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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-720

Medical Review(s)

Review and Evaluation of Clinical Data

NDA (Serial Number)	21720 (000)
Sponsor:	Eisai
Drug:	Donepezil
Proposed Indication:	Alzheimer's Disease
Material Submitted:	Original New Drug Application
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Reviewer:	Ranjit B. Mani, M.D.

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EXECUTIVE SUMMARY

Recommendations

I recommend that this application be approved

Proposed Indication

This application seeks the approval of an orally disintegrating tablet formulation of Aricept® for the treatment of mild to moderate dementia of the Alzheimer's type

Aricept® is currently approved as a standard tablet formulation (5 mg and 10 mg) for the treatment of mild to moderate dementia of the Alzheimer's type

Clinical Studies Supporting This Application

The two key studies supporting this application are

- A single-dose bioequivalence study (E2020-A001-015) comparing 10 mg of the orally disintegrating tablet formulation with the 10 mg approved tablet
- A single-dose bioequivalence study (E2020-A001-016) comparing 5 mg of the orally disintegrating tablet formulation with the 5 mg approved tablet

The above studies enrolled healthy male and female subjects whose ages ranged from 18 to 45 years. A total of 42 subjects were enrolled in the 2 studies.

Additional studies that were intended to support the safety of the orally disintegrating tablet formulation included the following

- A single-dose bioequivalence study (E2020-E044-017) which compared 5 mg of an orally disintegrating tablet formulation with 5 mg of the standard tablet formulation, and 10 mg of an orally disintegrating tablet formulation with 10 mg of the standard tablet formulation. This study enrolled 46 healthy male and female subjects whose ages ranged from 18 to 45 years
- A single-dose study (E2020-J081-007) which evaluated the pharmacokinetics of a 5 mg orally disintegrating tablet formulation administered without water. This study enrolled 6 healthy male subjects, aged 20 to 35 years
- A single-dose study (E2020-J081-008) which evaluated the pharmacokinetics of a 3 mg orally disintegrating tablet formulation administered with and without water, and a 3 mg film-coated tablet administered with water. This study enrolled 14 healthy male subjects, aged 20 to 35 years
- A single-dose study (E2020-J081-009) which evaluated the pharmacokinetics of a 5 mg orally disintegrating tablet formulation administered with and without water, and a 5 mg film-coated tablet administered with water. This study enrolled 12 healthy male subjects, aged 20 to 35 years

Safety Data From Clinical Pharmacology Studies In This Application

Safety monitoring in the above studies included the assessment of adverse events, vital signs, electrocardiograms, physical examinations and safety laboratory tests at appropriate intervals

Safety data from the studies in this application revealed no items of concern and the following

- No deaths or serious adverse events occurred
- Adverse events that merited discontinuation from the study were vomiting, influenza-like symptoms with conjunctivitis, dizziness, and a fall.
- The spectrum of adverse events seen in these studies was broadly similar to those previously noted in subjects administered Aricept®
- Vital signs, safety laboratory tests, electrocardiograms, and physical examination results were unremarkable

Clinical Pharmacology And Biopharmaceutics Review

The Clinical Pharmacology and Biopharmaceutics reviewer of this application has concluded that the 5 mg and 10 mg orally disintegrating tablet formulations of donepezil, are bioequivalent to the currently marketed 5 and 10 mg tablets of Aricept®, respectively.

Chemistry Review

The Chemistry reviewer of this submission has concluded that

- Sufficient data has been provided to establish the reproducibility of the manufacturing process and the purity and stability of the drug product
- The application is approvable, pending a change in the name of the drug product from "Aricept® Rapidly Disintegrating Tablets" to "Aricept® Orally Disintegrating Tablets"

Labeling

The name of this formulation as originally proposed by the sponsor is Aricept® RDT (donepezil hydrochloride rapidly disintegrating tablets). That proprietary name has been changed at the instance of the Agency to Aricept® ODT (donepezil hydrochloride orally disintegrating tablets)

The blister, pouch, and carton labels for the drug product were modified in accordance with the recommendations of this Division

Agreement has been reached with the sponsor on the contents of the package insert for this application.

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1. Background

This submission is an original New Drug Application for a rapidly disintegrating tablet formulation (5 mg and 10 mg) of donepezil hydrochloride (Aricept®). The product name for this formulation, as used in this submission, is Aricept® RDT (donepezil hydrochloride rapidly disintegrating tablets) 5 mg and 10 mg.

Another original New Drug Application (#21719) for a formulation designated as Aricept® C (donepezil hydrochloride oral solution) 1 mg/mL has been submitted and reviewed concurrently.

Donepezil (Aricept®) is a cholinesterase inhibitor approved in this country on November 25, 1996, in a tablet formulation, for the treatment of mild to moderate dementia of the Alzheimer's type.

