N) | P-value |
|---|---|---|---|
| ITT, LOCF | 4.23 (908) | 4.29 (459) | 0.18 |
| ITT, OC | 4.18 (682) | 4.28 (395) | 0.06 |
| Concomitant Memantine | 4.40 (338) | 4.52 (161) | 0.14 |
| No Memantine | 4.12 (570) | 4.16 (298) | 0.38 |
| US Population, LOCF | 4.38 (292) | 4.57 (141) | 0.03 |
| MMSE 3-14 | 4.37(478) | 4.47 (254) | 0.05 |
| MMSE 5-14 | 4.34 (438) | 4.45 (242) | 0.05 |
| MMSE 0-16 | 4.31 (642) | 4.42 (329) | 0.03 |
| MMSE 17-20 | 4.02 (340) | 3.95 (170) | 0.6 |

The following analyses of results in various sub-groups defined by baseline MMSE were done:

| | Mean Change in CIBIC+ | | |
|---|---|---|---|
| MMSE 0-16 | 4.31 | 4.42 | 0.03 |
| MMSE 0-17 | 4.29 | 4.37 | 0.07 |
| MMSE 0-18 | 4.25 | 4.33 | 0.1 |
| MMSE 0-19 | 4.23 | 4.31 | 0.1 |
| MMSE 0-20 | 4.23 | 4.29 | 0.18 |

The following results are presented for the secondary outcomes.

Mean Change From Baseline to Week 24 ADCS-ADL

| | |
|---|---|
| Aricept 23 mg | -1.2 |
| Aricept 10 mg | -1.2 |
| P-value | 0.48 |

Mean Change From Baseline to Week 24 MMSE

| | |
|---|---|
| Aricept 23 mg | 0.4 |
| Aricept 10 mg | 0.2 |
| P-value | 0.2 |

In the original protocol (dated 10/30/06), a total of 1200 patients were to have been enrolled, with an interim analysis (safety and effectiveness) performed when 400 patients had completed the study. On 5/07, a protocol amendment increased the sample size to 1600 (based on a reconsideration of power issues). A request for a Special Protocol Assessment (SPA), was submitted in 9/17/07, with included an interim effectiveness analysis, and presumably included a sample size of 1600. An amendment was submitted on 6/20/08, decreasing the sample size to 1200, and replacing the plan for an interim effectiveness analysis with a plan for an interim "futility" analysis and safety analysis. A statistical analysis plan was submitted on 3/31/09 that states that the interim analysis will be performed when 400 patients had completed the study, but that the analysis would evaluate safety only (and no mention of the futility analysis).

However, in the final study report, the sponsor noted that there had been a "late surge of enrollment…", and that by the time 400 patients had completed, all patients had been enrolled. For this reason, the sponsor considered it "inappropriate" to conduct the interim (efficacy) analysis but presumably did conduct the interim safety analysis.

Safety

There were no substantive differences between the two groups in the controlled trial in the number of deaths or patients with serious adverse events (SAEs).

The following chart displays the incidence of discontinuations due to adverse events for some selected events:

| Event | Aricept 23 | Aricept 10 |
|---|---|---|
| Vomiting | 2.9% | 0.4% |
| Nausea | 1.9% | 0.4% |
| Diarrhea | 1.7% | 0.4% |
| Dizziness | 1.1% | 0% |
| Agitation | 0.8% | 0.2% |
| Confusional state | 0.7% | 0% |
| Bradycardia | 0.7% | 0% |
| Somnolence | 0.6% | 0% |

Common Adverse Events

The following chart displays the relative incidence of certain selected adverse events:

| Event | Aricept 23 (%) | Aricept 10 (%) |
|---|---|---|
| Nausea | 11.8 | 3.4 |
| Vomiting | 9.2 | 2.5 |
| Diarrhea | 8.3 | 5.3 |
| Anorexia | 5.3 | 1.7 |
| Dizziness | 4.9 | 3.4 |
| Weight decreased | 4.7 | 2.5 |
| Urinary incontinence | 2.5 | 1.3 |
| Fatigue | 2.4 | 0.8 |
| Asthenia | 2.1 | 0.6 |
| Contusion | 2.1 | 0.2 |
| Somnolence | 2.1 | 1.1 |

Comments

The sponsor has submitted the results of a single controlled trial that they assert establishes the effectiveness of Aricept 23 mg once a day in the treatment of patients with moderate to severe AD. The protocol specified that, in order for the study to be "positive", there had to be statistically significant differences between the treatment groups on both co-primary outcomes: the SIB and CIBIC+.

There was clear statistical significance between treatments for the SIB, not only for the primary population, but for numerous sub-groups defined by concomitant medications, baseline cognitive status, etc. Dr. Massie has performed numerous additional analyses to account for the differential dropout rates between the treatment groups, and finds that under several more or less worst case scenarios, statistical significance is lost. Despite these results, in my view, the trial clearly establishes a significant effect of Aricept 23 mg on the SIB.