2. Contents Of Submission

This application is in standard NDA format and is contained in 20 volumes. Key elements in this application are the following

- Proposed new labeling
- Chemistry, manufacturing, and controls data for the oral solution formulation of donepezil
- Reports of 2 pharmacokinetic studies
 - E2020-A001-015 (a bioequivalence/bioavailability study comparing the 10 mg rapidly disintegrating tablet formulation to a reference tablet formulation of donepezil)
 - E2020-A001-016 (a bioequivalence/bioavailability study comparing the 5 mg rapidly disintegrating tablet formulation to a reference tablet formulation of donepezil)
- Safety data from additional pharmacokinetic studies: E2020-E044-019, E2020-J081-007, E2020-J081-008, and E2020-J081-009

3. Contents Of Review

This review will be limited to the following in the same order as below

- Relevant regulatory history
- Outline of clinical studies

- Sponsor's proposed changes to labeling
- Safety data from clinical studies
- Clinical Pharmacology and Biopharmaceutics review
- Chemistry, Manufacturing, and Controls review
- Nomenclature of formulation
- Site inspections
- Financial disclosure information

4. Relevant Regulatory History

In a letter dated September 19, 2000, the sponsor sought the advice of the Division regarding a proposal for the development of this formulation.

The following is a summary of the key items contained in the Division's reply, dated October 27, 2000

- A bioequivalence study comparing the 10 mg rapidly disintegrating tablet formulation with the standard 10 mg tablet formulation is appropriate. A bio-waiver may be requested for the 5 mg tablet if the two strengths are proportional in composition
- A food effect study is not required for the rapidly disintegrating tablet formulation
- Complete dissolution performance data should be provide for the 10 mg rapidly disintegrating tablet (bio-batch) and the 5 mg rapidly disintegrating tablet and between the 1/10 scale rapidly disintegrating tablet pilot plant batches and batches produced at the selected commercial site
- The sponsor had proposed, as primary data for NDA approval, providing 6-month accelerated and 12-month long term stability data on 3 pilot scale batches of each strength proposed, that were produced at the pilot plant. The Division indicated that the addition of commercial site-specific data with [] accelerated and available long-term data on 3 batches of each strength (as also proposed by the sponsor) should be sufficient for NDA filing.

Study	E2020-A001-015	E2020-A001-016
	(bioavailability) and safety	(bioavailability) and safety
Design	Randomized, open-label, single-dose, 2-sequence, 2-period cross-over study	Randomized, open-label, single-dose, 2-sequence, 2-period cross-over study
Study Population	Healthy male and female subjects, aged 18 to 45 years	Healthy male and female subjects, aged 18 to 45 years
Sample Size	22 subjects (20 completed study)	20 subjects
Dose*	10 mg of test formulation 10 mg of reference formulation	5 mg of test formulation 5 mg of reference formulation
Pharmacokinetic Outcome Measures	Plasma levels of donepezil	Plasma levels of donepezil
Safety Outcome Measures	Adverse events, pulse, blood pressure, safety laboratory tests, electrocardiograms, physical examinations	Adverse events, pulse, blood pressure, safety laboratory tests, electrocardiograms, physical examinations

The test formulation was the rapidly disintegrating tablet of donepezil
 The reference formulation was the currently marketed Aricept® tablet formulation
 * A minimum 14 day washout periods intervened between doses

The schedule for safety monitoring in each of these studies is summarized below as it applies to each dosing period [all parameters below were assessed at screening as well]

Study	E2020-A001-015	E2020-A001-016
Adverse Events	Continually up to 240 hours post-dose	Continually up to 240 hours post-dose
Sitting Pulse And Blood Pressure	Baseline, pre-dose, and 1, 2, 4, 8, 12, 24, and 240 hours post-dose	Baseline and 1, 2, 4, 8, 12, 24, and 240 hours post-dose
Electrocardiograms	Baseline and 240 hours post-dose	Baseline and 240 hours post-dose
Safety Laboratory Tests*	Baseline and 240 hours post-dose	Baseline and 240 hours post-dose
Physical Examinations	Baseline and 240 hours post-dose	Baseline and 240 hours post-dose

*Hematology, clinical chemistry, urinalysis
 Baseline assessments of sitting pulse and blood pressure, electrocardiograms, safety laboratory tests, and baseline physical examinations were done the day prior to dosing

6.2 Additional Pharmacokinetic Studies

Additional pharmacokinetic studies were conducted in the United Kingdom and Japan. These studies are summarized separately

6.2.1 United Kingdom Study

This study is summarized in the following table

Study	E2020-E044-017
Objective	Evaluation of pharmacokinetics (bioequivalence) and safety
Design	Randomized, open-label, single-dose, 2-sequence, 2-period cross-over study
Study Population	Healthy male and female subjects, aged 18 to 45 years
Sample Size	46 subjects completed study (51 were enrolled)

Study	E2020-E044-017
	Group 1 (5 mg): 22 subjects Group 2 (10 mg): 24 subjects
Dose*	Group 1: 5 mg rapid-disintegration tablet and 5 mg marketed tablet Group 2: 10 mg rapid-disintegration tablet and 10 mg marketed tablet
Pharmacokinetic Outcome Measures	Plasma levels of donepezil
Safety Outcome Measures	Adverse events, vital signs, safety laboratory tests, electrocardiograms, physical examinations

*21 day washout period intervened between doses

The schedule for safety monitoring for this study is summarized below as it applies to each dosing period [all parameters below were assessed at screening as well]

Study	E2020-E044-019
Adverse Events	Continually up to 240 hours post-dose
Semi-Recumbent Pulse And Blood Pressure	Baseline, pre-dose and 1, 2, 4, 8, 12, 24, and 240 hours post-dose
Electrocardiograms	Baseline and 240 hours post-dose
Safety Laboratory Tests*	Pre-dose and 240 hours post-dose
Physical Examinations	Pre-dose and 240 hours post-dose

*Hematology, clinical chemistry, urinalysis

Baseline assessments of sitting pulse and blood pressure and electrocardiograms were done the day prior to dosing

6.2.2 Japanese Studies

These studies are summarized in the following table

Study	E2020-J081-007	E2020-J081-008	E2020-J081-009
Objective	Evaluation of pharmacokinetics and safety	Evaluation of pharmacokinetics (bioequivalence) and safety	Evaluation of pharmacokinetics (bioequivalence) and safety
Design	Open-label, single-dose, single-period study (Absorption study)	Open-label, single-dose, 3-period crossover study	Open-label, single-dose, 3-period crossover study
Study Population	Healthy male subjects, aged 20 to 35 years	Healthy male subjects, aged 20 to 35 years	Healthy male subjects, aged 20 to 35 years
Sample Size	6 subjects	14 subjects	12 subjects
Dose	5 mg rapidly disintegrating tablet (without water)	2 x 3 mg rapidly disintegrating tablets without water 2 x 3 mg rapidly disintegrating tablets with water 2 x 3 mg film-coated tablet with water	2 x 5 mg rapidly disintegrating tablets without water 2 x 5 mg rapidly disintegrating tablets with water 2 x 5 mg film-coated tablet with water
Pharmacokinetic Outcome Measures	Plasma levels of donepezil	Plasma levels of donepezil	Plasma levels of donepezil
Safety Outcome Measures	Adverse events, safety laboratory tests, vital signs (?)	Adverse events, safety laboratory tests, vital signs, physical examinations	Adverse events, safety laboratory tests, vital signs, physical examinations

The schedule for safety monitoring in these studies has not been provided. Protocol synopses alone have been submitted.

7. Safety Data From Study E2020-A001-015

7.1 Disposition

22 subjects were enrolled in the study, of whom 20 completed both dosing periods. 2 subjects discontinued prematurely on account of vomiting after being exposed to a single dose of the drug

7.2 Deaths And Other Serious Adverse Events

There were no deaths or other serious adverse events

7.3 Discontinuations Due To Adverse Events

2 subjects discontinued the study on account of vomiting, one after being dosed with the 10 mg test formulation, and one after being dosed with the 10 mg reference formulation.

7.4 All Adverse Events

The incidence of individual adverse events is summarized by treatment that they occurred in relation to in the following table

	Test n (%)	Reference n (%)
Total number of subjects	21 (100)	21 (100)
Number of subjects with any adverse event	14 (66.7)	11 (52.4)
INDIVIDUAL ADVERSE EVENTS		
Headache	3 (14.3)	4 (19.0)
Viral infection	1 (4.8)	0 (0.0)
Anorexia	1 (4.8)	0 (0.0)
Constipation	2 (9.5)	1 (4.8)
Dyspepsia	0 (0.0)	1 (4.8)
Flatulence	0 (0.0)	1 (4.8)
Nausea	5 (23.8)	2 (9.5)
Rectal disorder	0 (0.0)	1 (4.8)
Vomiting	2 (9.6)	1 (4.8)
Arthralgia	1 (4.8)	1 (4.8)
Myasthenia	0 (0.0)	1 (4.8)
Dizziness	2 (9.5)	2 (9.5)
Insomnia	3 (14.3)	1 (4.8)
Hiccup	0 (0.0)	1 (4.8)
Polyuria	1 (4.8)	0 (0.0)
Urinary tract infection	1 (4.8)	0 (0.0)

The majority of adverse events were mild to moderate in severity. Only a single adverse event – vomiting – was considered severe. Note that the overall incidence of adverse events, and the incidence of nausea in particular, was higher in the reference formulation than in the test formulation.

7.5 Safety Laboratory Tests

There were no noteworthy changes in laboratory values during the study.