The results on the CIBIC+, however, though favoring the 23 mg dose numerically, clearly did not reach statistical significance (p=0.18). The sponsor has performed numerous post hoc analyses of this measure, establishing, in their view "nominal" significance in various sub-groups of patients (for example, in the Observed Cases, p=0.06; US population, p=0.03).

In particular, the sponsor has performed numerous analyses of the CIBIC+ based on sub-sets of patients defined by baseline MMSE scores; the relevant results are repeated here:

| | Mean Change in CIBIC+ | | P-value |
|---|---|---|---|
| MMSE 0-16 | 4.31 | 4.42 | 0.03 |
| MMSE 0-17 | 4.29 | 4.37 | 0.07 |
| MMSE 0-18 | 4.25 | 4.33 | 0.1 |
| MMSE 0-19 | 4.23 | 4.31 | 0.1 |
| MMSE 0-20 | 4.23 | 4.29 | 0.18 |

Although post hoc, these results, in the view of the sponsor, suggest that the drug is effective in the subset of patients with the worst MMSE scores at baseline. However, as Dr. Massie points out, other MMSE subsets do not necessarily show results consistent with this trend (for example, MMSE 0-14, p=0.16 [N=769]; MMSE 0-15, p=0.09 [N=858]). For this reason, although the p-values for the MMSE subsets presented by the sponsor appear to be monotonically increasing with increasing baseline cognitive function, I do not find

the results presented by the sponsor in particular MMSE subsets identified retrospectively to be particularly compelling.

What of the results in the US?

The US contributed 32% of the total patients in the study, and the results here were nominally statistically significant on both the SIB and CIBIC+. However, Dr. Massie has noted that, in the US patients, the baseline SIB was about 3.5 points higher in the 10 mg group compared to the 23 mg group (p=0.07). Also, compared to patients outside the US, there was much greater use of memantine in the US (75% vs 19%), and baseline severity of the patients was better than outside the US (CIBIS+ 4.49 US vs 4.37 non-US, p=0.02). Dr. Massie also performed additional analyses for the US subset, including several worst case analyses; in these, statistical significance is lost.

Regarding Dr. Massie's additional analyses of the US data (although acknowledging that all of these analyses are post hoc), I am less concerned about the differences between US and non-US patients, and how these may affect the analyses, for the simple reason that we are most concerned, in essence, about how the drug would perform in this country. To this extent, (again, putting aside the post hoc nature of the findings), clearly the results in the US study population are likely to be most representative of how the drug would perform in the US. Given this point of view, the one finding of a difference between the two study groups in the US would take on the most importance; that is, the finding that at baseline, in the US, that the patients in the 10 mg group has somewhat less severe disease (at least as assessed by the CIBIS+). How this affected the outcome in the US I do not know (one could argue that the US finding is more compelling given this baseline difference). For these reasons, I find the results in the US interesting, if not entirely persuasive (in particular, the post hoc nature of the finding is, of course, of concern).

The primary question, I believe, is what is the meaning of the lack of difference between the treatment groups on the CIBIC+.

As both Drs. Massie and Mani point out, it is difficult, if not impossible, to conclude much about the effect of the 23 mg dose on the patients' overall functioning based on the comparison between it and the 10 mg dose group in this study. Not only was there no statistical significance between the treatments on the primary measure of overall functioning, but there was a clear lack of significance on another accepted measure of functioning, the ADCS-ADL. As Dr. Massie also notes, previous placebo controlled trials of Aricept 10 mg did not show a consistent effect on the CIBIC+. This observation makes it essentially impossible to conclude that this study demonstrated an effect of the 23 mg on the CIBIC+ based on a non-inferiority argument (as far as I know, the sponsor did not attempt to make such an argument). Therefore, I believe it is reasonable to

conclude that the result in this study does not **directly** permit a conclusion about the effect of the 23 mg dose on the CIBIC+.

However, can the study still be interpreted to mean that the 23 mg dose is effective?

This is not a simple question. Clearly, it has an effect on the SIB. Indeed, this study demonstrates that the 23 mg dose is superior to the 10 mg dose, at least on a measure of cognitive function.

The critical question is how to interpret the absence of a difference on the measures of global functioning.

In this study, either the 10 mg dose had an effect on overall functioning, or it did not; in the absence of a placebo group, we cannot tell. If it did have an effect on overall functioning, then it would be reasonable, in my view, to conclude that the 23 mg dose did so as well (although, again, we cannot perform a formal non-inferiority test, the 23 mg dose was numerically superior to the 10 mg dose in this study).

If the 10 mg dose did not have an effect on overall functioning in this study, then we have no direct evidence that the 23 mg dose did either (although, again, it was numerically superior to the 10 mg dose). However, we do know that, in general, the 10 mg dose does have an effect on overall functioning (after all, it was approved on the basis of it's having demonstrated this effect in several studies). So, we would consider this study as not having assay sensitivity for this measure for the 10 mg dose, and we would have to conclude the same for the 23 mg dose.