7.6 Vital Signs

There were no vital sign measurements that were of concern, except for a single blood pressure reading of 80/70 mmHg in a subject 240 hours after receiving the reference formulation

7.7 Electrocardiograms

There were no electrocardiogram abnormalities of clinical significance after either treatment

7.8 Physical Examinations

No subject had an improvement or worsening in physical examination compared with baseline after either treatment

8. Safety Data From Study E2020-A001-016

8.1 Disposition

20 subjects were enrolled in the study; all completed both treatment periods

8.2 Deaths And Other Serious Adverse Events

There were no deaths or serious adverse events during this study

8.3 Discontinuations Due To Adverse Events

There were no discontinuations due to adverse events during this study

8.4 All Adverse Events

The incidence of individual adverse events is summarized by treatment that they occurred in relation to in the following table

	Test n (%)	Reference n (%)
Total number of subjects	20 (100)	20 (100)
Number of subjects with any adverse event	5 (25.0)	7 (35.0)
INDIVIDUAL ADVERSE EVENTS		
Abdominal pain	0 (0.0)	1 (5.0)
Back pain	1 (5.0)	0 (0.0)
Headache	2 (10.0)	0 (0.0)
Viral infection	1 (5.0)	0 (0.0)
Syncope	1 (5.0)	0 (0.0)
Anorexia	0 (0.0)	1 (5.0)
Nausea	2 (10.0)	0 (0.0)
Dizziness	1 (5.0)	1 (5.0)
Insomnia	0 (0.0)	1 (5.0)
Somnolence	1 (5.0)	3 (15.0)

	Test n (%)	Reference n (%)
Twitching	0 (0.0)	1 (5.0)

All adverse events were mild and their incidence low

8.5 Safety Laboratory Tests

The only noteworthy laboratory abnormality was a creatine kinase of 385 IU/L in a single subject 240 hours after receiving the reference formulation

8.6 Vital Signs

There were no notable differences in vital signs measurements between formulations

8.7 Electrocardiograms

No subject had any electrocardiogram abnormality that was considered clinically significant

8.8 Physical Examinations

No subject had an improvement or worsening in physical examination compared with baseline after either treatment

9. Safety Data From Additional Studies

9.1.1 Study E2020-E044-019

9.1.1.1 Disposition

- 51 subjects were enrolled in the study; 23 were in the 5 mg group and 28 were in the 10 mg
- 46 subjects completed the study: 22 were in the 5 mg group and 24 were in the 10 mg group [all these subjects received both doses of medication]
- 5 subjects were withdrawn from the study, all on account of adverse events

9.1.1.2 Deaths And Other Serious Adverse Events

There were no deaths or other serious adverse events

9.1.1.3 Discontinuations Due To Adverse Events

These are summarized below

- 1 subject developed influenza-like symptoms and conjunctivitis, and fell during an episode of dizziness, all after receiving the 5 mg rapidly-disintegrating tablet
- 2 subjects developed vomiting after receiving the 10 mg reference tablet
- 2 subjects developed vomiting after receiving the 10 mg rapidly-disintegrating tablet

9.1.1.4 All Adverse Events

The number of patients with the most common individual adverse events (headache, nausea, and dizziness/lightheadedness) is summarized by treatment that they occurred in relation to, in the following table.

	5 mg standard tablet	5 mg rapidly disintegrating tablet	10 mg standard tablet	10 mg rapidly disintegrating tablet
	n	n	n	n
Total number of subjects	22	22	24	24
INDIVIDUAL ADVERSE EVENTS				
Headache	5	6	3	6
Lightheadedness/dizziness	5	1	3	4
Nausea	0	1	4	4

The incidence of other adverse events, including vomiting, diarrhea, and increased perspiration, was lower than those displayed in the above table. Vomiting occurred in 2 subjects after the 10 mg standard dose and in 2 subjects after receiving the 10 mg rapidly disintegrating tablet; diarrhea occurred in 3 subjects who received the rapidly disintegrating tablet. Apart from vomiting in 2 patients and diarrhea in 1 patient, all other adverse events were mild to moderate in severity

9.1.1.5 Safety Laboratory Tests

The following were noteworthy, all in relation to creatine kinase

- A subject had an elevated creatine kinase to a peak of 2106 IU/L immediately prior to receiving the 5 mg rapidly disintegrating tablet (Dosing Period 2), and after normal screening, pre-dose, and 240 hour post-dose values after receiving the standard 5 mg tablet during Dosing Period 1. The 240 hour post-dose value during Dosing Period 2 was 214 IU/L
- A subject had an elevated creatine kinase of 378 IU/L 240 hours after receiving the 10 mg rapidly disintegrating tablet during Dosing Period 1. This test was normal at other timepoints
- A subject had an elevated creatine kinase of 356 IU/L 240 hours after receiving the 10 mg standard tablet during Dosing Period 1, which peaked at 659 IU/L immediately pre-dose during Dosing Period 2. This test was normal at other timepoints

- A subject had an elevated creatine kinase of 306 IU/L 240 hours after receiving the 10 mg rapidly disintegrating tablet during Dosing Period 1. This test was normal at other timepoints
- A subject who received the 5 mg rapidly disintegrating tablet followed by the 5 mg standard tablet, had respective 240-hour post-dose values of 252 IU/L and 318 IU/L, with normal values at other timepoints

9.1.1.6 *Vital Signs*

All vital signs were within an acceptable range, according to the sponsor

9.1.1.7 *Electrocardiograms*

All 12-lead electrocardiograms were reported to be normal, according to the sponsor

9.1.1.8 *Physical Examinations*

There were no abnormalities of significance

9.1.2 *Study E2020-J081-007*

The study synopsis states that "no clinically meaningful adverse reactions, abnormal laboratory values, or physiological findings were observed in this study

9.1.3 *Study E2020-J081-008*

The study synopsis states the following:

- 2 subjects who received the rapidly disintegrating tablet with water developed headache
- 2 subjects who received the film-coated tablet with water developed diarrhea
- 1 subject who received the film-coated tablet with water developed headache and abdominal pain

All the above adverse events were mild

9.1.4 *Study E2020-J081-009*

The study synopsis states the following:

- 1 subject who received the rapidly disintegrating tablet without water developed a running nose

- 1 subject who received the film-coated tablet with water developed diarrhea and raised GGT
- 1 subject who received the rapidly disintegrating tablet with water developed diarrhea, pain, and an elevated creatine kinase

All the above adverse events were mild

10. Clinical Pharmacology And Biopharmaceutics Review

The following summary is derived from the Clinical Pharmacology and Biopharmaceutics review of this submission by Robert Kumi, PhD. I will summarize the contents of his review under the following headings

10.1 Summary Of Pharmacokinetic Data

The following tables taken from Dr Kumi's review summarize the key pharmacokinetic findings for Studies E2020-A001-015 and E2020-A001-016

Donepezil Mean ± SE Pharmacokinetic Measures in Studies E2020-A001-015 and E2020-A001-016

Pharmacokinetic Measure	10 mg donepezil hydrochloride single dose (n = 18)	
	Study 015: 10 mg ODT (Test)	Study 015: 10 mg Aricept Tablet (Reference)
AUC ₀₋₂₄₀ (ng·h/mL)	615 ± 57	647 ± 66
C _{max} (ng/mL)	17.7 ± 1.0	17.3 ± 0.8
T _{max} ^s (h)	3.11 ± 0.18	3.33 ± 0.31
Half-life (h)	61.6 ± 3.8	64.4 ± 5.1
Pharmacokinetic Measure	Single Dose Treatments 5 mg donepezil Formulations	
	Study 016: 5 mg ODT (Test)	Study 016: 5 mg Aricept Tablet (Reference)
AUC ₀₋₂₄₀ (ng·h/mL)	273 ± 18	272 ± 18
C _{max} (ng/mL)	7.1 ± 0.3	7.3 ± 0.4
T _{max} ^s (h)	3.2 ± 0.2	3.3 ± 0.2
Half-life (h)	61.3 ± 4.5	62.4 ± 3.8

Donepezil HCl Bioequivalence Evaluations (ODT vs. Aricept) in Studies E2020-A001-015 and E2020-A001-016

Pharmacokinetic Measure	Ninety Percent (90 %) Confidence Intervals (CI) for the Ratio (ODT/tablet) of Log Transformed Mean donepezil AUC and C _{max} (10 mg dose)
C _{max} (ng/mL)	100.30 – 107.40
AUC ₀₋₂₄₀ (ng·h/mL)	93.79 – 103.54
Pharmacokinetic Measure	Ninety Percent (90 %) Confidence Intervals (CI) for the Ratio (ODT/tablet) of Log Transformed Mean donepezil AUC and C _{max} (5 mg dose)
C _{max} (ng/mL)	93.95 – 105.76
AUC ₀₋₂₄₀ (ng·h/mL)	92.65 – 104.81

10.2 Key Conclusions

- The 5 mg donepezil hydrochloride orally disintegrating tablet is bioequivalent to the 5 mg Aricept® tablet that is currently marketed
- The 10 mg donepezil hydrochloride orally disintegrating tablet is bioequivalent to the 10 mg Aricept® tablet that is currently marketed
- Donepezil hydrochloride exposure increases dose-proportionally from the 5 mg to the 10 mg dose and $t_{1/2}$ as well as T_{max} were comparable at the 5 mg and 10 mg dose levels
- Dissolution data has been provided supporting a dissolution specification for the donepezil orally disintegrating tablet, and a manufacturing site change
- **Overall, the clinical pharmacology and biopharmaceutics information provided in NDA 21-720 is acceptable provided that satisfactory agreement is reached between the applicant and the Agency regarding labeling language, there is a satisfactory outcome to an inspection by the Division of Scientific Investigations, and the applicant adequately addresses certain specific comments**

10.3 Comments To Sponsor

Dr Kumi has recommended that the following comments be conveyed to the sponsor

- The dissolution specification should be changed to $Q = []$ in 20 minutes. In the absence of adequate stability data this specification could be used as an interim specification. Upon completion of adequate stability studies a final dissolution specification should be established and submitted for review. Please provide this information within 18 months from the date of the action letter.
- Please merge the labels for donepezil hydrochloride (Aricept®) tablets, orally disintegrating tablets and [] into one label or provide justification for not merging the labels. In addition, please review the labeling changes made to the Clinical Pharmacokinetics Section; the changes are related to bioequivalence and food effect information.
- Please note that the FDA does not accept the Rapidly Disintegrating Tablet terminology because we consider the term to be potentially misleading. We refer to these tablets as orally disintegrating tablets (ODT); please modify the name of these new tablets in the application as needed.