But the 23 mg dose is clearly superior to the 10 mg dose on the cognitive measure. In my view, this strongly argues for a conclusion that the 23 mg dose is very likely to also have an effect on overall functioning, despite this not having been demonstrated directly in this study. That is, there is clearly no evidence that the 23 mg dose should be considered worse (in reality) than the 10 mg dose on overall functioning (I am not convinced that the increased number of dropouts in this group, and particularly the increased incidence of adverse events should be considered to undermine any conclusions about the effect on overall functioning of the 23 mg dose; the measure of overall functioning is largely designed to assess whether the cognitive effects of the drug translate into improved functioning, not whether the "sum" of positive cognitive and "negative" adverse reactions is in the aggregate positive or negative), and the clear superiority on the cognitive measure argues, in my view, for a conclusion that the 23 mg dose group is likely at least as effective on overall functioning as the 10 mg dose.

(b) (4) as noted, I also believe the results do not support a conclusion that the 23 mg dose group offers a greater benefit on overall functioning than the 10 mg dose.

Given these conclusions, should the 23 mg dose be approved?

In this regard, I would note the findings in the US population, as well as the numerical superiority of the 23 mg dose compared to the 10 mg dose on various (admittedly post hoc) analyses of the CIBIC+. I agree, of course, that the analysis of the US patients, like many others, is post hoc, and it is difficult to know how to interpret the nominally significant p-value. However, I am not particularly persuaded by the p-value per se, but, again, I do believe that the observation is somewhat intriguing, especially given that there is at least a question about how AD may be diagnosed in some of the countries that participated in this study (we do not have extensive experience, for example, with studies of AD patients in some of these areas, including several of the Eastern European and Asian countries included).

For these reasons, I conclude that the effectiveness data support the conclusion that the 23 mg dose can offer some benefit to patients above that conferred by the 10 mg dose.

(b) (4)


Regarding safety, there is a clear increase in the incidence of adverse events on the 23 mg dose compared to the 10 mg dose, especially in the incidence of nausea, vomiting, diarrhea, anorexia, and possibly fatigue. These are not trivial events; in these patients, these could lead to significant morbidities and even increased mortality. These are of particular concern, given that these patients had all been receiving treatment with 10 mg once a day for at least three months. That is, even though they had been tolerating (more or less) a dose of 10 mg, the increase to 23 mg was clearly accompanied by a significant increase in the incidence of these events.

Does the absence of a demonstration of any superiority of the 23 mg dose to the 10 mg dose on measures of overall functioning, coupled with the increased incidence of potentially significant adverse events, argue against the approval of this product?

As noted above, I do believe there is some evidence suggesting that the 23 mg dose may be superior to the 10 mg dose on measures of overall functioning (and there is clearly superiority on the cognitive measure, albeit numerically small). For these reasons, I believe that the 23 mg dose might be useful in patients who do not respond adequately to the 10 mg dose, although I believe labeling should make explicitly clear that this dose is associated with a significant increase in the incidence of adverse events that can have significant clinical sequelae.

I recognize that Drs. Mani and Massie have expressed reservations about approving the 23 mg formulation, but, for the reasons discussed above, I disagree.

Non-clinical

Dr. Hawver notes that an article published in the literature describes a combination study of donepezil and memantine in rats that demonstrated significantly increased neurotoxicity compared to that induced by memantine

itself. For this reason, he recommends that an additional combination study be performed in Phase 4. I agree that such a study should be performed, and that it should be considered a Post-Marketing Requirement (PMR).

Clinical Pharmacology

The sponsor submitted this application for the 23 mg dose to be considered a modified release formulation. However, despite the formulation having some manufacturing aspects designed to produce a modified release preparation, the product's in vivo performance does not establish it as such a formulation (for instance, it is not given less frequently than the currently available immediate release formulations). Indeed, the plasma levels achieved with the 23 mg tablet are about twice those achieved with the 10 mg tablet. In other words, in our view, the new formulation is rightly seen simply as an increased dosage.

Dr. Yang notes that the potential for donepezil to inhibit CYP2B6, 2C8, and 2C19 has not been adequately addressed, and recommends that studies to examine this should be done in Phase 4. Similarly, Dr. Yang notes that whether or not donepezil is a substrate for p-glycoprotein has not been adequately characterized, and she therefore recommends that a study examining this question should also be done in Phase 4. I agree, and these studies should be PMRs.

DMEPA

Dr. Chan has recommended several changes to the carton and container labels, several of which the sponsor has made, and several of which they have committed to making shortly after the drug is approved. She finds this acceptable, as do I.

Conclusion

For the reasons given above, I believe that the sponsor has demonstrated that the 23 mg dose of Aricept is effective, and that there is sufficient reason to believe that it may produce an increased benefit compared to the 10 mg dose in some patients. For these reasons, then, I will approve this application, with the agreed upon labeling, and with the PMRs discussed above imposed.

Russell Katz, M.D.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22568 | ORIG-1 | EISAI MEDICAL RESEARCH INC | DONEPEZIL HYDROCHLORIDE |

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/s/

RUSSELL G KATZ
07/23/2010