10.4 Recommended Changes To Labeling

Note that Dr Kumi has recommended that information for all formulations of donepezil should be in a single label. The changes in language that he has recommended are intended to facilitate the creation of a single label, and apply to the common labeling that he has proposed for all formulations of Aricept®.

10.4.1 CLINICAL PHARMACOLOGY/Clinical Pharmacokinetics

In this section, Dr Kumi has

- Provided bioequivalence information for the orally disintegrating tablet (and \mathcal{L} \mathcal{T}) formulations
- Included a statement that while a food effect study was not conducted with the orally disintegrating tablet, such an effect was unlikely to be clinically significant

Detailed recommended changes to this section, edited by me to a minor extent, are below. The background document is the sponsor's proposed labeling.

Clinical Pharmacokinetics

ARICEPT® \mathcal{L} \mathcal{T} and ARICEPT® ODT are bioequivalent to ARICEPT®.
Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning vs. evening dose) influences the rate or extent of absorption. A food effect study has not been conducted with ARICEPT® ODT; however, the effect of food with ARICEPT® ODT is expected to be minimal. ARICEPT® and ARICEPT® ODT can be taken without regard to meals. \mathcal{L}

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The elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The steady state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly

to albumins (about 75%) and alpha₁ - acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.

10.5 DOSAGE AND ADMINISTRATION

Detailed recommended changes to this section are below

DOSAGE AND ADMINISTRATION

The dosages of ARICEPT[®] shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT[®] might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

ARICEPT[®], ARICEPT[®] ODT, and ARICEPT[®] [] should be taken in the evening, just prior to retiring. Allow ARICEPT[®] ODT tablet to dissolve on the tongue and follow with water.

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Deleted: ARICEPT[®] can be taken with or without food. ¶

Deleted: RDT

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ARICEPT[®], ARICEPT[®] ODT, and ARICEPT[®] [] can be taken with or without food.

11. Chemistry Review

The Chemistry review of this application has been completed by Dr Janusz Rzeszotarski , in 2 separate documents with review dates of 7/12/04 and 9/27/04

Dr Rzeszotarski's conclusions in his main review (completed 7/12/04) are as follows

- Sufficient data has been provided to establish the reproducibility of the manufacturing process and the purity and stability of the drug product
- The application is approvable, pending the following
 - Completion of establishment inspections
 - A change in the name of the drug product from "Aricept® Rapidly Disintegrating Tablets" to "Aricept® Orally Disintegrating Tablets"

Dr Rzeszotarski's second review (completed 9/27/04) confirmed that, based on a report from the Office of Compliance, all establishment inspections were acceptable. In the interim (9/3/04), the sponsor had proposed that the new formulation be designated Aricept® [] (donepezil hydrochloride rapidly disintegrating tablets) in response to an earlier Divisional communication; Dr Rzeszotarski did not find that name acceptable and recommended once again that the application be designated approvable pending resolution of the proprietary name issue.

12. Nomenclature Of Formulation And Related Matters

The sponsor's proposed name of the new formulation proposed under this application is Aricept® RDT.

A letter from the Division to the sponsor, dated 7/2/04, responded to the proposed nomenclature for the new formulation. The key text of this letter is reproduced verbatim below.

Our reviews of the Nomenclature proposal by this Division and the Division of Medication Errors and Technical Support (DMETS) are complete. We have identified the following deficiencies.

1. The proposed name Aricept RDT (donepezil hydrochloride rapidly disintegrating tablets) is not acceptable. As an alternative, it would be acceptable to change the name to Aricept ODT (donepezil hydrochloride orally disintegrating tablets).
2. DMETS has recommended the implementation of the following label revisions in order to minimize potential errors with the use of the product.

GENERAL COMMENT

1. In order to minimize confusion between dosage forms, please ensure that the unit-dose packaging of Aricept RDT is different from the unit-dose packaging of Aricept.

2. The color for both the 5 mg and 10 mg blister is the same. Consider implementing a method to distinguish between two strengths, i.e. contrasting color, boxing or other method to provide differentiation. Revise accordingly.

BLISTER LABEL (5 mg and 10 mg)

1. See General Comments.

2. Revise the label to read "tablet" rather than "tablets", since only one tablet is contained in each blister.

POUCH LABEL (5 mg and 10 mg)

1. See General Comments.

2. We note that the Aricept RDT blisters are packaged in a pouch. If this is for stability, it is unlikely that the blisters will remain in the pouch, particularly in an in-patient setting where medications are delivered to the nursing units in unit-dose packaging. Additionally, there are no directions to the patient/health care practitioner that indicate that the product must remain in the pouch. Please elaborate.

3. Decrease the prominence of the manufacturing and marketing information.

CARTON LABELING (5 mg and 10 mg)

1. See General Comments.

2. We note that this carton containing 30 tablets appears to be "Unit-of-Use" packaging. Please indicate whether the carton is child-resistant.

Based on the above recommendations please submit revised carton and container labels (black & white are acceptable).

13. Site Inspection

Both the clinical and analytical aspects of Study E2020-A001-015 were audited by the Division of Scientific Investigations. The report by Michael F. Skelly, PhD, of that Division, dated August 30, 2004, recommends that data from this study may be considered for Agency review. Please see his report for further details.

14. Financial Disclosure Information

Only a single type of financial disclosure certification has been found applicable to those investigators who participated in Studies E2020-A001-015 and E2020-A001-016

14.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in Studies E2020-A001-015 and E2020-A001-016. In regard to this list the sponsor has

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

This certification has been provided on FDA Form 3454

14.2 Reviewer's Comments

It appears unlikely that any financial arrangements disclosed to the sponsor introduced significant bias into the results of Studies E2020-A001-015 and E2020-A001-016.

15. Sponsor's Conclusions

- Both the 5 mg and 10 mg rapidly disintegrating tablet formulations of donepezil hydrochloride are bioequivalent to the reference formulations (Aricept® 5 mg and 10 mg tablets)
- The safety of the rapidly disintegrating tablet formulation of donepezil hydrochloride is comparable with that of the tablet formulation
- The rapidly disintegrating formulation of donepezil hydrochloride is an acceptable substitute for the tablet formulation in the treatment of mild to moderate dementia of the Alzheimer's type

16. Agency Labeling Proposal: August 27, 2004

In response to the sponsor's labeling proposal as contained in the original submission under this application, the following changes to the Clinical Pharmacokinetics and DOSAGE AND ADMINISTRATION sections of the currently approved labeling for Aricept® were proposed by the Division in a

communication dated August 27, 2004. The Division had proposed a package insert that combined information for 3 formulations of Aricept: the standard tablet formulation, the \square \square formulation, and the orally disintegrating tablet formulation.

The changes proposed by the Division are below. Note that the Division was in agreement with the additions/changes to the DESCRIPTION, WARNINGS, and HOW SUPPLIED sections of the label proposed in the original submission under this application.

Clinical Pharmacokinetics

ARICEPT® [\square] and ARICEPT® ODT are bioequivalent to ARICEPT®. Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning vs. evening dose) influences the rate or extent of absorption. A food effect study has not been conducted with ARICEPT® ODT; however, the effect of food with ARICEPT® ODT is expected to be minimal. ARICEPT® and ARICEPT® ODT can be taken without regard to meals. \square

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The elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The steady state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha₁ - acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.

10.4.2 DOSAGE AND ADMINISTRATION

Detailed recommended changes to this section, edited by me to a minor extent, are below

DOSAGE AND ADMINISTRATION

The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional

benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

ARICEPT® should be taken in the evening, just prior to retiring. Deleted: ARICEPT® can be taken with or without food.

Allow ARICEPT® ODT tablet to dissolve on the tongue and follow with water. Deleted: RDT
Deleted: a sip of

ARICEPT®, ARICEPT® ODT, and ARICEPT®  can be taken with or without food.

17. Amendment: September 3, 2004

17.1 Contents Of Submission

In this submission the sponsor had responded to the following

- The Division's letter of July 2, 2004 addressing the nomenclature of the formulation, and the blister, pouch and carton labeling
- The labeling proposal sent to the sponsor on August 27, 2004

17.2 Reviewer's Observations And Comments

17.2.1 Nomenclature Of Formulation And Labeling Of Blister, Pouch, And Carton

The sponsor proposed that the proprietary name for the formulation be changed to Aricept®   (donepezil hydrochloride orally disintegrating tablets)

Changes have been made to the blister, pouch, and carton labeling for this formulation in accordance with the Division's letter

17.2.2 New Labeling Proposal

The sponsor proposes a separate packet insert for each formulation of Aricept®. In response to the Division's communication of 8/27/04, the sponsor had proposed the following text for the Clinical Pharmacokinetics and DOSAGE AND ADMINISTRATION SECTIONS

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

18. Amendment: October 4, 2004

18.1 Contents Of Amendment

In this amendment the sponsor has

- Provided a new version of the package insert in which "Aricept® ODT" has been substituted for [] in accordance with a communication received from the Division on 9/24/04. [The full currently proposed name for this formulation is Aricept® ODT (donepezil hydrochloride orally disintegrating tablets), 5 mg and 10 mg]. Apart from the change in proprietary name, the text of the package insert is identical to that in the Amendment of September 3, 2004
- Substituted "Aricept® ODT" for [] in the blister, pouch, and carton labeling for this formulation. Apart from the change in proprietary name, these items are identical to that in the Amendment of September 3, 2004
- Responded to 2 questions from the Division in the July 2, 2004 letter as follows
 - The Aricept® ODT blisters are contained in a pouch so as to maintain the stability of the formulation
 - Each Aricept® ODT blister is child-resistant, incorporating a tear-open child-resistance feature

18.2 Agreement On Labeling Text

The Division reviewed the above Amendment, made further modifications to the labeling text, and conveyed the modified text to the sponsor on October 12, 2004. The sponsor agreed to that text.

Note that the proprietary name of the formulation under review was further modified to "Aricept® ODT (donepezil hydrochloride) Orally Disintegrating Tablets."

The final agreed-upon text differed from the currently approved Aricept® labeling in the DESCRIPTION, Clinical Pharmacokinetics, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections. These sections are reproduced below

2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

19. Summary And Comments

- This New Drug Application seeks the approval of an orally disintegrating tablet formulation (5 mg and 10 mg) of donepezil hydrochloride (Aricept®), which is currently approved for the treatment of mild to moderate dementia of the Alzheimer's type only as a standard tablet formulation (5 mg and 10 mg). A concurrently submitted, but separate, New Drug Application (#21719) seeks the approval of an oral solution formulation of Aricept® (donepezil hydrochloride; 1 mg/mL).
- The two key studies supporting this application are
 - A single-dose bioequivalence study (E2020-A001-015) comparing 10 mg of the orally disintegrating tablet formulation with the 10 mg approved tablet
 - A single-dose bioequivalence study (E2020-A001-016) comparing 5 mg of the orally disintegrating tablet formulation with the 5 mg approved tablet

The above studies enrolled healthy male and female subjects whose ages ranged from 18 to 45 years. A total of 42 subjects were enrolled in the 2 studies.

- Additional studies that were intended to support the safety of the orally disintegrating tablet formulation included the following
 - A single-dose bioequivalence study (E2020-E044-017) which compared 5 mg of an orally disintegrating tablet formulation with 5 mg of the standard tablet formulation, and 10 mg of an orally disintegrating tablet formulation with 10 mg of the standard tablet formulation. This study enrolled 46 healthy male and female subjects whose ages ranged from 18 to 45 years
 - A single-dose study (E2020-J081-007) which evaluated the pharmacokinetics of a 5 mg orally disintegrating tablet formulation administered without water. This study enrolled 6 healthy male subjects, aged 20 to 35 years
 - A single-dose study (E2020-J081-008) which evaluated the pharmacokinetics of a 3 mg orally disintegrating tablet formulation administered with and without water, and a 3 mg film-coated tablet administered with water. This study enrolled 14 healthy male subjects, aged 20 to 35 years
 - A single-dose study (E2020-J081-009) which evaluated the pharmacokinetics of a 5 mg orally disintegrating tablet formulation

administered with and without water, and a 5 mg film-coated tablet administered with water.. This study enrolled 12 healthy male subjects, aged 20 to 35 years

- Safety monitoring in the above studies included the assessment of adverse events, vital signs, electrocardiograms, physical examinations and safety laboratory tests at appropriate intervals
- Safety data from the studies in this application revealed no items of concern and the following
 - No deaths or serious adverse events occurred
 - Adverse events that merited discontinuation from the study were vomiting, influenza-like symptoms with conjunctivitis, dizziness, and a fall.
 - The spectrum of adverse events seen in these studies was broadly similar to those previously noted in subjects administered Aricept®
 - Vital signs, safety laboratory tests, electrocardiograms, and physical examination results were unremarkable
- The Clinical Pharmacology and Biopharmaceutics reviewer of this application has concluded that the 5 mg and 10 mg orally disintegrating tablet formulations of donepezil, are bioequivalent to the currently marketed 5 and 10 mg tablets of Aricept®, respectively. He has recommended changes to the product name, dissolution specification and labeling, and the creation of a single package insert for all formulations of Aricept, and confirmation that assay cross-validation was performed for Studies E2020-A001-013 and E2020-A001-018.
- The Chemistry reviewer of this submission considers the application approvable pending agreement on the proprietary name of this product.
- This Division had earlier sent a letter to the sponsor on 7/2/04 stating the following, based on the Division's own review and a consultation from the Division of Medical Errors and Technical Support
 - The proposed product name Aricept RDT (donepezil hydrochloride rapidly disintegrating tablets) is not acceptable. As an alternative, it is acceptable for the sponsor to change the name to Aricept ODT (donepezil hydrochloride orally disintegrating tablets). [Note that the Clinical Pharmacology and Biopharmaceutics Reviewer had a similar recommendation].
 - Changes to the blister, pouch, and carton labels
- In Amendments to this application, the sponsor has

- Changed the proposed product name to Aricept® ODT (donepezil hydrochloride) Orally Disintegrating Tablets, 5 mg and 10 mg
- Made changes to the blister, pouch, and carton labels consistent with the Agency's recommendations, and satisfactorily answered the Division's questions about product packaging
- Modified the product labeling in communication with this Division

Agreement has been reached with the sponsor on the text of product labeling

20. Recommendations

I recommend that this application be approved

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 10/13/04
cc:
HFD-120
NDA 21720 (000)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ranjit Mani
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MEDICAL OFFICER